THE JOURNAL OF Organic Chemistry

Volume 29

JANUARY–APRIL 1964

(Pages 1–992)

EASTON, PENNSYLVANIA
MACK PRINTING CO.
1964

THE JOURNAL OF Organic Chemistry®

VOLUME 29, NUMBER 1

JANUARY 13, 1964

α-Fluorinated Ethers. I. Aryl Fluoroalkyl Ethers[1]

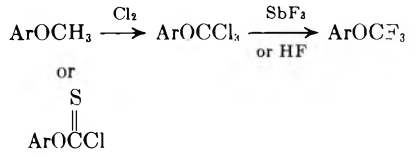
WILLIAM A. SHEPPARD

Contribution No. 860 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware

Received July 1, 1963

The reaction of sulfur tetrafluoride with aryl fluoroformates or perfluoroalkyl esters is a new, general, and direct method for synthesis of aryl perfluoroalkyl ethers. The chemical and physical properties of these ethers are discussed. In particular, the perfluoroalkoxy groups are shown to possess exceptional stability as aromatic substituents.

Aryl trifluoromethyl ethers have been synthesized by the reaction of hydrogen fluoride or antimony fluorides with aryl trichloromethyl ethers, which were in turn prepared by chlorination of anisoles or phenyl esters of chlorothiocarbonic acid.[2] Although these methods are fairly general, the aromatic substituents

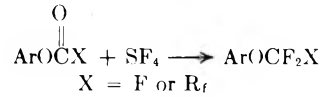


are limited to inert groups such as nitro, halogens, and acid halides. A very low yield of phenyl trifluoromethyl ether has been obtained along with fluorobenzene by the irradiation of trifluoromethyl hypofluorite (CF_3OF) in benzene.[3] The trifluoromethoxy group was shown to be stable to normal chemical transformations of the aromatic ring such as reduction of nitro groups, hydrolysis of nitriles, diazotization of amino groups, and nitration (*ortho–para* orientation).[2,4] Potential dyes[4b] and pharmaceutical chemicals[5] containing the OCF_3 group also have been reported.

Aryl difluoromethyl ethers have been prepared by reaction of phenols with difluorocarbene generated from chlorodifluoromethane or dibromodifluoromethane.[6] This class of α-fluorinated ethers is hydrolyzed by acid and decomposes on standing if not pure. Aryl tetrafluoroethyl ethers are readily obtained by the base-catalyzed addition of phenols to tetrafluoroethylene[7] and appear to have stability more nearly comparable to that of the trifluoro- than that of the difluoroanisoles.

Results and Discussion

Synthesis.—The reaction of sulfur tetrafluoride[8] with aryl fluoroformates[9] or perfluoroalkyl esters[10] provides a general direct synthesis of aryl perfluoroalkyl ethers (eq. 1). The reaction was run in a "Hastelloy"-lined pressure vessel at autogeneous pressure and



(1)

required a temperature of 160 to 175° for several hours with anhydrous hydrogen fluoride as catalyst. In most cases, the product was obtained in a yield of 50 to 80% and was isolated by distillation in a high state of purity after removal of hyrogen fluoride with sodium fluoride or a base wash. Examples of this reaction are given in Table I.

As a convenient procedure for the preparation of aryl trifluoromethyl ethers, phenols were treated with

(1) This work was reported in preliminary form by W. A. Sheppard, *J. Am. Chem. Soc.*, **83**, 4860 (1961).

(2) (a) British Patent 765,527 (1957); (b) L. M. Yagupolsky, *Dokl. Akad. Nauk SSSR*, **105**, 100 (1955); *Chem. Abstr.*, **50**, 11270 (1956); (c) N. N. Iarovenko and A. S. Vasileva, *J. Gen. Chem. USSR* **28**, 2539 (1958).

(3) J. A. C. Allison and G. H. Cady, *J. Am. Chem. Soc.*, **81**, 1089 (1959).

(4) (a) L. M. Yagupolsky and V. I. Troitskaya, *J. Gen. Chem. USSR*, **27**, 587 (1957); (b) L. M. Yagupolsky and M. S. Marenets, *ibid.*, **27**, 1479 (1957); (c) L. M. Yagupolsky and V. I. Troitskaya, *ibid.*, **31**, 845 (1961).

(5) (a) L. M. Yagupolsky and V. I. Troitskaya, *ibid.*, **30**, 3102 (1960); (b) French Patent 1,245,552 (1960); (c) B. Blank and J. F. Kerwin, U. S. Patent 3,021,368 (1962).

(6) (a) T. G. Miller and J. W. Thanassi, *J. Org. Chem.*, **25**, 2009 (1960); (b) R. F. Clark and J. H. Simons, *J. Am. Chem. Soc.*, **77**, 6618 (1955).

(7) (a) D. C. England, L. R. Melby, M. A. Dietrich, and R. V. Lindsey, Jr., *ibid.*, **82**, 5116 (1960); (b) α,α-difluoroperhalogenalkyl aryl ethers, $ArOCF_2CCl_3$, were reported by H. Hahn, *Ber.*, **96**, 48 (1963), prepared chlorination of $ArOCF_2CCl_2H$ [from base-catalyzed addition of phenols to 1,1-dichloro-2,2-difluoroethylene, E. T. McBee and R. O. Bolt, *Ind. Eng. Chem.*, **39**, 412 (1947); U. S. Patent 2,516,403 (1950); *Chem. Abstr.*, **45**, 2964 (1951)].

(8) (a) C. W. Tullock, F. S. Fawcett, W. C. Smith, and D. D. Coffman, *J. Am. Chem. Soc.*, **82**, 539 (1960); (b) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *ibid.*, **82**, 543 (1960).

(9) H. J. Emeleus and J. F. Wood, *J. Chem. Soc.*, 2183 (1948).

(10) (a) R. F. Clark and J. H. Simons, *J. Am. Chem. Soc.*, **75**, 6305 (1953); (b) M. Green, *Chem. Ind.* (London), 435 (1961).

TABLE I

PREPARATION OF ARYL PERFLUOROALKYL ETHERS FROM FLUOROFORMATES OR PERFLUOROALKYLCARBOXYLATES[a]

$$ArO\overset{\overset{O}{\|}}{C}R_f + SF_4 \xrightarrow{HF} ArOCF_2R_f \quad (R_f = F \text{ or } (CF_2)_nF)$$

Reactant (ester of formate), g. (mole)	SF_4, g. (mole)	HF, g.	Product	Yield, G.	Yield, %
$C_6H_5O\overset{\overset{O}{\|}}{C}F$ 264 (1.89)	216 (2.0)	0	$C_6H_5OCF_3$	19	6
			$C_6H_5O\overset{\overset{O}{\|}}{C}F$	213	81
$C_6H_5O\overset{\overset{O}{\|}}{C}F$ 183 (1.30)	150 (1.4)	10	$C_6H_5OCF_3$	120	57
			$C_6H_5O\overset{\overset{O}{\|}}{C}F$	13	7
$2\text{-}O_2NC_6H_4O\overset{\overset{O}{\|}}{C}F$ 24 (0.13)	16 (0.15)	6	$2\text{-}O_2NC_6H_4OCF_3$	18.5	69
$2,4\text{-}Br_2C_6H_3O\overset{\overset{O}{\|}}{C}F$[b] 20 (0.067)	8 (0.074)	3	$2,4\text{-}Br_2C_6H_3OCF_3$	6.9	32
$C_6H_5O\overset{\overset{O}{\|}}{C}CF_3$ 28.5 (0.15)	19 (0.18)	7	$C_6H_5OCF_2CF_3$	19.4	61
$4\text{-}O_2NC_6H_4O\overset{\overset{O}{\|}}{C}CF_3$ 23.5 (0.10)	15 (0.14)	5	$4\text{-}O_2NC_6H_4OCF_2CF_3$	17.8	69
$3\text{-}O_2NC_6H_4O\overset{\overset{O}{\|}}{C}CF_3$ 155 (0.66)	86 (0.80)	25	$3\text{-}O_2NC_6H_4OCF_2CF_3$	142	83
$C_6H_5O\overset{\overset{O}{\|}}{C}(CF_2)_2CF_3$ 22.5 (0.078)	10 (0.10)	7	$C_6H_5O(CF_2)_3CF_3$	<1.9	
$4\text{-}O_2NC_6H_4O\overset{\overset{O}{\|}}{C}(CF_2)_2CF_3$ 33.5 (0.10)	15 (0.14)	5	$4\text{-}O_2NC_6H_4C(CF_2)_3CF_3$	10.7	30

[a] Reactions run in "Hastelloy"-lined pressure vessel of 140-, 240-, or 1000-ml. capacity at autogenous pressure. Normal heating pattern was 2 hr. successively at each temperature of 100, 150, and 160 or 175°. [b] See ref. 18. [c] Product not isolated in pure form. Characterized by F^{19} n.m.r. analysis in pentane solution.

carbonyl fluoride[9,11] in an autoclave at 100°; without isolation of the fluoroformate intermediate, the sulfur tetrafluoride then was added, and the reaction mixture was heated for several hours at 150–175°. The hydrogen fluoride by-product from the carbonyl fluoride reaction served as catalyst for the sulfur tetrafluoride reaction. For example, the yield of ether from phenol and *m*- and *p*-nitrophenols was 60 to 80% over-all for the two steps. The reaction is applicable to substituted phenols, including hydroquinone and resorcinol, provided that substituents on the aromatic ring do not react with hydrogen fluoride or sulfur tetrafluoride. The ethers prepared by the two-step method are listed in Table II.

Trifluoroacetate and heptafluorobutyrate esters of phenols were prepared from the corresponding anhydride[10] or acid chloride (the latter in the presence of a tertiary amine). By reaction of these esters with sulfur tetrafluoride (hydrogen fluoride catalyst) as described previously, the new aryl pentafluoroethyl and heptafluorobutyl ethers were obtained. This method appears to be general for the preparation of aryl perfluoroalkyl ethers. However, the yield of ether dropped with increasing chain length of the perfluoroalkyl group; thus, *p*-nitrophenyl nonafluoro-*n*-butyl ether was obtained in only 30% yield compared to 80% and 69% for the corresponding trifluoromethyl and pentafluoroethyl ethers, respectively.

Phenyl chloroformate also reacted with sulfur tetrafluoride in the presence of hydrogen fluoride, but the yield of phenyl trifluoromethyl ether was only a few per cent.

From a limited exploration of conditions, it is concluded that the temperature for the sulfur tetrafluoride reaction is critical. At temperatures below 150° the carbonyl group reacted to only a small extent, and the major portion of the fluoroformate or ester was recovered. At temperatures over 175° the formation of tar increased, and the yield of ether decreased. It is considered likely that the main side reactions leading to tars are Friedel–Crafts-type condensations (see the subsequent discussion of by-products). The yield of ether was also extremely low if hydrogen fluoride was not used as a catalyst and in one experiment where titanium tetrafluoride replaced hydrogen fluoride tar formation became predominant.

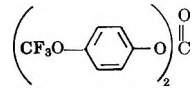
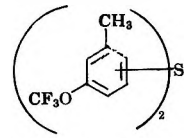
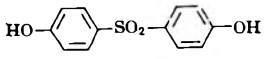
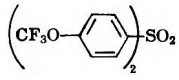
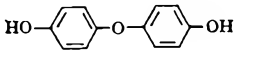
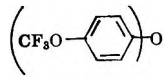
The amount of hydrogen fluoride generally used, particularly when it was present as by-product in the fluoroformate preparation, is greatly in excess of that needed as a catalyst. It is possible that the hydrogen

(11) M. W. Farlow, E. H. Mann, and C. W. Tullock, *Inorg. Syn.*, **6**, 155 (1960). A convenient synthesis of carbonyl chloride from sodium chloride and phosgene in acetonitrile is described by F. S. Fawcett, C. W. Tullock, and D. D. Coffman, *J. Am. Chem. Soc.*, **84**, 4275 (1962).

TABLE II

PREPARATION OF ARYL TRIFLUOROMETHYL ETHERS BY TWO-STEP METHOD FROM PHENOLS[a]

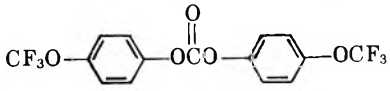
$$ArOH + COF_2 \longrightarrow HF + ArO\overset{\overset{O}{\|}}{C}F \xrightarrow{SF_4} ArOCF_3$$

Phenol, g. (mole)	COF_2, g. (mole)	SF_4, g. (mole)	Product	Yield G.	Yield %
C_6H_5OH 235 (2.5)	200 (3.0)	270 (2.5)	$C_6H_5OCF_3$	375–437	46–62[b]
4-$C_6H_4(OH)_2$ 55 (0.50)	100 (1.5)	120 (1.1)	4-$C_6H_4(OCF_3)_2$	68.4	56
				13	7
3-$C_6H_4(OH)_2$ 16.5 (0.15)	25 (0.38)	35 (0.32)	3-$C_6H_4(OCF_3)_2$	6.4	17
4-$O_2NC_6H_4OH$ 139.1 (1.0)	100 (1.5)	120 (1.1)	4-$O_2NC_6H_4OCF_3$	166.4	81
3-$O_2NC_6H_4OH$ 65 (0.47)	50 (0.75)	60 (0.55)	3-$O_2NC_6H_4OCF_3$	73.9	76
4-$CH_3C_6H_4OH$ 27 (0.25)	25 (0.38)	30 (0.28)	4-$CH_3C_6H_4OCF_3$	12.0	27
3-$CH_3C_6H_4OH$ 108 (1.0)	90 (1.35)	130 (1.2)	3-$CH_{36}CH_4OCF_3$	16.2	9
				72.9	38
4-ClC_6H_4OH 32 (0.25)	25 (0.38)	30 (0.28)	4-$ClC_6H_4OCF_3$	28.4	58
			4-$ClC_6H_4O\overset{\overset{O}{\|}}{C}F$[c]	4.9	11
3-ClC_6H_4OH 32 (0.25)	25 (0.38)	30 (0.28)	3-$ClC_6H_4OCF_3$	22.7	46
2-ClC_6H_4OH 32 (0.25)	25 (0.38)	30 (0.28)	2-$ClC_6H_4OCF_3$	8.4	17
4-BrC_6H_4OH 34.6 (0.20)	20 (0.30)	24 (0.22)	4-$BrC_6H_4OCF_3$	13.2	27.4
			4-$BrC_6H_4O\overset{\overset{O}{\|}}{C}F$	7.8	18
3-BrC_5H_4OH 43.2 (0.25)	25 (0.38)	32 (0.30)	3-$BrC_6H_4OCF_3$	10.8	18
4-FC_6H_4OH 15 (0.13)	15 (0.22)	17 (0.16)	4-$FC_6H_4OCF_3$	10.1	42
3-FC_6H_4OH 15 (0.13)	15 (0.22)	17 (0.16)	3-$FC_6H_4OCF_3$	7.7	32
 35 (0.14)	25 (0.38)	33 (0.30)		2.5 (no solvent)	5
				31.0 (solvent, 40 g. of $C_6H_5NO_2$)	56
 35 (0.17)	30 (0.45)	40 (0.37)		3.1	5

[a] Reactions run in "Haselloy-lined pressure vessel of 140-, 240-, or 1000-ml. capacity at autogenous pressure. Normal heating pattern was 1 hr. at 100° followed by 2 to 3 hr. at 140° (or higher temperatures above phenol melting point) for the COF_2 reaction; 2 hr. successively at 100, 140, or 150°, and 160 or 175° for the SF_4 reaction. [b] See ref. 18. [c] Boiling point 93° (30 mm.), characterized by F^{19} n.m.r. analysis only.

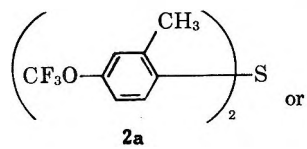
fluoride also may serve as a solvent.[12] The use of an inert solvent such as nitrobenzene also was found necessary for the reaction of high-melting phenols, such as 4,4′-dihydroxydiphenyl sulfone. It is concluded that the reactants must be liquids or in solution for the reaction with carbonyl fluoride or sulfur tetrafluoride to proceed to completion at a reasonable rate.

As by-products in several reactions, small amounts of the fluoroformate intermediates were isolated as a higher boiling fraction after distillation of the trifluoromethyl ethers. From hydroquinone the main by-product was the carbonate, **1**, and as expected its relative



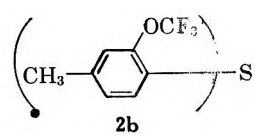
1

amount compared to 1,4-bis(trifluoromethoxy)benzene increased when the molar ratio of COF_2 to hydroquinone was decreased. An unusual by-product was formed in the reaction of *m*-cresol. Only a 10% yield of the normal product, *m*-tolyl trifluoromethyl ether, was isolated; the main product in 40% yield was a sulfide which, on basis of analysis and spectral properties, was assigned one of two structures, **2a** or **2b**.



2a

or



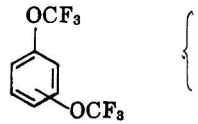
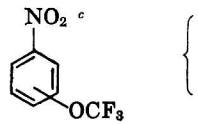
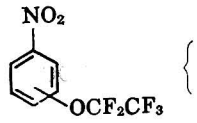
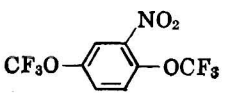
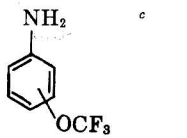
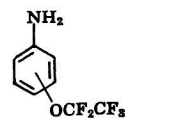
2b

Structure **2a** is preferred since the OCF_3 group direct electrophilic reagents predominantly to the *para* posi-

(12) The use of hydrogen fluoride as a catalyst was demonstrated in the original report on the use of sulfur tetrafluoride as a fluorinating agent, see ref. 8b. Recently, D. C. Martin and F. Kagan, *J. Org. Chem.*, **27**, 3164 (1962), described the reaction of sulfur tetrafluoride with the carbonyl functions of steroids and stated that high yields of fluorinated steroids were obtained only when the sulfur tetrafluoride contained 20% hydrogen fluoride. In discussing these results, the authors commented that the concentration of hydrogen fluoride was critical.

TABLE III

ARYL FLUOROALKYL ETHERS, ESTERS, AND FLUOROFORMATES[a]

Compound	M.p., °C., and/or $n^{25}D$	B.p., °C. (mm.)	Method of preparation (% yield)[b,i]	Analyses, % Carbon[b,2] Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Fluorine Calcd.	Fluorine Found	Other Calcd.	Other Found
$C_6H_5OCF_3$[c]	−50 1.4029	106	C, D[d]	51.9	52.1	3.11	3.25	35.2	35.7		
$C_6H_5OCF_2CF_3$	−29 1.3790	115	C	45.3	45.9	2.38	2.54	44.8	45.2		
 *meta*	−50 1.3673	123	D	39.0	39.5 39.3	1.64	1.91 1.91	46.3	46.5		
para	6 1.3683	129	D	39.0	39.3	1.64	1.73	46.3	46.4		
 *ortho*	1.4575	93 (9.5)	C	40.6	41.1	1.95	2.09	27.5	27.8	N, 6.8	7.0
meta	1.4591	96 (20)	D	40.6	40.9	1.95	1.98	27.5	27.5	N, 6.8	6.6
para	15 1.4653	101 (22)	C, D	40.6	41.0	1.59	2.18	27.5	27.5	N, 6.8	7.0 7.2
 *meta*	1.4293	66 (2.3)	C					37.0	36.7	N, 5.4	5.6
para	35.8–36.8	88 (8.3)	C	37.4	37.4	1.57	1.81	37.0	37.0	N, 5.4	5.0
$O_2NC_6H_4OCF_2CF_2H$ *meta*	1.4580	91 (1.8)	E (70)					31.8	31.2	N, 5.9	5.7
$O_2NC_6H_4O(CF_2)_3CF_3$ *para*	1.4048	80 (2.2)	C					47.9	48.1	N, 3.9	4.4
$2,4\text{-}(O_2N)_2C_6H_3OCF_3$[c]	1.4969	107 (2)	F1 (36)	33.4	33.8	1.20	1.49	22.6	22.8	N, 11.1	10.6
$2,4\text{-}(O_2N)_2C_6H_3OCF_2CF_2H$	1.4950	120 (0.7)	F1 (61)					26.3	26.8	N, 9.9	9.6 9.8
2 and $3\text{-}O_2N\text{-}4\text{-}ClC_6H_4OCF_3$[d]	1.4783	65 (1.1)	F1 (72)					23.6	23.7	Cl, 14.7	14.6
	1.4139	90 (9.5)	F1 (63)					39.2	39.3	N, 4.8	4.5 4.7
 *ortho*	1.4601	64.5 (21)	F3 (88)	47.5	48.0	3.42	3.71	32.2	32.2	N, 7.9	8.0
meta	1.4637	70 (7)	F3 (93)	47.5	47.8	3.42	3.65	32.2	32.1		
para	1.4605	94 (24)	F3 (84)	47.5	47.5	3.42	3.42	32.2	32.2		
 *meta*	1.4300	95 (22)	F3 (84)	42.3	42.6	2.66	2.86	41.8	41.9		
para	1.4269	84 (9)	F3 (87)					41.8	41.8	N, 6.2	6.5

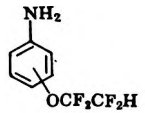
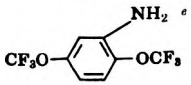
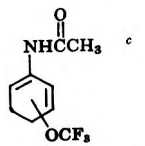
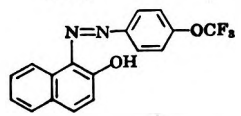
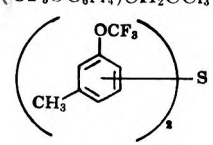
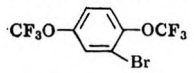
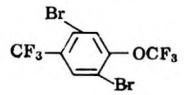
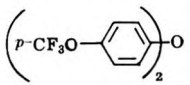
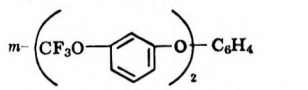
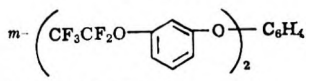
	*meta*	1.4636	100 (6.6)	F3 (89)	46.0	46.5	3.38	3.53	36.3	35.7	N, 6.7	6.8
	para	1.4600	96 (5.7)	E (70)	46.0	46.3	3.38	3.47			N, 6.7	7.0
 [e]		1.4120	70 (20)	F3 (55)	36.8	37.3	1.93	2.08				
 [c]	*meta*	92.6–93.2		F (97)					26.0	26.5	N, 6.4	6.0
	para	113–114		F (93)	49.4	49.7	3.68	3.80	26.0	25.9		
		110–110.4		F (95)[f]	61.4	61.6	3.44	2.92	17.2	16.7	N, 8.4	8.7
$CH_3C_6H_4OCF_3$	*meta*	1.4144	131	D	54.6	54.9	4.01	4.34	32.4	32.8		
	para	1.4128	134–135	D	54.6	54.7	4.01	4.19	32.4	32.1		
$CH_3C_6H_4OCF_2CF_2H$	*meta*	1.4210	98 (65)	E (49)					36.5	36.6		
	para	1.4197	94 (53)	E (56)					36.5	36.7		
p-$CF_3OC_6H_4CH(OH)CH_3$ [e]		1.4477	82–83 (8)	F (60)[g]	52.4	52.5	4.40	4.50				
p-$CF_3OC_6H_4CH{=}CH_2$ [e]			60 (21)	F (32)[h]	57.4	58.1	3.74	4.01				
p-$CF_3OC_6H_4CH_2OH$ [e]		1.4476	108 (25)	F (39)[i]	50.0	50.2	3.67	3.84				
p-$CF_3OC_6H_4C(NNHC_6H_5)CH_3$ [e]		175–175.5		F (5)[j]	46.9	47.1	2.89	2.80				
$(CF_3OC_6H_4)_2CHCCl_3$		1.4956	140 (2.3)	F6 (26–30)	42.4	42.7	2.00	2.32	25.1	24.8	Cl, 23.5	23.4
$(CF_3OC_6H_4)CH_2CCl_3$		1.4978	58 (0.06)	F6 (16)	33.0	33.2	1.54	1.65	17.4	17.0	Cl, 43.2	44.0
											Mol. wt., 328	314
		1.4986	107 (0.7)	D					29.8	29.8	S, 8.4	8.3
$CF_3OC_6H_4CO_2H$	*meta*	91.4–92.0		F4b (42), F4c (58)	46.6	46.7	2.45	2.70	27.7	27.5	Neut. equiv., 206	204, 205
	para	152.2–153.8		F4a (46), F4c (66)	46.6	46.9 47.0	2.45	2.73 2.61	27.7	27.6	Neut. equiv., 206	205, 204
$HCF_2CF_2OC_6H_4CO_2H$	*meta*	127.4–128.6		F4b (38)	45.4	47.0 45.4	2.54	2.64 2.41	31.9	31.7	Neut. equiv., 238	238, 233
	para	177.4–178.4		F4b (55)	45.4	45.6	2.54	2.92	31.9	32.0	Neut. equiv., 238	237
$FC_6H_4OCF_3$	*meta*	1.3914	105	D	46.7	46.7	2.24	2.22	42.2	42.2		
	para	1.3912	108	D	46.7	46.4	2.24	2.56	42.2	41.7		

TABLE III (*Continued*)

Compound	M.p., °C., and/or $n^{25}D$	B.p., °C. (mm.)	Method of preparation (% yield)[b1]	Analyses, % Carbon[b2] Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Fluorine Calcd.	Fluorine Found	Other	Other Found
$ClC_6H_4OCF_3$ *ortho*	1.4362	144.5	D	42.8	43.0	2.05	2.45	29.0	28.8	Cl, 18.0	18.0
$ClC_6H_4OCF_3$ *meta*	1.4338	140	D					29.0	29.4	Cl, 18.0	17.9
$ClC_6H_4OCF_3$ *para*	1.4338	81 (100)	D	42.8	43.2	2.05	2.36	29.0	28.7	Cl, 18.0	18.0
$BrC_6H_4OCF_3$ *meta*	1.4586	81 (50)	D					23.7	23.8	Br, 33.2	33.5
$BrC_6H_4OCF_3$ *para*	1.4586	80 (50)	D					23.7	23.7	Br, 33.2	33.1
2,4- and 3,4-$Br_2C_6H_3OCF_3$[d]	1.5068	76–79 (7)	F2					17.8	18.1	Br, 50.0	50.2
	1.4148	58.5 (20)	F2b (22–30)	29.6	30.1	0.93	1.20	24.6	24.4	Br, 35.1	34.6
	1.4571	110 (30)	F2b (15–22)	23.8	24.0	0.50	0.65	39.6	39.9	Br, 28.2	28.1
$HOC_6H_4OCF_3$ *meta*	1.4436	69.5 (12)	F (45)[k]	47.2	47.3	2.83	3.05	32.0	32.1		
$HOC_6H_4OCF_3$ *para*	1.4469	92 (25)	F (80)[l]	47.2	47.8	2.83	3.03	32.0	31.5		
$HOC_6H_4OCF_2CF_3$ *meta*	1.4125	84 (14)	F (44)[k]	42.1	42.8	2.21	2.43	41.7	41.1		
$HOC_6H_4OCF_2CF_3$ *para*	62.6–64.2	89 (20)	F (44)[k]	42.1	41.7	2.21	2.04	41.7	41.5		
	1.4643	111.5 (3.3) 252	D					33.7	33.2	Mol. wt., 338	289
	1.5048 (glass at −40)	143 (0.95)	F7 (61)	55.8	56.2	2.81	2.93	26.5	26.7		
	1.4700 (glass at −30)	129 (0.25)	F7 (56)	49.8	50.2	2.28	2.56	34.8	34.4		
$(p\text{-}CF_3OC_6H_4O)_2C{=}O$	57.5–59	111 (4)	D	47.2	47.7	2.11	2.27	29.8	30.0	Mol. wt., 382	373
$(p\text{-}CF_3OC_6H_4)_2SO_2$	107.5–108	154 (6)	D	43.5	43.5	2.09	2.11	29.5	28.8	S, 8.3	8.4
$p\text{-}CF_3OC_6H_4HgCl$	246.6–251.5		F (15)[m]					14.4	14.3	Hg, 50.5	49.1
$(m\text{-}CF_3OC_6H_4)_4Si$	1.4915 (glass at −30)	136 (0.7)	F5 (32)					33.9	33.1	Si, 4.2	4.0
$(p\text{-}CF_3OC_6H_4)_2SiCl_2$	1.4790	107–109 (0.7)	F (6)[n]					27.1	27.8	Si, 6.7	6.8
$(p\text{-}CF_3OC_6H_4)_3P$	1.5088	150 (1.0)	F (56)[o]	49.0	49.5	2.35	2.62	33.3	33.2	P, 6.0	6.0
$(p\text{-}CF_3OC_6H_4)_2P{=}O$	91.6–94.0		F (77)[p]	47.6	47.5	2.28	2.50	32.2	32.2	P, 5.9	5.7
			Fluoroformates								
$O_2NC_6H_4OCF(=O)$ *ortho*	1.5094	96.5 (107)	A (68)[q]								
$O_2NC_6H_4OCF(=O)$ *para*	39–39.5	88 (0.75)	A (39)	45.4	45.8	2.18	2.35	10.3	10.2		
$p\text{-}BrC_6H_4OCF(=O)$	1.5166	65 (1.5)	D	38.4	38.8	1.84	2.06	8.7	8.4		
2,4-$Br_2C_6H_3OCF(=O)$[e]		117–118 (15)	A (73)					6.4	6.3	Br, 53.7	53.9

				Fluorocarboxylates							
O ‖ $O_2NC_6H_4OCCF_3$	*meta*	41–41.6	92 (1.2)	B1 (88)			24.3	23.7	N, 6.0		6.3
	para	1.4751	104 (4)	B1 (72), B2 (35)	40.9	41.1	1.72	2.12	24.3	23.7	N, 6.0	6.3
O ‖ p-$O_2NC_6H_4OC(CF_2)_2CF_3$		1.4285	95.5 (1.4)	B2 (76)[g]								

[a] Compounds reported in this table also were characterized by infrared, ultraviolet, F^{19} and H′ n.m.r. spectra. [b] Letter and numbers refer to procedure listed in Experimental. Yields in preparation by methods C and D are reported in Tables I and II. Where appropriate, references to typical literature procedures for compounds prepared by method F are given in footnotes. [b2] It has been observed in compounds containing C, F, and other elements that the C analysis is often 0.4 to 0.7% high, although not reproducibly so. [c] These compounds have been claimed previously in the Russian literature, ref. 2 and 4. [d] See Ref. 17. [e] See Ref. 18. [f] Diazotized *p*-trifluoromethoxyaniline coupled to β-naphthol, B. C. McKusick, R. E. Heckert, T. L. Cairns, D. D. Coffman, and H. F. Mower, *J. Am. Chem. Soc.*, **80**, 2806 (1958). [g] Grignard reagent from *p*-bromophenyl trifluoromethyl ether added to acetaldehyde, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 200. [h] Corresponding alcohol was dehydrated over potassium persulfate or the acetate was pyrolyzed, M. W. Renoll, *J. Am. Chem. Soc.*, **68**, 1159 (1946). [i] Grignard reagent from *p*-bromophenyl trifluoromethyl ether added to formaldehyde, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 188. [j] Friedel–Crafts reaction of acetyl fluoride with aluminum chloride on phenyltrifluoromethyl ether. Acetophenone product isolated as phenylhydrazone. [k] Hydrolysis of diazotized aniline, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 404. [l] Basic hydrolysis of bis(*p*-trifluoromethoxyphenyl)carbonate. [m] Diazotized *p* trifluoromethoxyaniline coupled with mercuric chloride in presence of copper powder, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 432. [n] Prepared from Grignard reagent of *p*-bromophenyl trifluoromethyl ether with silicon tetrachloride. Lower boiling fraction was shown to contain *p*-trifluoromethoxyphenyltrichlorosilane and a large fraction of higher boiling material was shown to be a mixture of the dichlorosilane with tris(*p*-trifluoromethoxyphenyl)chlorosilane. [o] Prepared from corresponding Grignard reagent with phosphorus trichloride, F. G. Mann and E. J. Chaplin, *J. Chem. Soc.*, 527 (1937). [p] Oxidized phosphine with 30% hydrogen peroxide. [q] Characterized only by infrared, ultraviolet, and n.m.r. (F^{19} resonance at +1 c.p.s. at 40 Mc./sec. reference to CF_3CO_2H) spectra. [r] Characterized only by infrared, ultraviolet, and n.m.r. analyses.

tion. The formation of this sulfide is postulated to occur *via* a Friedel–Crafts-type reaction of thionyl fluoride with tolyl trifluoromethyl ether, followed by an oxidation–reduction reaction with the remaining thionyl fluoride. As an analogy, the reaction of anisole with thionyl chloride is reported to give 4,4′-bis(methoxy)-diphenyl sulfide.[13] In sulfur tetrafluoride chemistry, this is the first example of formation of a sulfide in reactions with an aromatic derivative.

The preparation of *o*-nitrophenyl trifluoromethyl ether also requires special comment. Because of hydrogen bonding of the OH with NO_2, carbonyl fluoride does not react with the phenol unless sodium fluoride is used as a base. In this case, the intermediate fluoroformate must be isolated and charged into a clean autoclave with hydrogen fluoride and sulfur tetrafluoride.

For comparison purposes a number of aryl tetrafluoroethyl ethers also have been synthesized by the literature procedure.[7] The fluoroalkyl ethers prepared in this work are tabulated in Table III, and physical properties and analytical data are given.

Physical and Spectral Properties.—The melting points, boiling points, and densities of selected aryl fluoroalkyl ethers are summarized in Table IV and compared with those of anisole, phenetole, and benzotrifluoride. In this series, as is generally recognized, the complete replacement of aliphatic hydrogen by fluorine causes a marked decrease in boiling point. For OCF_3 groups a melting point decrease also is observed, and this phenomenon is particularly significant when the OCF_3 group is in the *meta* position in aromatic derivatives. It also is noted that the density of the ethers increases with increasing fluorine content. These ethers are all colorless and have a sweetish odor with typical aromatic character.

TABLE IV

PHYSICAL PROPERTIES OF ARYL FLUOROALKYL ETHERS

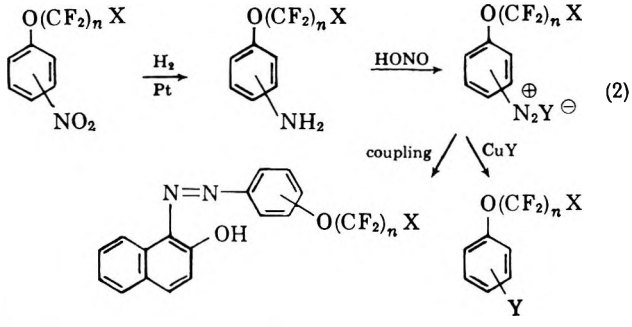
X of C_6H_5X (or $C_6H_4X_2$)	M.p., °C.	B.p., °C.	Density, d^{25}_{25}
OCH_3	−37	155	1.00
OCH_2CH_3	−30	172	0.97
CF_3	−29	102	1.19
OCF_3	−50	106	1.23
OCF_2CF_3	−29	115	1.30
OCF_2CF_2H[l]		147	
OCF_2H[l]		145	
		(Extrapolated)	1.18
m-$(OCH_3)_2$	−52	217	1.08
m-$(OCF_3)_2$	−55	123	1.41

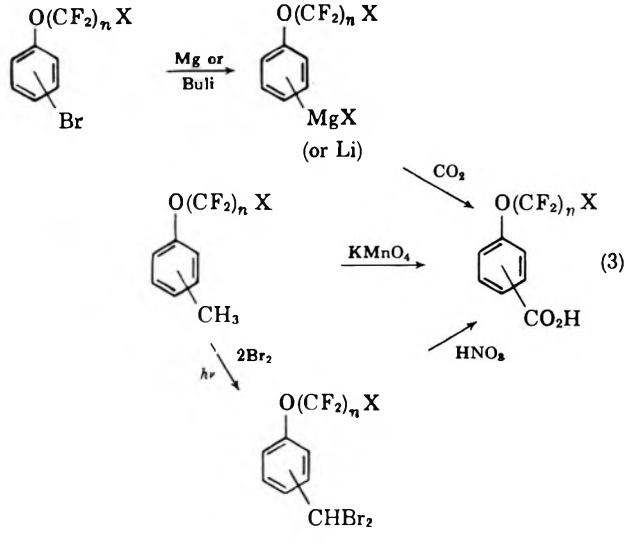
The infrared spectra of these ethers show typical strong C–O absorption at 7.8 to 8 μ and very strong C–F absorption in the 8–9-μ region. The remainder of the spectra contains absorption typical of the aromatic nucleus and substituents. The ultraviolet spectra are in general similar to those of the corresponding tolyl derivatives. The F^{19} n.m.r. spectra of aryl trifluoromethyl ethers show a single resonance in the region of −700 to −800 c.p.s. at 40 Mc./sec. with reference (external) to CF_2ClCF_2Cl (no solvent). This resonance is approximately 1600 c.p.s. downfield to that of a normal CF_3 group. In some cases, a small amount of spin–spin coupling (about 1 c.p.s.) between the ortho-H

(13) F. Loth and A. Michaelis, *Ber.*, **27**, 2543 (1894).

and the F^{19} was noted. The pentafluoroethyl group has resonances at +814 and +769 c.p.s. with relative intensity of 2 to 3. The downfield shift of the fluorines on the carbon adjacent to oxygen is apparent also in the spectra for the aryl nonafluoro-*n*-butyl ethers which have the normal *n*-heptafluoropropyl group resonances (CF_2 at +2347 c.p.s.) and the OCF_2 resonance at +618 c.p.s. Quantitative correlations of the F^{19} n.m.r. chemical shifts with substituents and quantitative measurements that show that the perfluoroalkoxy groups are halogen-like in inductive and resonance effects on the aromatic ring and adjacent groups are described in other publications.[1-14]

Chemical Properties.—The inert character of the OCF_3 group when attached to an aromatic residue was indicated in earlier reports.[2-4] Numerous additional chemical transformations clearly have demonstrated the unusual stability of the OCF_3 group to strong acids and bases (including organometallic reagents) as well as to strong oxidizing and reducing conditions. Representative reactions for preparation and reactions of the anilines and preparation of benzoic acids are shown by eq. 2 and 3. In general, yields were comparable to those of analogous reactions described in the literature. The OCF_2CF_3, $OCF_2CF_2CF_2CF_3$, and OCF_2CF_2H groups, when attached to the aromatic ring, although not examined so thoroughly, also appear to have





stability comparable with that of the OCF_3 group. The thermal stability of the aryl trifluoromethyl ethers is exceptional, and these compounds do not show extensive degradation in the gas phase (as determined by mass spectrometric analysis) until heated to approximately 600° in a sealed nickel tube.

In substitution studies on the aryl perfluoroalkyl ethers, it was found that the OR_f group orients an attacking electrophilic reagent to the *ortho-para* positions. Nitration of phenyl trifluoromethyl ether at room temperature with fuming nitric acid in concentrated sulfuric acid gave approximately an equal mixture of mono- and dinitration products. The mononitro product was shown by gas chromatographic analysis, with conformation from spectral (infrared, ultraviolet, and n.m.r.) analysis, to be *para*, and no trace was detected of *ortho* or *meta* isomers (a synthetic mixture of *o*-, *m*-, and *p*-nitrophenyl trifluoromethyl ether was cleanly separated by gas chromatography on a column of 20% diglyceride on Columpak). The dinitro product was shown by spectral analysis to have 2,4-orientation.[15] Bromination in the presence of iron catalyst also gives only *para* orientation for the monobromo derivative. If excess bromine is used, dibromination also occurs; from gas chromatographic and spectral analysis, it was shown that the dibromophenyl trifluoromethyl ether is a mixture of 2,4 and 3,4 isomers in the ratio of two to one. Mononitration of *p*-chlorophenyl trifluoromethyl ether gave the two possible isomers in approximately equal amounts. From these experiments it is concluded that the OCF_3 group is very similar to the halogens (in particular bromine and chlorine) in its influence on the aromatic system to substitution by an electrophilic reagent.

The over-all deactivating effect of the OCF_3 group, analogous to that of the halogens, also is reflected in the low yield obtained in a Friedel–Crafts acylation and in the forcing conditions required for condensation with chloral.

In the bromination of 1,4-bis(trifluoromethoxy)benzene with excess bromine, a mixture of recovered starting material, monobromo and dibromo products, was formed. The dibromo derivative proved to be almost solely the 2,5 isomer by virtue of only a single fluorine resonance in the n.m.r. spectrum (two resonances are observed for the monobromo product and are expected also for the 2,6-dibromo isomer).

Because of the exceptional chemical and thermal stability combined with a good liquid range for the aryl perfluoroalkyl ethers, a series of stable fluids containing perfluoroalkoxy groups was prepared also. In particular, the phenylene ethers substituted with perfluoroalkoxy groups were found to have better properties over-all as stable fluids than the unsubstituted derivative.

Experimental

Materials.—The phenols were purchased from Eastman Kodak Company or other chemical supply houses. Carbonyl fluoride was prepared by the recently reported synthesis from phosgene and sodium fluoride in acetonitrile.[11] Sulfur tetrafluoride was obtained from Organic Chemicals Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware. Trifluoroacetic anhydride, trifluoroacetyl chloride, and heptafluorobutyryl chloride were purchased from Columbia Organic Chemicals. Anhydrous hydrogen fluoride was purchased from Harshaw Chemical Company. Sodium hydride, as a 53% dispersion in

(14) W. A. Sheppard, *J. Am. Chem. Soc.*, **85**, 1314 (1963); D. R. Eaton and W. A. Sheppard, *ibid.*, **85**, 1310 (1963).

(15) Since completion of this work, similar results were reported for the nitration of phenyl trifluoromethyl ether in the Russian literature.[16] The orientation of the nitro groups was proven by classical chemical methods only.

mineral oil, was obtained from Metal Hydrides, Inc., Beverly, Massachusetts.

A. Preparation of Fluoroformates.—A modification of the literature procedure[9] was employed. The phenol was charged in a "Hastelloy"-lined pressure vessel (140-, 240-, or 1000-ml. capacity). The vessel was cooled in Dry Ice, evacuated, and a 25 to 50% molar excess of COF_2 was added. The reactants were heated under autogenous pressure for 1–4 hr. at 100 to 200°. The product was dissolved in an inert solvent, normally methylene chloride, and stirred in a polyethylene bottle with a molar excess of sodium fluoride powder or pellets until the hydrogen fluoride was removed. The solution was filtered and distilled. The fluoroformate, if liquid, was fractionated at reduced pressure or, if solid, was recrystallized. For preparation of *o*-nitrophenyl fluoroformate, it was found necessary to charge a molar amount of NaF powder in the pressure vessel with the reactants. The fluoroformates not described previously in the literature are listed in Table III.

B. Preparation of Aryl Fluoroalkylcarboxylates.—Two procedures were employed. (1) The reaction of the phenol with trifluoroacetic anhydride was carried out as described in the literature.[10a] (2) The phenol and an equimolar amount of pyridine was dissolved in ether and a slight molar excess of trifluoroacetyl chloride was bubbled into the solution, or heptafluorobutyryl chloride was added dropwise with stirring. The pyridine hydrochloride was separated by suction filtration, and the product distilled (or recrystallized if solid). The esters not previously reported in the literature are listed in Table III.

C. Preparation of Aryl Perfluoroalkyl Ethers from the Fluoroformate or Perfluoroalkyl Ester.—The aryl fluoroformate or perfluorocarboxylate was charged into a "Hastelloy"-lined pressure vessel (140-, 240-, or 1000-ml. capacity). The vessel was cooled in Dry Ice, evacuated, and anhydrous hydrogen fluoride and sulfur tetrafluoride were added. The reactants were then heated under autogenous pressure, generally for 2-hr. successive periods at temperatures of 100, 150, and 175°. The product was treated with sufficient sodium fluoride (powder or pellets) to remove all of the hydrogen fluoride (or alternatively washed with water and sodium bicarbonate solution) and fractionated. Normally a 45-cm. spinning-band column was employed for the distillation and the product was obtained in an exceptionally high state of purity (for phenyl trifluoromethyl ether better than 99.9% pure as determined by gas chromatographic analysis). The reactions run by this route are summarized in Table I, and the ethers are described in Table III.

D. Preparation of Trifluoromethyl Ethers. General Two-Step Procedure from Phenols.—The phenol was treated with 25 to 50% molar excess of COF_2 as described in section A; generally the reactions were heated under autogenous pressure at 100° for 1 hr. and at 130 to 150° for 2–3 hr. The vessel was first cooled to 0° to vent the excess COF_2; then, after cooling to −80°, 10 to 20% molar excess of SF_4 was added. The reactants were heated under autogenous pressure and the product worked up as described in section C. The reactions run by this method are summarized in Table II, and the ethers are listed in Table III.

E. Preparation of Aryl Tetrafluoroethyl Ethers.—The procedure described previously[7a] was employed with the following modifications.[16] The phenol (0.25 to 0.50 mole) was dissolved in 150 ml. of dimethoxyethane (glyme), and 10 to 20 molar % of 53% sodium hydride dispersion in mineral oil was added. When the reaction was complete, the solution was diluted with 150 ml. of dimethylformamide and transferred to the reactor. The tetrafluoroethylene reaction was carried out as described[7a] and the product worked up in the normal manner.

F. Reactions of Aryl Perfluoroalkyl Ethers (on the Aromatic Ring).—A number of reactions involving the aromatic ring of aryl trifluoromethyl ethers have been described in the Russian literature.[2,4,5] Also in many reactions, standard conditions (such as described in "Organic Syntheses") were employed to carry out classical conversions on the ring or on substituents. Consequently, experimental details are provided only where conditions are unusual or important. The perfluoroalkyl ethers, with physical properties and analytical data, are listed in Table III, along with the methods of preparation (including references to literature methods where pertinent) and yields also are given.

1. **Nitration. a. Phenyl Trifluoromethyl Ether.**—A mixture of 4.86 g. (0.030 mole) of phenyl trifluoromethyl ether with 18 ml. of concentrated sulfuric acid was placed in a 35-ml. flask fitted with a thermometer, magnetic stirrer, and addition funnel with a Drierite guard tube. Approximately 5 ml. of fuming nitric acid was added dropwise to the mixture with stirring while the temperature was maintained between 20° and 30° by an ice bath. The reaction was extremely exothermic during addition, and after the addition was completed and the ice bath removed, a slight exothermic reaction continued. After approximately 30 min., the mixture was poured over approximately 100 g. of cracked ice, and the product extracted in ether. The ether extracts were washed with 15% sodium hydroxide solution, then with water, and dried over anhydrous magnesium sulfate. The product was distilled through a 30-cm. spinning-band column to obtain 2.9 g. (47%) of *p*-nitrophenyl trifluoromethyl ether, b.p. 82° (9.7 mm.), $n^{25}D$ 1.4659, and 2.7 g. (36%) of 2,4-dinitrophenyl trifluoromethyl ether, b.p. 106–107° (2 mm.), $n^{25}D$ 1.4969.

The lower boiling fraction was characterized as *p*-nitrophenyl trifluoromethyl ether. Infrared and gas chromatographic analysis of this sample showed it to contain no *ortho* or *meta* isomer. (Authentic samples of *o*-, *m*-, and *p*-nitrophenyl trifluoromethyl ethers were employed for comparison and synthetic mixtures of the three isomers were readily separated on a 2-m. column of 20% diglyceride on 40- to 60-mesh Columpak heated at 150°.) The 2,4-dinitrophenyl trifluoromethyl ether was characterized by elemental analyses and n.m.r., ultraviolet, and infrared spectra.

b. *p*-Chlorophenyl Trifluoromethyl Ether.[17]—A solution of 11.39 g. (0.0574 mole) of *p*-chlorophenyl trifluoromethyl ether in 25 ml. of concentrated sulfuric acid was nitrated with 5 g. of fuming nitric acid as described previously. The chloronitrophenyl trifluoromethyl ether, b.p. 65° (1.1 mm.) was obtained in a yield of 10.0 g. (72%) and was shown to be approximately a 50:50 mixture of the 2- and 3-nitro-4-chlorophenyl trifluoromethyl ether by F^{19} n.m.r. analysis.

2. **Bromination. a. Phenyl Trifluoromethyl Ether.**[18]—A mixture of 143 g. (0.89 mole) of phenyl trifluoromethyl ether and 3 g. of iron powder was heated to reflux with stirring, and 50 ml. (155 g., 0.97 mole) of bromine was added rapidly. The reaction mixture was then cooled, decanted, and taken up in pentane. The pentane solution was washed successively with 50-ml. portions of 6 *N* hydrochloric acid, 10% sodium bisulfite, and saturated sodium chloride solutions, dried, and distilled. The *p*-bromophenyl trifluoromethyl ether, b.p. 155°, was obtained in a yield of 175 g. (82%) and was characterized as *para* isomer only by gas chromatographic and spectral comparison to an authentic sample prepared by method D. If an excess of bromine was used, dibromophenyl trifluoromethyl ether, b.p. 76–79° (7 mm.), $n^{25}D$ 1.5068, was obtained as a by-product and was shown to be a mixture of 2,4- and 3,4-dibromo isomers in ratio 2:1, respectively, by F^{19} n.m.r. and gas chromatographic analysis employing for comparison an authentic sample of 2,4-dibromophenyl trifluoromethyl ether prepared by method D.

b. 1,4-Bis(trifluoromethoxy)benzene.—A mixture of 49.2 g. (0.20 mole) of 1,4-bis(trifluoromethoxy)benzene and 1.5 g. of iron powder was heated to reflux, and 24 g. (0.15 mole) of bromine was added over a period of approximately 15 min. The reaction mixture was stirred and refluxed overnight. An additional 16 g. (0.10 mole) of bromine was added and refluxing continued for an additional 36 hr. The reaction was cooled, and the product extracted in pentane. The pentane solution was washed, in turn, with 80 ml. of 6 *N* hydrochloric acid, 120 ml. of 10% sodium bisulfite solution, and saturated sodium chloride solution. The pentane solution was dried over magnesium sulfate, filtered, and distilled. A total of 21.5 g. (44%) of 1,4-bis(trifluoromethoxy)benzene, b.p. 49.5° (20 mm.), was recovered. A second fraction of 14.4 g. (22%), b.p. 58.5° (20 mm.), $n^{25}D$ 1.4148, was characterized as 2-bromo-1,4-bis(trifluoromethoxy)benzene. The third fraction of 13.1 g. (16%), b.p. 110° (30 mm.), $n^{25}D$ 1.4571, was characterized as 2,5-dibromo-1,4-bis(trifluoromethoxy)benzene. In a second run on double the scale, the yields were recovered starting material, 38%; monobromo product, 30%; and dibromo product, 15%. The dibromo derivative was found to have a single F^{19} n.m.r. resonance (−360 c.p.s. with internal reference to CF_2ClCF_2Cl

(16) We would like to thank Dr. D. C. England of this laboratory for suggesting these modifications.

(17) We are indebted to Dr. W. W. Prichard of this laboratory for this experiment.

(18) We are indebted to Dr. P. E. Aldrich of this laboratory for the experiment.

at 40 Mc./sec.). split into a doublet, and a single proton resonance split into a quadruplet (J_{HF} = 1.2 c.p.s.). This spectra is consistent only with the 2,5 isomer since the 2,6 isomer would show two chemically shifted F^{19} resonances, one of which should be split into a triplet. (The monobromo product shows two equal F^{19} resonances at −363 and −341 c.p.s. with reference to CF_2ClCF_2Cl at 40 Mc./sec.)

3. Reduction of Nitro Group. Aminophenyl Perfluoroalkyl Ethers.—The general procedures are illustrated by the following examples.

a.—A solution of 7.75 g. (0.030 mole) of *p*-nitrophenyl pentafluoroethyl ether in 100-ml. absolute ethanol containing 0.036 mole of hydrogen chloride was hydrogenated at approximately 3 atm. pressure in a Parr apparatus using 0.30 g. of platinum oxide as catalyst. The theoretical amount of hydrogen was absorbed in a few minutes. The catalyst was removed by filtration, and the alcohol solution evaporated under nitrogen. The residual solid was triturated with 100 ml. of ether and filtered. The pentafluoroethoxyaniline hydrochloride was obtained as white platelets in a yield of 6.0 g. (87%). The free aniline was obtained by adding the hydrochloride to an excess of stirred 10% solution of sodium carbonate layered with ether. The aniline obtained from the dried ether extract was distilled, b.p. 95° (22 mm.).

b.—*m*-Nitrophenyl trifluoromethyl ether (36.3 g., 0.175 mole) in 50 ml. of absolute alcohol with 1 g. of 5% palladium-on-charcoal catalyst was reduced in a pressure vessel at 50° and 69 atm. of hydrogen; approximately the theoretical amount of hydrogen was absorbed. The resulting reaction mixture was filtered to remove catalyst and distilled to obtain 26.8 g. (92.5%) of *m*-aminophenyl trifluoromethyl ether, b.p. 89° (20 mm.), $n^{26}D$ 1.4633.

4. Carboxyphenyl Perfluoroalkyl Ethers.—As shown in eq. 3, three different procedures were employed for the preparation of the acids. The stability of the OR_f to organometallic reagents and strong oxidizing conditions is illustrated by these methods.

a. Carbonation of Grignard Reagent.—The Grignard reagent was prepared in the normal manner by addition of 8.1 g. (0.036 mole) of *p*-bromophenyl trifluoromethyl ether in 15 ml. of ether to 1.0 g. (0.042 g.-atom) of magnesium turnings in 5 ml. of ether. The reaction was exothermic, and the bromo derivative was added at a rate sufficient to maintain reflux. After addition was complete, the reaction mixture was stirred at room temperature for 30 min. and then cooled to −5° in an ice–acetone bath. Dry carbon dioxide was passed over the stirred solution. An exothermic reaction resulted, and the temperature increased to approximately 0°. Hydrolysis was accomplished with 15 ml. of 6 *N* sulfuric acid, and the product was separated by ether extraction. The crude product was obtained as oily white crystals (yield, 9.5 g.). The *p*-trifluoromethoxybenzoic acid was recrystallized several times from hexane to constant m.p. 153.2–153.8°.

b. Permanganate Oxidation.—A mixture of 5.64 g. (0.032 mole) of *m*-trifluoromethoxytoluene with 12.0 g. (0.076 mole) of potassium permanganate dissolved in 140 ml. of water was gradually heated to reflux with stirring. The mixture was refluxed overnight until all of the permanganate color had disappeared. Unchanged starting material (2.0 g., 39%) was removed by distillation of approximately 100 ml. of water from the reaction mixture. The remaining dark aqueous mixture was treated with sulfur dioxide until all of the manganese dioxide had dissolved. A white crystalline solid was filtered from the solution and washed thoroughly with water. The crude *m*-trifluoromethoxybenzoic acid was obtained in a yield of 2.77 g. (42%) and was recrystallized from hexane to constant m.p. 91.4–92.0°.

c. Bromination, Hydrolysis, and Oxidation.—A solution of 8.80 g. (0.05 mole) of *p*-tolyl trifluoromethyl ether and 16.0 g. (0.10 mole) of bromine in 100 ml. of carbon tetrachloride was irradiated under reflux overnight with a G. E. sun lamp. At the end of this time, the bromine color had disappeared and considerable hydrogen bromide evolution had occurred. The carbon tetrachloride was evaporated at room temperature under a nitrogen stream, and 75 ml. of concentrated nitric acid was added. The mixture was stirred vigorously overnight, bromine gradually evolved, and finally the product separated from the aqueous phase as a solid. The mixture was poured into several 100 ml. of ice–water, and the solid product was separated by suction filtration and washed thoroughly with water. The yield of *p*-trifluoromethoxybenzoic acid, recrystallized from hexane, m.p. 153–154°, was 6.8 g. (66%).

5. Tetrakis(trifluoromethoxyphenyl)silane.—A solution of butyllithium in ether was prepared in the usual way from 13.7 g. (0.10 mole) of butyl bromide, 1.53 g. (0.22 g.-atom) of lithium wire, and 30 ml. of ether. To this was added dropwise a solution of 24.1 g. (0.10 mole) of *m*-trifluoromethoxybromobenzene in 20 ml. of ether keeping the reaction temperature at 0°. After the mixture had been stirred for approximately 2 hr. (the solution turned yellowish in color), a solution of 3.1 g. (0.018 mole) of silicon tetrachloride in 20 ml. of ether was added dropwise. A very exothermic reaction resulted, and the temperature was maintained at 0 to 5° with an acetone–ice bath. The solution was allowed to warm gradually to room temperature overnight and was then hydrolyzed with 25 ml. of 5% hydrochloric acid solution. The ether layer was separated, and the aqueous phase extracted with additional portions of ether. The combined ether extracts were dried over magnesium sulfate, filtered, and evaporated under nitrogen. The residue of pale yellow oil was fractionated on a 30-cm. spinning-band column. Tetrakis(*m*-trifluoromethoxyphenyl)silane, b.p. 136° (0.7 mm.), was obtained in a yield of 5.4 g. (32%). A forecut of 4.4 g. of material, b.p. 106–136° (0.7 mm.), was shown to contain saturated C–H and is believed to be a mixture containing chiefly tris(trifluoromethoxyphenyl)butylsilane. The tetrakis(*m*-trifluoromethoxyphenyl)silane is a glass at −80° and becomes fluid at approximately −30°. The open tube boiling point is 352°, and the silane is stable to reflux in a tube open to the air. Although this silane is considerably more volatile than tetraphenylsilane (b.p. 530°, m.p. 273.5°), it has a much lower melting point so that the over-all liquid range is extended significantly. No reference has been found to any other tetraarylsilane which is a liquid at room temperature.

6. 1,1,1-Trichloro-2,2-bis(trifluoromethoxyphenyl)ethane.—Sulfuric acid (50 g., 98–100%) was placed in a 100-ml. flask fitted with a thermometer, magnetic stirrer, and dropping funnel with a Drierite guard tube. A solution of 3.68 g. (0.025 mole) of anhydrous chloral and 8.1 g. (0.050 mole) of phenyl trifluoromethyl ether was added dropwise to the sulfuric acid with stirring. After addition was almost complete, an exothermic reaction occurred, and the temperature increased to 40°. The solution was stirred overnight and then poured into 25 ml. of methylene chloride. The methylene chloride layer was separated, and the sulfuric acid further extracted with methylene chloride. The combined methylene chloride extracts were washed with water and 10% sodium carbonate solution and dried over anhydrous sodium sulfate. The methylene chloride was distilled, and the residue fractionated through a 30-cm. spinning-band column to obtain 2.9 g. (26%), b.p. 134–140° (2.3 mm.), $n^{26}D$ 1.4952, of 1,1-bis(trifluoromethoxyphenyl)-2,2,2-trichloroethane. In a large-scale preparation, a lower boiling by-product was identified as 1,1,1-trifluoro-2-(trifluoromethoxyphenyl)ethane, b.p. 58° (0.06 mm.). If 96% sulfuric acid was used in the condensation, only this by-product was isolated. This by-product must result from a reduction of an intermediate by the chloral. It is suggested that this reduction can compete successfully with the normal condensation reaction because of deactivation by the trifluoromethoxy group.

7. *m*-Bis(*m*-trifluoromethoxyphenoxy)benzene.—A solution of 10.2 g. (0.057 mole) of *m*-trifluoromethoxyphenol in 30 ml. of toluene was mixed with 3.8 g. (0.068 mole) of potassium hydroxide in a Dean–Starke apparatus and heated to reflux for several hours until all the water had been removed as an azeotrope. Approximately 15 ml. of toluene was distilled, and 6.76 g. (0.827 mole) of *m*-dibromobenzene and 0.5 g. of cupric carbonate were added to the reaction mixture. The temperature was gradually raised to 200°, and the remaining toluene distilled. The reaction mixture was then heated under reflux at 220–240° overnight. After cooling, the product was extracted from the pasty dark solid with several portions of ether. The ether extracts were evaporated, and the residual oil distilled to obtain a total of 7.59 g. (61%) of *m*-bis(*m*-trifluoromethoxyphenoxy)-benzene, b.p. 138–143° (0.59 mm.), $n^{26}D$ 1.5048. This product turned to a glass at −80° and was a mobile liquid to approximately −40°. The open tube boiling point was 336°. The product obtained previously had a slight odor of phenol and was purified further by distillation from anhydrous sodium carbonate. For comparison the parent *m*-bis(phenoxy)benzene has m.p. 47–48° and b.p. 372°.

G. **Pyrolysis Experiments.**[19]—Samples of the aryl perfluoroalkyl ethers were distilled into an evacuated 10-ml. stainless steel pressure vessel connected to the inlet system of a mass spectrometer. The vessel was heated for 20-min. periods in succession at temperatures of 400, 475, 550, 625 and 700°. After each period, a sample was removed for mass spectrometric analysis, and the per cent decomposition and major decomposition products were determined. In this study, $C_6H_5OCF_3$, $C_6H_5OCF_2CF_3$, $C_6H_5OCF_2CF_2H$, and p-$(CF_3O)_2C_6H_4$ were compared with benzotrifluoride and fluorobenzene. In each case a measurable amount of decomposition (5 to 10%) was noted between 550 and 570°. At 625° the decomposition was 60–70% for the pentafluoro- and tetrafluoroethyl ethers, but only 30 to 40% for the other compounds in the series. The initial course of decomposition in all cases appeared to be formation of biphenyls. For the ethers, formation of carbon monoxide, carbon dioxide, and fluorobenzene derivatives becomes significant at higher temperatures.

H. **Spectral Properties.**—A description of the infrared and n.m.r. spectra of the aryl perfluoroalkyl ethers was presented in the discussion. The ultraviolet spectra of these ethers are in general very similar to those of corresponding toluene derivatives, as illustrated by the following examples in Table V.

TABLE V

	λ_{max} mμ (log ε)			
$C_6H_5OCF_3$[a]	267 (2.2)	264 (2.4)	255 (2.2)	249 (2.2)
$C_6H_5CH_3$[b]	268 (2.4)	262 (2.5)	255 (2.4)	248 (2.2)
p-$C_6H_4(OCF_3)_2$[a]		269 (2.5)	264 (2.6)	259 (2.5)
p-$C_6H_4(CH_3)_2$[b]	275 (2.7)	268 (2.7)	261 (2.5)	256 (2.3)

[a] The solvent was isooctane. [b] Literature value.

Acknowledgment.—The author is grateful to Dr. R. V. Lindsey, Jr., and Dr. P. E. Aldrich for helpful discussions and suggestions during the course of this work and wishes to acknowledge the special assistance of Mr. R. M. Berdt for the pyrolysis studies employing the mass spectrometer and Mrs. Adah Richmond for the gas chromatographic analysis.

(19) A qualitative study of the stability of derivatives of perfluorobenzene was described recently by L. A. Wall, R. E. Donadia, and W. J. Pummer, *J. Am. Chem. Soc.*, **82**, 4846 (1960).

α-Fluorinated Ethers. II. Alkyl Fluoroalkyl Ethers[1]

P. E. ALDRICH AND WILLIAM A. SHEPPARD

Contribution No. 861 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington 98, Delaware

Received July 1, 1963

Aliphatic alcohols are converted to the corresponding trifluoromethyl ethers by reaction with carbonyl fluoride and treatment of the resulting fluoroformate with sulfur tetrafluoride. This reaction has synthetic value only when the alcohol is substituted with a deactivating substituent in the β-position. The scope and extensions of this reaction and the physical and chemical properties of these ethers, particularly trifluoromethyl vinyl ether and substituted ethyl trifluoromethyl ethers, are described.

Perfluoroalkyl ethers have been prepared in low yield by electrolytic fluorination.[2] Other methods useful for preparation of α-fluorinated ethers are base-catalyzed additions of alcohols to fluoroolefins and fluoride exchange reactions with chlorinated ethers. However, none of these methods is generally useful for the preparation of alkyl trifluoromethyl ethers.[3]

Results and Discussion

Synthesis.—The new general method for preparation of aryl trifluoromethyl ethers described in the previous paper[1] has been extended to the aliphatic series.

$$ROH + COF_2 \longrightarrow ROCF \overset{O}{\parallel} + HF \xrightarrow{SF_4} ROCF_3$$

Alcohols were converted to the corresponding fluoroformates by reaction with carbonyl fluoride[4,5] in an autoclave at 100 to 200°. In a second step, the fluoroformates were converted to trifluoromethyl ethers by reaction with sulfur tetrafluoride[6] at 150 to 200°. In general, the intermediate fluoroformate was not isolated, and the hydrogen fluoride by-product from the first step served as a catalyst and/or solvent for the sulfur tetrafluoride reaction. In one case where the fluoroformate was isolated, anhydrous hydrogen fluoride was added with the sulfur tetrafluoride, since it had been shown with aryl fluoroformates and other carbonyl derivatives[1] that hydrogen fluoride is necessary to catalyze the conversion to the respective α-fluorinated ethers and difluoro derivatives.

This reaction is useful as a synthetic method only if the β-carbon is substituted with one or more electron-withdrawing groups, such as F, Cl, Br, OCF_3 (or $OCF \overset{O}{\parallel}$), and fluoroalkyl groups. Although methanol afforded methyl trifluoromethyl ether, other aliphatic alcohols composed of only hydrocarbon chains gave tars or carbonaceous products. With one electronegative substituent, the over-all yield of ether from alcohol was in the range of 30 to 40% but increased to 50 to 60% when three deactivating substituents were present in the β-position. These reactions are summarized in Table I, and the trifluoromethyl ethers,

(1) Paper I: W. A. Sheppard, *J. Org. Chem.*, **29**, 1 (1964).

(2) A general review describing synthesis and properties of fluoroalkyl ethers is presented in (a) A. M. Lovelace, D. A. Rausch, and W. Postelnek, "Aliphatic Fluorine Compounds," Reinhold Publishing Corp., New York, N. Y., 1958, Chap. V, p. 155; (b) M. Hudlicky, "Chemistry of Organic Fluorine Compounds," The MacMillan Co., New York, N. Y., 1962, pp. 141 and 238. (c) K. Weissermel and M. Lederer, *Ber.*, **96**, 77 (1963), describe preparation of α-fluorinated ethers by addition of *t*-butyl hypochlorite to fluoroolefins.

(3) A trichlorodimethyl ether has been treated with antimony trifluoride to give a trifluorodimethyl ether, H. S. Booth and P. E. Burchfield, *J. Am. Chem. Soc.*, **57**, 2070 (1935). No proof of structure was presented, but, on the basis of physical properties (see Discussion) and ease of hydrolysis, the structure must have been FCH_2OCF_2H and not CH_3OCF_3 as suggested in ref. 2a.

(4) Fluoroformates also may be obtained by fluoride ion exchange on chloroformates (ref. 2b, page 111).

(5) Carbonyl fluoride was prepared by a convenient new synthesis from sodium fluoride and phosgene in acetonitrile as described by F. S. Fawcett, C. W. Tullock, and D. D. Coffman, *J. Am. Chem. Soc.*, **84**, 4275 (1962).

(6) (a) C. W. Tullock, F. S. Fawcett, W. C. Smith, and D. D. Coffman, *ibid.*, **82**, 539 (1960); (b) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *ibid.*, **82**, 543 (1960).

TABLE I

PREPARATION OF ALKYL TRIFLUOROMETHYL ETHERS BY TWO-STEP METHOD FROM ALCOHOLS[a]

$$ROH + COF_2 \longrightarrow HF + R\overset{\overset{O}{\|}}{O}CF \xrightarrow{SF_4} ROCF_3$$

Alcohol	COF_2 G.	COF_2 (Moles)	SF_4 G.	SF_4 (Moles)	Product	Yield G.	Yield %
$ClCH_2CH_2OH$	61.2	(0.76)	75	(1.14)	$ClCH_2CH_2OCF_3$	28–48	24–42
$BrCH_2CH_2OH$	50	(0.40)	40	(0.61)[b]	$BrCH_2CH_2OCF_3$	30	15
CH_3OH	15.8	(0.50)	50	(0.76)[b]	CH_3OCF_3[c]	17	29
CCl_3CH_2OH	200	(1.34)	125	(2.00)	$CCl_3CH_2OCF_3$	208	72
$CClF_2CH_2OH$	140	(1.20)	84	(1.28)	$CClF_2CH_2OCF_3$	84.5	38
$HCF_2CF_2CH_2OH$[f]	132	(1.00)	90	(1.35)	$HCF_2CF_2CH_2OCF_3$	127.1	63.5
$H(CF_2CF_2)_2CH_2CH$	34.8	(0.15)	15	(0.27)	$H(CF_2CF_2)_2CH_2OCF_3$	15.7	35
					$H(CF_2CF_2)_2CH_2O\overset{\overset{O}{\|}}{C}F$	14.3	29
$H(CF_2CF_2)_3CH_2OH$[d]	166	(0.50)	45	(0.68)	$H(CF_2CF_2)_3CH_2OCF_3$	102.1	51
					$H(CF_2CF_2)_3CH_2O\overset{\overset{O}{\|}}{C}F$	70.8	37

[a] Reactions were run in "Hastelloy"-lined pressure vessel of 140-, 240-, 500-, or 1000-ml. capacity at autogenous pressure. Normal heating pattern was 1–2 hr. at 100° followed by 1–4 hr. at 140–150° for the reaction with COF_2, and 2 hr. successively at 100°, 150° and 175° for the reaction with SF_4. [b] Heated only at 100° for 2 hr. [c] Gas chromatographic analysis indicated that the product was 85% pure. [d] Additional 2 hr. at 200° added to heating schedule for the SF_4 reaction.

TABLE II

PREPARATION OF α-FLUORINATED ETHERS BY REACTION OF CARBONATES OR ESTERS WITH SULFUR TETRAFLUORIDE[a]

$$R\overset{\overset{O}{\|}}{O}CR_f + SF_4 \xrightarrow{HF} ROCF_2R_f \ (R_f = F, CF_3, \text{or } OR)$$

Reactants (carbonate or ester)	G.	(Moles)	SF_4 G.	SF_4 (Moles)	HF, g.	Product	Yield G.	Yield %
$FCO\overset{\overset{O}{\|}}{C}H_2CH_2O\overset{\overset{O}{\|}}{C}F$	183	(1.19)	270	(2.50)	10	$CF_3OCH_2CH_2OCF_3$	128	54
						$CF_3OCH_2CH_2O\overset{\overset{O}{\|}}{C}F$	6.5	3
$CF_3OCH_2CH_2O\overset{\overset{O}{\|}}{C}F$[b]	224	(1.27)	160	(1.48)	25	$CF_3OCH_2CH_2OCF_3$	132.5	53
						$CF_3OCH_2CH_2F$	31[c]	
$(CF_3\overset{\overset{O}{\|}}{C}O)_2CH_2$	18.8	(0.078)	19.0	(0.18)	3	$CF_3CF_2OCH_2F$	[d]	
						$CF_3C\overset{\overset{O}{\|}}{F}$		
$(CF_3CH_2O)_2C{=}O$[e]	16.7	(0.074)	10	(0.093)	5	$(CF_3CH_2O)_2CF_2$	3.4	18
						Recovered starting material	3.5	21
$(HCF_2CF_2CH_2O)_2C{=}O$[e]	29.0	(0.10)	15	(0.14)	5	$(HCF_2CF_2CH_2O)_2CF_2$	7.2	23
						Recovered starting material	8.6	30
$[H(CF_2CF_2)_2CH_2O]_2C{=}O$[e]	49.0	(0.10)	20	(0.18)	4	$[H(CF_2CF_2)_2CH_2O]_2CF_2$	17.5	34
						Recovered starting material	20.7	42

[a] Reactions were run in "Hastelloy"-lined pressure vessel of 140-, 240-, or 1000-ml. capacity at autogenous pressure. Normal heating pattern was 2 hr. successively at temperatures of 100, 150, and 175°. [b] Obtained in large quantities from reaction of COF_2 with ethylene oxide in presence of pyridine (see paper IV in this series by F. S. Fawcett). [c] Forecut, b.p. 50–68°, also contained CF_3OCH_2-CH_2OCF_3. [d] Yield, 5 ml.; from low-temperature distillation; yield approximates 60%. [e] Heated at 150° for 2 hr., 200° for 2 hr., 225° for 2 hr., 250° for 4 hr.

with physical properties and analytical data, are listed in Table III.

In the preparation of 1,2-bis(trifluoromethoxy)-ethane, it was necessary to prepare and isolate the bisfluoroformate of ethylene glycol by a low-temperature reaction of glycol with excess carbonyl fluoride in the presence of sodium fluoride as base. From the reaction of this fluoroformate with sulfur tetrafluoride in the presence of hydrogen fluoride (see Table II), two by-products were isolated in addition to the normal product. One was β-trifluoromethoxyethyl fluoroformate, a product of incomplete reaction; the other was β-fluoroethyl trifluoromethyl ether[7] which can form by fluoride ion displacement of the fluoroformate group or by intramolecular decomposition of the fluoroformate.[4]

Extension of the reaction to preparation of alkyl

(7) This product has been reported from reaction of CF_3OF with ethylene, J. A. C. Allison and J. H. Cady, *J. Am. Chem. Soc.*, **81**, 1089 (1959).

TABLE III

ALKYL FLUOROALKYL ETHERS AND ESTERS[a]

Compound	B.p. (mm.), °C.	$n^{25}D$	F^{19} n.m.r.[b] chemical shifts in c.p.s. (relative intensity), 40 Mc./sec.	Analyses: Carbon[c] Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Fluorine Calcd.	Fluorine Found	Other Calcd.	Other Found
CH_3OCF_3	−25 to −19[d]		[e]							(Mass spectrometry)	
$ClCH_2CH_2OCF_3$	62–65	1.3292	[e]	24.3	24.5	2.71	2.72	38.3	38.6	Cl, 23.9	23.8
$BrCH_2CH_2OCF_3$	77–81	1.3605	[e]					29.5	29.3	Br, 41.4	41.5
$CCl_3CH_2OCF_3$	98.5	1.3769	−233	16.6	16.9	0.93	1.12	26.2	25.8	Cl, 48.9	48.9
$CClF_2CH_2OCF_3$	34–35		[e]	19.5	19.4	1.1	1.3				
$CH_2{=}CHOCF_3$	−18 to −15		[e]					50.9	50.9		
$CCl_2{=}CHOCF_3$	63.5	1.3572	−191[f]	19.9	20.2	0.56	0.75	31.5	31.2	Cl, 39.2	39.0
$CF_3OCH_2CH_2OCF_3$	71	<1.30	−208[g]	24.3	24.8	2.04	2.35	57.6	57.6		
$CF_3OCH_2CH_2O\overset{O}{\overset{\|}{C}}F$	117		−288 (3) −1933 (1)	27.3	28.0	2.29	2.63	43.2	43.1		
$CF_3OCHClCHClOCF_3$ (2)[h]			−505 (1)								
$CF_3OCH_2CCl_2OCF_3$ (1)	91.0	1.3209	−266 (2) −257 (2) −233 (1)	18.0	18.2	0.76	0.92	42.7	42.2	Cl, 26.6	26.4
$CF_3OCCl_2CClHOCF_3$	110	1.3455	−475 (1) −223 (1)	15.9	16.3	0.34	0.84	37.8	38.2	Cl, 35.3	35.7
$CF_3OCCl_2CCl_2OCF_3$	128	1.3690	−257	14.3	14.7			34.0	33.7	Cl, 42.2	42.6
$CF_3OCH{=}CClOCF_3$[i]	54	1.299	−231 (1)[h] −177 (1) −139 (1) −128 (1)	20.9	21.1	0.44	0.88	49.5	49.3	Cl, 15.4	16.0
$CF_3OCCl{=}CClOCF_3$[i]	73	1.3270	−336 (1) −327 (1)	18.1	18.5			43.0	43.6	Cl, 26.8	26.5
$CF_3OCClBrCBrHOCF_3$	94–95	1.3920	[e]	12.3	12.8	0.26	0.67	29.2	29.1	Cl, 9.1 Br, 40.9	9.5 41.0
$HCF_2CF_2CH_2OCF_3$	45.5	<1.30	−531[k]	24.0	25.0	1.51	2.00	66.5	66.3		
$H(CF_2CF_2)_2CH_2OCF_3$	99	<1.30	−569[k]	24.0	24.4	1.01	1.20	69.7	70.7		
$H(CF_2CF_2)_3CH_2OCF_3$	140–141	<1.30	−534[k]	24.0	24.7	0.76	0.96	71.2	72.7		
$CF_2CF_2OCH_2F$	16		[e]					67.8	68.3		
$(CF_3CH_2O)_2CF_2$	89.5	<1.30	406[l] (3) 0 (1)	24.2	24.6	1.63	2.24				
$(HCF_2CF_2CH_2O)_2CF_2$	83–86 (50)	1.3129	[e]	26.9	27.3	1.94	2.25	60.9	59.8		
$[H(CF_2CF_2)_2CH_2O]_2CF_2$	68 (1.7)	1.3123	−50[m]	25.8	26.2	1.16	1.54	66.8	66.7 66.6		
$H(CF_2CF_2)_2CH_2O\overset{O}{\overset{\|}{C}}F$	127	<1.30	−2255[n]	25.9	26.2	1.09	1.23				
$(CF_3CO)_2CH_2$	108	1.3091	[e]					47.5	47.3		

[a] Compounds reported in this table also were characterized generally by infrared and proton n.m.r. spectra. [b] Neat, relative to external $ClCF_2CF_2Cl$ at 0 c.p.s., no solvent; n.m.r. spectrometer was operated at approximately 9988 gauss. Negative frequency displacement indicates resonance occurring at lower field relative to the reference. [c] Carbon analyses of highly fluorinated compounds have frequently been found 0.4 to 0.7% high, although not reproducibly so. Purified by preparative gas chromatography for n.m.r. and mass spectrometric analysis. [d] Calibrated spectrum not obtained. [f] Proton n.m.r. single resonance at −6.55 p.p.m. relative to tetramethylsilane. [g] Proton n.m.r. single resonance at −4.16 p.p.m. relative to tetramethylsilane. [h] Approximate relative amounts estimated from F^{19} n.m.r. resonances. [i] Approximately 1:1 *cis–trans* mixture. Approximately equal proton resonances occur at −6.08 and −6.58 p.p.m. relative to tetramethylsilane. [j] Approximately 1:1 *cis–trans* mixture. [k] Resonances for OCF_2 group only. Other resonances (F^{19} and H^1 with proper relative intensities) observed at approximately same frequencies as in parent alcohols. [l] F^{19} resonance at 406 c.p.s. assigned to CF_3 group appeared as triplet (J = 9–10 c.p.s.) with additional fine structure. Resonance at 0 c.p.s. assigned to CF_2 group showed incompletely resolved fine structure. Proton n.m.r. quadruplet centered at −4.20 p.p.m. relative to tetramethylsilane with J = 9 c.p.s. [m] Assigned to CF_2; the remainder of the F^{19} spectra and the proton spectra approximately the same as parent alcohol. [n] Assigned to $\overset{O}{\overset{\|}{C}}F$.

perfluoroalkyl ethers was not investigated to any extent but is expected to proceed in a fashion analogous to that found for the aromatic ethers.[1] Partial success was attained in the one case studied. From the reaction of bis(trifluoroacetoxy)methane (1) with sulfur tetrafluoride in hydrogen fluoride only fluoromethylpentafluoroethyl ether (2) was isolated. Replacement of an acetoxy group by fluoride ion could occur either before or after one acetoxy group had reacted with sulfur tetrafluoride.

$$\underset{1}{(CF_3\overset{O}{\overset{\|}{C}}O)_2CH_2} + SF_4 \xrightarrow{HF} \underset{2}{CF_3CF_2OCH_2F}$$

This reaction was extended to the preparation of 1,1-difluoroformals (**3**), a new class of α-fluorinated ethers. The carbonate of a fluoroalkylmethyl alcohol (**4**) was treated with sulfur tetrafluoride in the presence

$$\underset{4}{(R_fCH_2O)_2C{=}O} + SF_4 \xrightarrow{HF} \underset{3}{(R_fCH_2O)_2CF_2}$$

of anhydrous hydrogen fluoride. In this case a higher temperature (about 225°, compared to a temperature of 175° normally used in the fluoroformate reaction) was required to obtain the difluoroformal in yields ranging from 20 to 30% (30% of the starting carbonate was recovered).

Chemical and Physical Properties.—The trifluoromethyl ethers are mobile, colorless liquids (with the exception of CH_3OCF_3 which has b.p. −25°), which are thermally and chemically stable.

β-Haloethyl trifluoromethyl ethers (**5**) were readily converted to vinyl ethers (**6**) by treatment with base.

$$\underset{5}{XCY_2CH_2OCF_3} \xrightarrow[\text{base}]{} \underset{6}{CY_2{=}CHOCF_3}$$

X = Cl or Br
Y = H, Cl

However, in the case of $ClCH_2CH_2OCF_3$, elimination of the OCF_3 group occurred to a significant extent so that the product was a mixture of vinyl ether **6** (Y = H) and $ClCH{=}CH_2$ in a ratio of three to one as determined by gas chromatography. No conclusion can be drawn from this experiment as to ease of elimination of $^{\ominus}OCF_3$ compared with $Cl^{\ominus}$ since the rate-controlling factor may be the acidity of the protons α to the trifluoromethoxy group in compound **5** (X = Cl, Y = H). The trifluoromethyl vinyl ether (**6**, Y = H) could be polymerized under the influence of radical initiators, but the dichloro analog (**6**, Y = Cl) was inert.

1,2-Bis(trifluoromethoxy)ethane was not attacked by bromine radicals but could be chlorinated photochemically to give a mixture of all possible isomers. By adjustment of time and temperature, the amount of chlorination could be controlled to make one isomer

$$CF_3OCH_2CH_2OCF_3 \xrightarrow[h\gamma]{Cl_2}$$

$$\underset{7}{CF_3OCHClCH_2OCF_3} + \underset{8}{CF_3OCH_2CCl_2OCF_3}$$

$$+ \underset{9}{CF_3OCHClCHClOCF_3} + \underset{10}{CF_3OCCl_2CHClOCF_3} +$$

$$\underset{11}{CF_3OCCl_2CCl_2OCF_3}$$

predominant. The trichloro and tetrachloro compounds (**10** and **11**) were readily separated in pure form by distillation. The dichloro substitution product distilled as a mixture with **9** predominant over **8** (ratio approximately two to one). Monochloro compound **7** codistilled with the starting material and could only be isolated in pure form by gas chromatography. Zinc dehalogenation of the tetrachloro derivative (**11**) gave the ethylene $CF_3OCCl{=}CClOCF_3$ (*cis–trans* mixture) and of the trichloro derivative (**10**) gave the ethylene $CF_3OCCl{=}CHOCF_3$. These ethylenes were stable to further treatment with dehalogenating reagents or to dehydrohalogenation with bases, but the monochloroethylene added bromine to give the ethane $CF_3OCBrClCHBrOCF_3$.

The trifluoromethyl ethers have boiling points 30 to 40° below those of the aliphatic analogs as would be expected from complete replacement of hydrogens on the methyl group by fluorines. These compounds are sweet smelling liquids. Toxicity studies conducted on a selection of these ethers indicate that they are toxic at 0.1 to 11% concentration in vapor inhalation.[8] For example, it was found that 2,2,3,3-tetrafluoropropyl trifluoromethyl ether at a vapor concentration of 0.5% caused violent convulsions and death of mice within 30 to 120 sec.

The infrared spectra of these ethers showed a typical strong C–O absorption in the 7.8 to 8-μ region and very strong C–F absorption in 8–9-μ region. The remainder of the spectra contain absorptions normal for the substituents and for the aliphatic system. F^{19} and H^1 n.m.r. spectra were obtained on the majority of compounds and conformed with predicted spectra. For the aryl trifluoromethyl ethers a single resonance was found for the OCF_3 group in the region of −700 to −800 c.p.s. at 40 Mc./sec. relative to CF_2ClCF_2Cl. For the aliphatic series, the resonance frequency was in the range of −130 to −500 c.p.s. under the aforementioned conditions. The lower frequency in aromatic systems is expected since ring currents generally cause a shift to lower fields. In the aliphatic series, the substituent is much closer to the OCF_3 group and has a more profound influence on the field with resultant greater frequency shifts.

Experimental

Materials.—The alcohols were purchased from chemical supply houses with the exception of the telomer alcohols $H(CF_2CF_2)_nCH_2OH$, which were obtained from Organic Chemicals Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware. Carbonyl fluoride was prepared by the recently reported synthesis from phosgene and sodium fluoride in acetonitrile.[5] Sulfur tetrafluoride was obtained from Organic Chemicals Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware. Anhydrous hydrogen fluoride was purchased from Harshaw Chemical Company. Bis(2,2,3,3-tetrafluoro-*n*-propyl)- and bis(octafluoro-*n*-amyl)-carbonates were supplied by Dr. W. B. McCormack of Jackson Laboratory, Organic Chemicals Department, E. I. du Pont de Nemours and Company.

Preparation of Alkyl Trifluoromethyl Ethers. General Two-Step Procedure from Alcohols.—The procedure described previously[1] for the conversion of phenols to aryl trifluoromethyl ethers was followed for the reaction of the aliphatic alcohols in two steps with carbonyl fluoride, then sulfur tetrafluoride. In general, a maximum temperature of 175° was employed for the sulfur tetrafluoride reaction since higher temperatures usually caused extensive formation of tar. However, the highly fluorinated alcohols were not prone to side reactions and were heated in the sulfur tetrafluoride reaction at 200° for several hours in order to improve the yield of ether.

The product was cautiously poured into a well-stirred slurry of a threefold molar excess of sodium fluoride powder or pellets in dichloromethane or xylene to remove hydrogen fluoride. (Dichloromethane was frequently used for the less volatile ethers.) The product was distilled through a spinning-band or packed column. Trifluoromethyl methyl ether is a gas at room temperature and was purified by passage through a tower of sodium fluoride pellets followed by distillation through a low-tempera-

(8) The authors are indebted to the Haskell Laboratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours and Co., for toxicological studies.

ture column. The experimental details are given in Table I, and the physical properties and analytical data of the ethers are given in Table III.

Ethylene Glycol Bisfluoroformate.—A mixture of 50 g. (1.2 moles) of sodium fluoride powder in 300 ml. of ether was cooled to −80° in a 1-l. four-necked flask fitted with a "Tru-bore" paddle stirrer addition funnel, gas inlet tube, and a methanol-slush condenser. Carbonyl fluoride (100 g., 1.5 moles) was condensed into the ether solution, and 31.0 g. (0.50 mole) of anhydrous ethylene glycol (purified by distillation) was added dropwise. The reaction was exothermic; after the addition was complete, the reaction mixture was allowed to warm gradually to room temperature while the excess of carbonyl fluoride was retained under reflux for 1 hr. The solid was separated by suction filtration and washed with ether. The ether solution was evaporated to give 58 g. of oil. Distillation afforded 56.0 g. (79%) of the bisfluoroformate, b.p. 36° (1.7 mm.). The fluoroformate decomposes at approximately 100–120°, and precautions were taken to avoid overheating the pot during distillation.

Methylene Bis(trifluoroacetate). A.—A 500-ml. flask with reflux condenser and drying tube was charged with 150 ml. of dimethylformamide (distilled from phosphorus pentoxide). Dry silver trifluoroacetate (81.7 g., 0.37 mole) was dissolved in the dimethylformamide, and methylene diiodide (49.3 g., 0.184 mole) was added. In a few minutes the mixture became warm, and a yellow precipitate formed. The temperature was maintained at 60–70° for 1 hr., the silver iodide was filtered off, and the filtrate was distilled to give 28 g. (58%) of methylene bis(trifluoroacetate), b.p. 108°. The infrared spectrum of the compound had ester carbonyl absorption at 5.60 μ.

B.—A 500-ml. flask with reflux condenser and drying tube was charged with 30 g. (1.00 mole, calculated as a monomer CH_2O) of paraformaldehyde (dried over phosphorus pentoxide), 200 ml. (298 g., 1.42 moles) of trifluoroacetic anhydride, and 50 ml. of trifluoroacetic acid. The mixture was refluxed until solution was complete and then was distilled to give 61.4 g. (26%) of methylene bis(trifluoroacetate), b.p. 108–110°, which was identical to that obtained *via* procedure A as shown by infrared spectra comparison.

In addition, higher boiling fractions, b.p. 75–76° (28 mm.) and 95–97° (28 mm.), were obtained. Since the infrared spectra of these fractions are similar to that of methylene bistrifluoroacetate, the structures $CF_3CO_2CH_2OCH_2O_2CCF_3$ and $CF_3CO_2CH_2OCH_2OCH_2O_2CCF_3$, respectively, are suggested.

Bis(2,2,2-trifluoroethyl)carbonate.—Trifluoroethanol (50 g., 0.50 mole) was added to a solution of 50 g. (0.50 mole) of phosgene in 39.5 g. (0.50 mole) of pyridine and 250 ml. of ether chilled in an ice bath. The pyridine hydrochloride was removed by suction filtration, and the ether solution was distilled. The bis(2,2,2-trifluoroethyl)carbonate, b.p. 62.5° (75 mm.), was obtained in a yield of 16%.

Reaction of Fluoroformates, Carbonates, and Esters with Sulfur Tetrafluoride.—The fluoroformates of ethylene glycol, the carbonate esters of the fluorinated alcohols, and methylene bistrifluoroacetate were treated with sulfur tetrafluoride in the presence of hydrogen fluoride as catalyst as described previously. In this case, the carbonyl reactant was charged into the pressure vessel with anhydrous hydrogen fluoride and sulfur tetrafluoride. The experimental details of the reactions are summarized in Table II, and the physical properties and analytical data of the products are given in Table III. For the conversion of carbonates to difluoroformates, heating the reactants for several hours at 225–250° (instead of 175°) was required.

Trifluoromethyl Vinyl Ether.—A three-necked flask was equipped with a dropping funnel, magnetic stirrer, and reflux condenser. The top of the condenser was connected to a trap cooled by solid carbon dioxide and acetone.

Into a refluxing solution of 56 g. (1 mole) of potassium hydroxide in 210 ml. of ethanol was dropped 41.3 g. (0.214 mole) of 2-bromoethyl trifluoromethyl ether or 36.6 g. (0.246 mole) of 2-chloroethyl trifluoromethyl ether. Refluxing was continued until no additional condensate gathered in the trap.

A.—The condensate from the addition of 2-bromoethyl trifluoromethyl ether was distilled in a low-temperature still to give 15 g. (63%) of vinyl trifluoromethyl ether, b.p. −18° to −15°. Gas chromatographic analysis indicated that the sample was 90% pure. The infrared spectrum of vinyl trifluoromethyl ether showed a strong absorption band at 6.00 μ (vinyl double bond) and very strong bands at 7.75, 8.05, and 8.40 μ (associated with the OCF_3 group).

B.—The condensate from the addition of 2-chloroethyl trifluoromethyl ether was distilled to give 18.8 g. of product, b.p. −18° to −14°. Gas chromatographic analysis of the product showed two peaks in the ratio 76:24. The retention time of the smaller peak was the same as that of vinyl chloride (b.p. −12°) while the retention time of the larger peak was the same as that of trifluoromethyl vinyl ether. The identities of these products were confirmed by separation of the components by preparative gas chromatography and examination of their infrared spectra.

2,2-Dichlorovinyl Trifluoromethyl Ether.—A solution of 3.8 g. (0.0175 mole) of 2,2,2-trichloroethyl trifluoromethyl ether and 2.0 g. (0.036 mole) of potassium hydroxide in 20 ml. of ethylene glycol was gradually heated at 100–120°, and the product was allowed to distil as formed. Redistillation of the product gave 2.25 g. (71%) of 2,2-dichlorovinyl trifluoromethyl ether, b.p. 63.5°.

Chlorination of 1,2-Bis(trifluoromethoxy)ethane.—1,2-Bis(trifluoromethoxy)ethane (30 to 50 g.) was placed in a quartz tube fitted with a gas inlet tube and a condenser charged with wet ice–acetone mixture. A slow stream of dry chlorine gas was bubbled through the ethane, which was irradiated with a low-pressure mercury lamp. After approximately 2 hr., evolution of hydrogen chloride ceased, and distillation of the product afforded a 72% yield of tetrachloro-1,2-bis(trifluoromethoxy)ethane (11), b.p. 128°. By chlorinating over a shorter period or by bubbling a stoichiometric amount (1, 2, or 3 moles) of chlorine condensed in a calibrated trap through the irradiated ethane, one could control the reaction to give a mixture of isomers (7 to 11), with the predominant isomer corresponding to the molar quantity of chlorine added. The monochloro derivative was never obtained in a pure state since it always codistilled with recovered starting material, but separation on a preparative scale could be accomplished by gas chromatography. The dichloro-product was determined to be a mixture of the two possible isomers by F^{19} n.m.r. analysis. The isomer found in lesser amount appeared to be unsymmetrical by virtue of two resonances of equal intensity, one occurring at low field and the other at much higher field. The predominant isomer of symmetrical form also showed two resonances very close together and at an intermediate frequency shift. The two resonances are thought to arise from restricted rotation.[9]

1,2-Bis(trifluoromethoxy)ethylenes. A. Dichloro Derivative.—A mixture of 10 g. of zinc and 60 ml. of acetic anhydride was heated to reflux (140°) for approximately 10 min. in a flask fitted with magnetic stirrer, thermometer, and a Vigreux column. The reaction mixture was cooled to 100–120° and 28.7 g. (0.086 mole) of tetrachlorobis(trifluoromethoxy)ethane (11) was added dropwise. The product, boiling range 72–85°, distilled as formed. The crude product (25.5 g.) was fractionated through a 45-cm. spinning-band column, and 14.7 g. (65%) of 1,2-dichloro-1,2-bis(trifluoromethoxy)ethylene was obtained as a colorless liquid, b.p. 72.0–73.5°. From the appearance of two F^{19} n.m.r. resonances, the product was characterized as approximately an equal mixture of *cis* and *trans* isomers. Although partial separation of the two isomers could be accomplished by analytical gas chromatography, separation was not successful on a preparative scale.

B. Monochloro Derivative.—Twenty-five grams (0.083 mole) of trichloro-1,2-bis(trifluoromethoxy)ethane (10) was dechlorinated with 10 ml. of zinc and 50 ml. of acetic anhydride as previously described. The product, chloro-1,2-bis(trifluoromethoxy)ethylene, was purified by fractionation through a 45-cm. spinning-band column, b.p. 54°, 19.1-g. (59%) yield; 4.8 g. (19%) of starting trichloro derivative (10) was recovered. From F^{19} and H^1 n.m.r. analysis, this material also was shown to be approximately an equal mixture of *cis* and *trans* isomers.

C. Chloro-1,2-dibromo-1,2-bis(trifluoromethoxy)ethylene.—A solution of 3.20 g. (0.020 mole) of bromine in 5.2 g. (0.023 mole) of crude chloro-1,2-bis(trifluoromethoxy)ethylene was allowed to stand in a stoppered flask. After 2 hr., all of the bromine color disappeared, and the colorless liquid was distilled to give 3.58 g. (41%) of bromo-1,2-dichloro-1,2-bis(trifluoromethoxy)ethane, b.p. 94–95° (200 mm.).

Acknowledgment.—The authors are grateful to R. V. Lindsey, Jr., for helpful discussions and suggestions during the course of this work.

(9) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 377.

Macrocyclic Diterpene Hydroxy Ethers from Tobacco and Cigarette Smoke

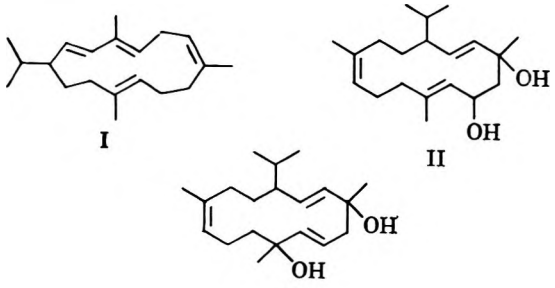
R. L. ROWLAND, ALAN RODGMAN, J. N. SCHUMACHER, DONALD L. ROBERTS, LAWRENCE C. COOK, AND W. E. WALKER, JR.

Research Department, R. J. Reynolds Tobacco Company, Winston-Salem, North Carolina

Received June 5, 1963

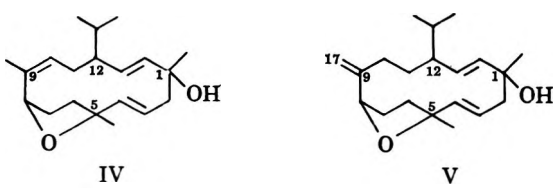
Diterpene ethers, isolated from tobacco and cigarette smoke, have been characterized as 12-isopropyl-1,5,9-trimethyl-5,8-oxido-3,9,13-cyclotetradecatrien-1-ol (α-IV) and two diastereoisomers of 12-isopropyl-1,5-dimethyl-9-methylen-5,8-oxido-3,13-cyclotetradecadien-1-ol (α- and β-V) by correlation with the previously characterized α-4,8,13-duvatriene-1,3-diol (α-II).

Within the past year, five naturally occurring diterpenes have been characterized as monocyclic compounds containing a C-14 ring. Cembrene (I), an unsaturated hydrocarbon isolated from *Pinus albicaulis*, was shown to be 14-isopropyl-3,7,11-trimethyl-1,3,6,10-cyclotetradecatetraene.[1] We reported earlier the isolation of four macrocyclic diterpene diols from tobacco leaf. Diterpenes designated α-4,8,13-duvatriene-1,3-diol (α-II) and β-4,8,13-duvatriene-1,3-diol (β-II) were characterized as diastereoisomers of 12-isopropyl-1,5,9-trimethyl-4,8,13-cyclotetradecatriene-1,3-diol (II).[2,3] The allylic isomers of II, designated α-3,8,13-duvatriene-1,5-diol (α-III) and β-3,8,13-duvatriene-1,5-diol (β-III), were shown to be diastereoisomers of 12-isopropyl-1,5,9-trimethyl-3,8,13-cyclotetradecatriene-1,5-diol (III).[3,4]



I II III

From tobacco and from tobacco smoke, we have isolated three additional diterpenes. At this time we wish to describe the characterization of these isomers, assigned the names α-5,8-oxido-3,9,13-duvatrien-1-ol (α-IV) and α- and β-5,8-oxido-3,9(17),13-duvatrien-1-ol (α- and β-V), as 12-isopropyl-1,5,9-trimethyl-5,8-oxido-3,9,13-cyclotetradecatrien-1-ol (IV) and 12-isopropyl-1,5-dimethyl-9-methylen-5,8-oxido-3,13-cyclotetradecadien-1-ol (V), respectively.



IV V

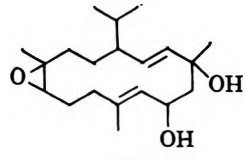
Isolation of the diterpene hydroxy ethers was accomplished by extraction of tobacco with organic solvents (methanol or hexane) followed by chromatographic separations of the extract. α-IV and α-V have been isolated from aged flue-cured, burley, and Turkish tobaccos while β-V was isolated from aged burley and Turkish tobaccos.

Elemental analysis of α-IV, m.p. 95–96°, $[\alpha]^{27}D$ +86°, indicates the formula $(C_{10}H_{16}O)_n$. The mass spectrum shows a parent mass of 304, which agrees with the formula $C_{20}H_{32}O_2$. Active hydrogen determinations show that only one of the oxygen atoms is present in a hydroxyl group.

The spectral properties of α-IV exhibited similarities to the macrocyclic diterpenes II and III. The infrared spectrum of α-IV includes a hydroxyl band at 2.9 and a strong band at 10.3 μ, characteristic of *trans* disubstituted double bonds. The n.m.r. spectrum[5] shows an isopropyl group (6 protons, 9.15), two CH_3-COR groups (6 protons, 8.70), one $CH_3C{=}C$ group (3 protons, 8.50), one —C*H*OR (1 proton, 5.5), and five olefinic protons (4.3–4.65 τ). Absence of selective ultraviolet absorption above 220 mμ establishes the absence of conjugated double bonds.

Catalytic hydrogenation of α-IV yielded the saturated compound, $C_{20}H_{38}O_2$, indicating that α-IV contains three double bonds and two rings. Like α-IV, the hydrogenation product contains only one active hydrogen atom and shows no carbonyl absorption in its infrared spectrum. Hexahydro α-IV was not oxidized by chromic oxide in pyridine. Accordingly, α-IV must contain one tertiary hydroxyl and one ether group.

The expectation that one of the rings is a cyclic ether was verified by synthesis of α-IV from α-II. Synthesis of α-IV was accomplished in 50% yield *via* reaction of α-4,8,13-duvatriene-1,3-diol (α-II)[2] with perbenzoic acid and subsequent conversion of the intermediate epoxide to α-IV by a variety of acidic dehydration conditions.



VI

(1) W. G. Dauben, W. F. Thiessen, and P. R. Resnick, *J. Am. Chem. Soc.*, **84**, 2015 (1962).

(2) D. L. Roberts and R. L. Rowland, *J. Org. Chem.*, **27**, 3989 (1962).

(3) Nomenclature used in the series of compounds isolated from tobacco is based upon the name duvane for the structure 12-isopropyl 1,5,9-trimethylcyclotetradecane. The α- and β-designations have no absolute stereochemical significance. The diol isolated from tobacco in largest quantity was assigned the α-designation (α-II). Compounds subsequently shown to have the same configuration at the 1-position have likewise been assigned the α-designation.

(4) R. L. Rowland and D. L. Roberts, *J. Org. Chem.*, **28**, 1165 (1963).

(5) N.m.r. values are reported in τ units: G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

The initial product from reaction of α-II with perbenzoic acid showed elemental analyses and a mass spectrum for $C_{20}H_{34}O_3$, which agrees with an epoxide of α-II. Reaction of α-II with one equivalent of perbenzoic acid could result in formation of three epoxides, with epoxidation occurring at the double bonds in the 4-, 8-, or 13-positions.

Selection of VI for the structure of α-II epoxide was accomplished from the n.m.r. spectrum. The n.m.r. spectrum of α-II epoxide shows peaks at 9.15 (6 protons, isopropyl multiplet), 8.80 (3 protons, CH_3 O / \ C—C), 8.62 (3 protons, CH_3COR), 8.20 (3 protons, O / \ CH_3C=C), 7.06 (1 proton, CH—C), 5.50 (1 proton, —CHOH), and 4.47–4.60 τ (3 olefinic protons). The epoxide which would result from epoxidation of the double bond in the 13-position of α-II was readily eliminated from consideration since it would contain two olefinic protons and two methyl groups attached to olefinic carbon.

Choice between structure VI, in which epoxidation had occurred at the double bond in the 8-position, and the compound which would have resulted from epoxidation of the double bond in the 4-position was made from consideration of the n.m.r. absorption of the methyl group attached to olefinic carbon. In the n.m.r. spectra of α-II and derivatives of α-II,[2] the 5-methyl group shows a split peak at 8.36 and the 9-methyl group shows a broad peak at 8.50 τ. The epoxide of α-II exhibits a split peak at 8.20 τ indicating that the 5-methyl group is attached to ethylenic carbon. Consequently, structure VI was assigned to the epoxide of α-II.[6]

Conversion of epoxide α-VI to α-IV was observed with acid, under conditions favorable for dehydration. Moderate yields of α-IV were obtained in reactions with anhydrous magnesium sulfate in refluxing toluene and with iodine in refluxing benzene. Convenient conversion of α-VI to α-IV was accomplished by room temperature contact of α-VI in chloroform solution with dilute aqueous sulfuric acid.

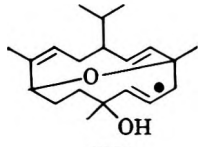
The conversion of epoxide α-VI ($C_{20}H_{34}O_3$) to α-IV ($C_{20}H_{32}O_2$) involves the elimination of water. This reaction cannot, however, be a simple dehydration. Dehydration of α-VI would be expected to yield an epoxide containing conjugated double bonds. The n.m.r. and ultraviolet spectra of α-IV show the absence of conjugated double bonds. The presence of an epoxide ring in α-IV is prohibited by the observations: (1) the ether ring of α-IV remains intact during catalytic hydrogenation; (2) α-IV was recovered from attempted reduction with lithium aluminum hydride; and (3) the n.m.r. spectrum of α-IV shows no absorption at 6.8–7.2 τ, the range expected for epoxide protons (—CH—C, with O). Accordingly, the epoxide ring of α-VI must be changed during the dehydration reaction to an ether ring containing more than two carbon atoms.

Assignment of structure to α-IV has been approached by consideration of all mechanisms by which α-VI could be converted to a compound possessing the chemical and physical properties of α-IV. These properties of α-IV, as reported earlier, require the following structural features: three double bonds, none of which is conjugated; five olefinic protons; one methyl group attached to olefinic carbon; one tertiary alcohol grouping, CH_3COH; and a cyclic ether containing the partial structure, CH_3COCH. Also utilized in the consideration of possible structures for α-IV was the absence of a methylene group located between two double bonds, $C{=}CCH_2C{=}C$. N.m.r. absorption at 7.1 τ has been reported[7] for a methylene group between two olefinic double bonds; α-IV shows no absorption between 5.7 and 7.5 τ.

Transformation of epoxide α-VI to the cyclic ether α-IV could occur only by reaction of the allylic alcohol systems with the epoxide ring (with allowance for rearrangement before or after the reaction). Three reaction mechanisms are discussed subsequently.

Application to VI of the accepted mechanism of reaction of an alcohol with the epoxide ring[8] could lead to four dihydroxy ethers, $C_{20}H_{34}O_3$. Subsequent dehydration could lead to twelve monohydroxy ether structures, $C_{20}H_{32}O_2$, each containing a seven-, eight-, or nine-membered ether ring. Consideration of the structural requirements for α-IV allows elimination of each of these twelve structures.

Since none of the structures resulting from dehydration following intramolecular reaction of the allylic hydroxyl groups with the epoxide ring of VI was acceptable for α-IV, consideration also was given to products which would result by this mechanism plus an allylic rearrangement. Two structures, VII and IV, which agree with the spectral properties of the hydroxy ether could be formed in such manner. Epoxide ring opening by the 1-hydroxyl group to form a 1,8-oxide bridge, dehydration to form the 9-double bond, and allylic rearrangement of the 3-hydroxyl group would yield VII. Structure IV could result from the sequence: allylic rearrangement of 3-hydroxyl to 5-hydroxyl, epoxide opening by the 5-hydroxyl group, and dehydration to form the 9-double bond.



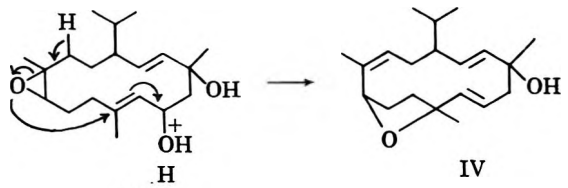
VII

A second mechanism considered for conversion of α-VI to α-IV consists of a concerted allylic displacement of the alcohol group by epoxide oxygen. This

(6) We feel that the assignment of structure VI is well justified from this consideration of the n.m.r. spectrum. It is interesting to note that the alternative 4,5-oxide structure also may be eliminated on the basis that we have been unable to propose any structure agreeing with the properties of α-IV which would be derived from the 4,5-oxide. The development of structure of α-IV has been possible, however, by proceeding from the epoxide structure VI, as described subsequently.

(7) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, p. 60.

(8) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

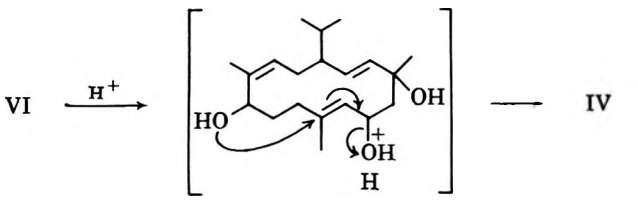


VI IV

mechanism is suggested by its similarity to the rearrangement of carotene epoxides to furanoid compounds.[9] In chloroform containing traces of mineral acid, carotene epoxides (VIII) were rearranged to IX. This rearrangement differs from dehydration of VI to IV only in that the displaced allylic oxygen function is also the epoxide oxygen.

VIII IX

A third mechanism for conversion of epoxide VI to IV would involve the isomerization of the oxide function to an allylic alcohol,[10] a reaction which has been observed under conditions similar to those effective in preparation of α-IV from α-VI. Formation of α-IV could then result from allylic displacement of the 3-hydroxyl group by the newly formed 8-hydroxyl.

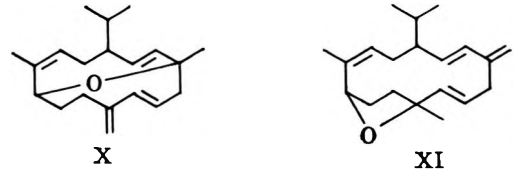


The preceding considerations of reactions whereby a cyclic ether could be formed from α-VI have led to only two structures acceptable for α-IV, structure VII and structure IV.

Elimination of structure VII was possible by consideration of the product isolated from dehydration of α-IV. Mild dehydration conditions (potassium hydrogen sulfate in refluxing dioxane for 3 hr., or *p*-toluenesulfonic acid in refluxing benzene for 3 min.) yielded an unsaturated ether, $C_{20}H_{30}O$, m.p. 41–42°. The ultraviolet absorption showed a maximum at 236 mμ (log ϵ 4.40). The n.m.r. spectrum showed peaks at 9.13 (6 protons, isopropyl), 8.70 (3 protons, CH_3COR), 8.50 (3 protons, $CH_3C{=}C$), 7.08 (2 protons, $C{=}CCH_2C{=}C$), 5.50 (1 proton, $-CHOR$), 5.04 (2 protons, $C{=}CH_2$), and 3.90–4.9 τ (5 olefinic protons). N.m.r. peaks for one vinyl methyl group and seven olefinic protons would require the dehydration product derived from structure VII to be an ether of structure X. However, structure X does not contain a methylene group between two double bonds, $C{=}CCH_2C{=}C$, required by n.m.r. absorption for two protons at 7.08 τ.[7] Consequently, structure VII is not acceptable for the ethereal alcohol isolated from tobacco.

(9) P. Karrer and E. Jucker, *Helv. Chim. Acta*, **28**, 300, 427 (1945).

(10) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 243, 244.

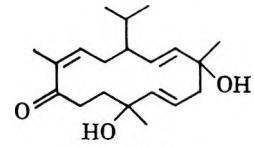


X XI

The properties of the ether formed by mild dehydration of α-IV are in agreement with structure XI. The dehydration of α-IV to XI with formation of an exocyclic double bond is in agreement with previous observation that elimination of the 1-hydroxyl by dehydration of the α isomers in the duvatriene family (*i.e.*, dehydration of α-4,8,13-duvatrien-1-ol-3-one) yields an exocyclic double bond.[2] Structure XI includes the $C{=}CCH_2C{=}C$ grouping, the absence of which eliminates structure X from consideration. Accordingly, the structure 12-isopropyl-1,5,9-trimethyl-5,8-oxido-3,9,13-cyclotetradecatrien-1-ol (IV) is proposed for α-IV.

It is important to note that the 1-hydroxyl group is not involved in the reaction sequence α-II → α-VI → α-IV. Accordingly, the configuration at the 1-position is identical in α-II and α-IV; *i.e.*, both compounds are of the α-series.

Oxidation of α-IV yielded an interesting product. Although hexahydro α-IV was recovered in 90% yield from attempted chromic oxide–pyridine oxidation, α-IV was oxidized by chromic oxide in pyridine. The oxidation product, $C_{20}H_{32}O_3$, contains two active hydrogen atoms. Strong infrared absorption at 6.05 μ and maximum ultraviolet absorption at 235 mμ (log ϵ 4.0) indicate an α,β-unsaturated ketone. The n.m.r. spectrum shows the presence of an isopropyl group, two CH_3COR groups, one $CH_3C{=}C$ group, and five olefinic protons. Structure XII, resulting from cleavage of the ether ring of α-IV, is proposed for the oxidation product.



XII

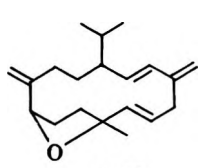
A second ethereal diterpene isolated from tobacco, α-V, is an isomer of α-IV. The mass spectrum, elemental analysis, and active hydrogen determination showed that α-V, m.p. 109–110°, $[\alpha]^{25}D$ +77.4°, possesses the formula $C_{20}H_{31}O(OH)$. Catalytic hydrogenation of α-V yielded a product identical with that obtained by catalytic hydrogenation of α-IV. Consequently, on the basis of the structure assigned to α-IV in the preceding discussion, α-V contains the duvane ring system with the 5,8-oxide bridge, a hydroxyl group of the α-configuration at the 1-position, and three double bonds. Structure assignment for α-V, exclusive of configuration, then requires the location of the double bonds.

Comparison of the n.m.r. spectrum of α-V with that of α-IV is of particular interest. α-V was similar to α-IV in showing an isopropyl multiplet (9.13), two methyl groups of the type CH_3COR (8.72), and one

proton of the type —C*H*OR (5.65 τ). The remainder of the n.m.r. spectrum of α-V showed general similarity to the n.m.r. spectrum of α-IV with two major differences: α-V did not show absorption for methyl attached to ethylenic carbon and α-V contained six olefinic protons (4.55–5.25 τ), including the protons of an exocyclic methylene group. The presence of only four methyl groups in the n.m.r. spectrum of α-V, compared to five methyl groups in the n.m.r. spectrum of α-IV, requires that one of the three double bonds of α-V be utilized in attachment of an exocyclic methylene group at the 9-position.

Assignment of the two other double bonds to the 3- and 13-positions was accomplished by further consideration of the n.m.r. spectrum. Absorption of —C*H*OR as a triplet, the appearance of the isopropyl multiplet at 9.13 τ, and the absence of conjugated double bonds eliminate location of double bonds at the 6-, 11-, 12-, and 10-positions, leaving only the 2-, 3-, and 13-positions available for the two double bonds. If the double bonds were located at the 2- and 13-positions, the greatly different environments of the 1- and 5-methyl groups would be expected to result in distinctly different n.m.r. peaks for these two methyls. Instead, the 1- and 5-methyl groups of α-V show absorption as a single peak at 8.72 τ. The equivalence of n.m.r. absorption of the two C*H*$_3$COR groupings is in agreement with locations of the double bonds in the 3- and 13-positions, whereby both methyl groups are in the similar $CH_2C(CH_3)(OR)CH{=}CH$ arrangement. Consequently, the double bonds were assigned to the 3- and 13-positions and the structure 12-isopropyl-1,5-dimethyl-9-methylen-5,8-oxido-3,13-cyclotetradecadien-1-ol (V) was assigned to α-V.

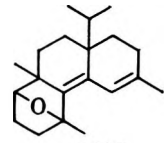
Assignment of structure V was verified by the products obtained by dehydration of α-V. Dehydration of α-V using potassium hydrogen sulfate yielded, as the major product, an unsaturated ether, m.p. 70–71°. The mass spectrum and elemental analysis indicated a molecular formula $C_{20}H_{30}O$. Maximum ultraviolet absorption occurs at 237 mμ (log ϵ 4.28). The appearance of eight olefinic protons in the n.m.r. spectrum shows that dehydration occurred without cyclization. Of the olefinic protons, four protons are present in terminal methylene groups (5.04 τ), in agreement with predominantly exocyclic dehydration in the α-duvane series. The n.m.r. spectrum (isopropyl multiplet, 9.12; C*H*$_3$COR, 8.70; —C*H*OR, 5.55; and especially C=CC*H*$_2$C=C, 7.07 τ) allows assignment of structure XIII



XIII

to the dehydration product; from the assignment of structure XIII to the dehydration product, the 3- and 13-positions of the endocyclic double bonds in α-V are confirmed.

Dehydration of α-V by *p*-toluenesulfonic acid yielded an interesting tetracyclic ether, $C_{20}H_{30}O$, m.p. 50–51°. From consideration of the n.m.r. spectrum (angular methyl, 9.25; isopropyl multiplet, 9.06; C*H*$_3$COR, 8.77; C*H*$_3$C=C, 8.22; —C*H*OR, 6.28; one olefinic proton, 3.98 τ) and the ultraviolet absorption (λ_{max} 251 mμ, log ϵ 3.99), structure XIV is proposed for the tetracyclic ether.



XIV

A third ethereal diterpene, β-V, isolated from tobacco in trace amounts, is assigned a structure differing from α-V only in configuration at the 1-position. The mass spectrum and elemental analysis showed that β-V, m.p. 108–109°, $[\alpha]^{25}D$ +72.5°, possesses the molecular formula $C_{20}H_{32}O_2$. The n.m.r. spectrum of β-V is remarkably similar to that of α-V. The only difference in the spectra of α- and β-V is the position of one of the methyl peaks of the C*H*$_3$COR groupings: in α-V, the C*H*$_3$COR methyl groups appear as a single peak (6 protons) at 8.72; in β-V, the C*H*$_3$COR groups appear as peaks at 8.70 (3 protons) and 8.62 τ (3 protons). The n.m.r. spectra suggest that β-V differs from α-V only in configuration at one of the CH$_3$COR groupings.

Dehydration of β-V using potassium hydrogen sulfate in dioxane yielded an unsaturated ether, m.p. 70–71°, which showed infrared, mass, and n.m.r. spectra identical with the spectra of the unsaturated ether XIII obtained from dehydration of α-V. Formation of XIII from β-V allows the assignment to β-V of the structure 12-isopropyl-1,5-dimethyl-9-methylen-5,8-oxido-3,13-cyclotetradecadien-1-ol (V) with configurations identical with those of α-V except at the 1-position. Accordingly, β-V is assigned to the β-series relative to configuration at the 1-position.

Isolation from tobacco of seven macrocyclic diterpenes (α- and β-II, α- and β-III, α-IV, and α- and β-V) suggests the tobacco leaf as a source for compounds of the newly characterized diterpene structure containing the cyclotetradecane ring. Unfortunately, the macrocyclic diterpenes have been isolated from tobacco in small quantities, with the total amount of all seven characterized diterpenes constituting less than 0.02% of the dry weight of tobacco.

Of special interest is the isolation of ethereal diterpenes from cigarette smoke. The observation that α-IV and α-V are present in tobacco smoke stands in contrast to the apparent absence of the diterpenediols II and III in cigarette smoke (although α- and β-II are present in tobacco in much larger quantities than α-IV and α-V). The absence of indications for presence of α- and β-II and α- and β-III in smoke is likely related to the previously noted instability of the

diols II and III.[2] Relative to II and III, α-IV and α-V are stable compounds.

Experimental[11]

Isolation of α-5,8-Oxido-3,9,13-duvatrien-1-ol (α-IV) and α- and β-5,8-Oxido-3,9(17),13-duvatrien-1-ol (α- and β-V) from Tobacco.—Isolation of α-IV and α- and β-V from tobacco was accomplished by procedures essentially the same as those reported earlier[2,4] for isolation of α- and β-II and α- and β-III. In chromatographic separations, α-IV and α- and β-V were eluted appreciably earlier than α- and β-II and III. From silicic acid, the diterpenes were eluted in the sequence: α-IV, α-V, β-V, α-III, β-III, α-II, and β-II.

α-IV and α-V have been isolated from aged, flue-cured burley, and Turkish tobacco. β-V has been isolated from aged burley and Turkish tobacco. The quantities of pure α-IV and α-V isolated from tobacco amounted to 0.00083% of the tobacco weight. β-V was isolated in only trace amounts.

Isolation of α-5,8-Oxido-3,9,13-duvatrien-1-ol (α-IV) and α-5,8-Oxido-3,9(17),13-duvatrien-1-ol (α-V) from Turkish Tobacco Smoke.—Partition fractions lower layers 2, 3, 2′, 3′, and 4′ from Turkish tobacco smoke after removal of pyrocoll and the homologous indoles and carbazoles,[12] were combined with lower layers 1, 1′, and 5′ to yield 308 g. of material. Repeated chromatography using silicic acid, Florisil, and alumina yielded an alcohol fraction weighing 3.0 g. Rechromatography using Florisil yielded three main fractions. The first, eluted by 1:49 ether–hexane, gave an infrared spectrum identical with that of α-V isolated from tobacco. The third, eluted by 1:24 ether–hexane, gave an infrared spectrum identical with that of α-IV isolated from tobacco. The second fraction contained both α-IV and α-V.

The fraction rich in α-IV, after repeated chromatography on Florisil, was crystallized from hexane at −27° to yield 0.31 g. of α-IV, m.p. 94–95°. A mixture melting point with a sample of α-IV from tobacco gave no depression. The infrared spectra of the smoke- and tobacco-derived samples were identical.

The fraction rich in α-V was treated in the same manner to yield 0.76 g. of α-V, m.p. 109–110°. A mixture melting point with a sample of α-V from tobacco gave no depression. The infrared and n.m.r. spectra of the smoke- and tobacco-derived samples were identical.

Physical Properties of α-5,8-Oxido-3,9,13-duvatrien-1-ol (α-IV).—α-IV crystallized from hexane in needles melting at 95–96°; $[\alpha]^{27}D$ +86°. α-IV shows no selective absorption of ultraviolet light. Infrared absorption occurs at 2.9, 9.6, 10.3, and 13.1 μ; n.m.r. spectrum, 9.13 (6), 8.70 (6), 8.50 (3), 5.5 (1), and 4.3–4.65 τ (5).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60; active H (1), 0.33; mol. wt., 304. Found: C, 78.99; H, 10.54; active H (Grignard), 0.3; active H (tritium exchange), 0.33; mass, 304.

α-IV was recovered in quantitative yield from attempted reduction using a large excess of lithium aluminum hydride in ether.

Catalytic Hydrogenation of α-5,8-Oxido-3,9,13-duvatrien-1-ol (α-IV).—From the hydrogenation of 223 mg. of α-IV using Adams' catalyst in ethyl acetate (24 hr. at 3 atm.), chromatography using silicic acid allowed the isolation of 190 mg. of hydrogenation product, m.p. 116–118°. Recrystallization from hexane at −27° raised the melting point to 118–120°.

Anal. Calcd. for $C_{20}H_{38}O_2$: C, 77.37; H, 12.33; active H (1), 0.32; mol. wt., 310. Found: C, 77.70; H, 12.43; active H (Grignard), 0.35; active H (tritium exchange), 0.28; mass, 310.

Hexahydro α-IV was recovered from attempted reaction with chromic oxide–pyridine at 25° for 22 hr.

Chromic Oxide–Pyridine Oxidation of α-5,8-Oxido-3,9,13-duvatrien-1-ol (α-IV).—To a slurry of 1.2 g. of chromic oxide in 10 ml. of pyridine was added α-IV (300 mg.). After 2 days at room temperature, the reaction mixture was processed by the standard procedure followed by chromatography using silicic acid to yield 220 mg. of material showing infrared absorption at 3.0 and 6.05 μ. The oxidation product, after recrystallization from an ether–hexane solution, melted at 144.5–146.5°; $[\alpha]^{26}D$ +63°; λ_{max}^{EtOH} 235 mμ (log ε 4.0); n.m.r. spectrum, 9.07 (6), 8.73 (3), 8.65 (3), 8.27 (3), 4.4–4.6 (4), and 3.4 τ (1).

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 74.96; H, 10.46; active H (2), 0.63; mol. wt., 320. Found: C, 74.92; H, 10.14; active H (tritium exchange), 0.59; mass, 302 (320–18).

The ketone obtained from oxidation of α-IV was recovered unchanged from refluxing with 1:1 ethanol–10% sodium hydroxide solution for 5 hr.

Dehydration of α-5,8-Oxido-3,9,13-duvatrien-1-ol (α-IV).—A mixture of 100 mg. of α-IV, 200 mg. of potassium hydrogen sulfate, and 10 ml. of anhydrous, peroxide-free dioxane was refluxed for 3 hr. The dioxane solution was decanted from the potassium hydrogen sulfate and concentrated to yield a pale yellow oil (93 mg.). Chromatography of this oil on Florisil yielded 49 mg. of a colorless solid, m.p. 41–42°; $\lambda_{max}^{cyclohexane}$ 236 mμ (log ε 4.4). Infrared absorption occurred at 6.10, 6.23, 10.35, 11.3, and 11.7 μ; n.m.r. spectrum, 9.13 (6), 8.70 (3), 8.50 (3), 7.08 (2), 5.50 (1), 5.04 (2), and 3.9–4.9 τ (5).

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.85; H, 10.56; mol. wt., 286. Found: C, 83.77; H, 10.68; mass, 286.

The same product was obtained in 40% yield when a mixture of α-IV (100 mg.), *p*-toluenesulfonic acid (60 mg.), and benzene (10 ml.) was refluxed for 3 min.

Perbenzoic Acid Oxidation of α-4,8,13-Duvatriene-1,3-diol (α-II).—To a chilled solution of α-4,8,13-duvatriene-1,3-diol (α-II, 4.8 g.) in 30 ml. of chloroform was added 27 ml. of cold chloroform solution containing 1.0 g. of perbenzoic acid. After the reaction mixture remained at 25° for 18 hr., it was diluted with 200 ml. of pentane and was washed with two 100-ml. portions of 10% sodium hydroxide solution. Concentration of the organic phase and chromatography using silicic acid yielded 2.5 g. of unchanged α-II and 2.0 g. of oxidation product. The oxidation product (α-VI), after two recrystallizations from ether–hexane solutions, melted at 103–105°. Infrared absorption occurred at 2.95, 8.45, 9.40, 9.9, and 10.20 μ; n.m.r. spectrum, 9.15 (6), 8.80 (3), 8.62 (3), 8.20 (3), 7.06 (1), 5.50 (1), and 4.47–4.60 (3).

Anal. Calcd. for $C_{20}H_{34}O_3$: C, 74.49; H, 10.62; mol. wt., 322. Found: C, 74.11; H, 10.46; mass, 304 (322–18).

Conversion of α-8,9-Oxido-4,13-duvadiene-1,3-diol (α-VI) to α-5,8-Oxido-3,9,13-duvatrien-1-ol (α-IV). Method A.—A solution of 0.967 g. of α-VI in 40 ml. of chloroform was allowed to stand with occasional shaking at 25° for 20 hr. with 1 ml. of 2 *N* sulfuric acid. The reaction mixture was diluted with 120 ml. of hexane and was washed successively with 30 ml. of water, with 50 ml. of 10% sodium hydroxide solution, and with three 30-ml. portions of saturated salt solution. The residue from concentration of the organic phase was separated by chromatography on silicic acid to yield 0.324 g. (30%) of α-IV and 0.620 g. of material showing the infrared absorption of α-VI. α-IV synthesized by this reaction showed infrared absorption identical with that of naturally occurring α-IV, melted at 95–97° after recrystallization from pentane, and showed no depression of melting point when mixed with authentic α-IV. Treatment of 0.402 g. of recovered α-VI with 15 ml. of chloroform and 12 drops of 2 *N* sulfuric acid for 40 hr. resulted in formation of an additional 0.200 g. of α-IV.

Method B.—A mixture of 0.130 g. of α-VI, 1.5 g. of anhydrous magnesium sulfate, and 15 ml. of toluene was heated under reflux for 2.5 hr. The residue from concentration of the solution was chromatographed twice on silicic acid to yield 30 mg. of material showing the infrared spectrum of α-IV.

Method C.—A mixture of 0.227 g. of α-VI, a catalytic amount of iodine, and 30 ml. of benzene was heated under reflux for 2.5 hr. The reaction mixture was diluted with 40 ml. of ether and was washed with two 25-ml. portions of sodium metabisulfite solution. The residue from concentration of the organic phase was chromatographed twice on silicic acid to yield 110 mg. of material with the infrared spectrum of α-IV.

(11) All melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. All rotations were measured in chloroform solutions. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Huffman Microanalytical Laboratories, Wheatridge, Colo. Active hydrogen determinations designated "tritium exchange" were made by the procedure of Giles, *Anal. Chem.*, **32**, 1716 (1960). Nuclear magnetic resonance (n.m.r.) spectra were run in deuterated chloroform solution using a Varian Associates HR-60 instrument and are reported by τ-values[5] with the number of protons in parentheses. We are indebted to John J. Whalen and Johnnie L. Stewart for infrared spectra, to George W. Young for mass spectra, to J. A. Giles and P. H. Ayers for active hydrogen determinations, to Bruce W. Woosley, Max A. Wagoner, Richard F. Walsh, Anthony Angel, and Earl Hester for technical assistance, and to Dr. M. Senkus and Dr. C. E. Teague, Jr., for helpful discussions.

(12) A. Rodgman and L. C. Cook, *Tobacco Sci.*, **6**, 174 (1962).

Journal of Organic Chemistry

Vol. 29

Jan. — April

(Pages 1 – 992)

1964

I

Physical Properties of α-5,8-Oxido-3,9(17),13-duvatrien-1-ol (α-V).—α-V, recrystallized from hexane or pentane, melts at 109–110°, and shows no selective absorption of ultraviolet light; $[\alpha]^{25}D$ +77.4°. Infrared absorption occurred at 2.95, 6.05, 9.3, 10.2, 11.1, and 11.6 μ; n.m.r. spectrum, 9.13 (6), 8.72 (6), 5.2 (2), and 4.55–4.9 τ (4).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60; active H (1), 0.33; mol. wt., 304. Found: C, 78.86; H, 10.69; active H (tritium exchange), 0.29; mass, 304.

Catalytic Hydrogenation of α-5,8-Oxido-3,9(17),13-duvatrien-1-ol (α-V).—Catalytic hydrogenation of 267 mg. of α-V using Adams' catalyst in ethyl acetate (24 hr. at 3 atm.), followed by chromatography of the product on silicic acid, allowed isolation of 250 mg. of hexahydro α-V, m.p. 117–119°. The infrared absorption of hexahydro α-V was identical with that of hexahydro α-IV and a mixture of hexahydro α-V and hexahydro α-IV melted at 118–119°.

Anal. Calcd. for $C_{20}H_{38}O_2$: C, 77.37; H, 12.33; mol. wt., 310. Found: C, 77.53; H, 12.18; mass, 310.

Dehydration of α-5,8-Oxido-3,9(17),13-duvatrien-1-ol (α-V) to 5,8-Oxido-1(15),3,9(17),13-duvatetraene (XIII).—A mixture of 0.20 g. of α-V, 0.40 g. of potassium hydrogen sulfate, and 20 ml. of anhydrous, peroxide-free dioxane was refluxed for 3 hr. The cooled solution was decanted from the potassium hydrogen sulfate, concentrated, and the residue (190 mg.) chromatographed on Florisil. The fractions eluted by 1:99 ether–hexane yielded a colorless oil (90 mg.) which slowly solidified. The solid, XIII, melted at 66–67°. Crystallization from methyl alcohol raised the melting point to 70–71°. XIII showed infrared absorption at 6.08, 6.25, 10.3, 11.3, and 11.6 μ; $\lambda_{max}^{cyclohexane}$ 237 mμ (log ε 4.28); n.m.r. spectrum, 9.12 (6), 8.70 (3), 7.07 (2), 5.55 (1), 5.06 (4), and 3.9–4.6 τ (4).

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.85; H, 10.56; mol. wt., 286. Found: C, 83.03; H, 10.46; mass, 286.

Dehydration and Cyclization of α-5,8-Oxido-3,9(17),13-duvatrien-1-ol (α-V).—A solution of α-V (200 mg.) and *p*-toluenesulfonic acid (120 mg.) in benzene (10 ml.) was refluxed for 30 min., cooled to 25°, diluted with ether (50 ml.), and washed with a total of 25 ml. of 5% sodium carbonate solution. The organic phase, after treatment with anhydrous sodium sulfate, was concentrated to yield 190 mg. of a pale yellow, viscous oil. Chromatography on Florisil yielded a colorless oil which readily solidified. The solid (XIV, 90 mg.) melted at 49–50°. Crystallization from hexane at −27° raised the melting point to 50–51°; $\lambda_{max}^{cyclohexane}$ 251 mμ (log ε 3.99). Infrared absorption occurred at 6.15, 9.75, and 12.0 μ; n.m.r. spectrum, 9.25 (3), 9.06 (6), 8.77 (3), 8.22 (3), 6.28 (1), and 3.98 τ (1).

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.85; H, 10.56; mol. wt., 286. Found: C, 83.11; H, 10.44; mass, 286.

Cyclization of 5,8-Oxido-1(15),3,9(17),13-duvatetraene.—A mixture of XIII (25 mg.) and *p*-toluenesulfonic acid (10 mg.) in benzene (5 ml.) was refluxed for 30 min. The reaction mixture was processed as in the preceding section to yield 22 mg. of pale yellow oil. Chromatography on Florisil yielded 13 mg. of a colorless solid, m.p. 46–48°, whose infrared and ultraviolet absorption spectra were identical with those previously recorded for the sample of XIV.

Physical Properties of β-5,8-Oxido-3,9(17),13-duvatrien-1-ol (β-V).—β-V, after recrystallization from hexane, melted at 108–109°, $[\alpha]^{25}D$ +72.5°. β-V shows no selective ultraviolet absorption other than end absorption; infrared spectrum, 3.10, 6.10, 8.95, 9.30, 10.25, 10.82, 11.30, and 11.60 μ; n.m.r. spectrum, 9.12 (6), 8.70 (3), 8.62 (3), 4.50–5.52 (6).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60; mol. wt., 304. Found: C, 78.77; H, 10.64; mass, 304.

A mixture of β-V and α-V melted at 70–95°.

Dehydration of β-5,8-Oxido-3,9(17),13-duvatrien-1-ol (β-V).—A mixture of β-V (188 mg.), potassium hydrogen sulfate (400 mg.), and 20 ml. of dioxane was heated under reflux for 3 hr. The residue from concentration of the dioxane solution was chromatographed on Florisil; the dehydration product was eluted with 1% ether in pentane. The infrared, mass, and n.m.r. spectra of the unsaturated ether (61 mg.), m.p. 70–71° after recrystallization from methyl alcohol, were identical with the spectra of the product obtained by potassium hydrogen sulfate dehydration of α-V.

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.85; H, 10.56; mol. wt., 286. Found: C, 84.14; H, 10.25; mass, 286.

Ion Radicals. IV.[1] The Electron Spin Resonance Spectra of Substituted Thianthrenes in Sulfuric Acid Solution

H. J. SHINE, C. F. DAIS, AND R. J. SMALL

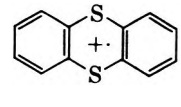
The Department of Chemistry, Texas Technological College, Lubbock, Texas

Received May 20, 1963

Fifteen thianthrenes with substituents in the 1-, 2-, and 2,7-positions have been prepared. Each of the thianthrenes dissolves in 96% sulfuric acid to give a colored, paramagnetic solution. The e.s.r., ultraviolet, and visible spectra of these solutions have been recorded. The hyperfine structures of the e.s.r. spectra are in accord with the recent proposals[1] for the structure of the thianthrene positive ion radical and the major coupling of the 2,3,7,8-protons. The *g*-values of all but one of the thianthrenes were close to 2.008–2.009. The exception was 2,7-dibromothianthrene with a *g*-value of 2.0101. Line widths and hyperfine splittings are reported.

Solutions of thianthrene in concentrated sulfuric acid are purple in color[2,3] and are paramagnetic.[1,4-10] Solutions of thianthrene in solvents containing Lewis acids such as aluminum chloride[1b,8,9] and antimony pentachloride[8,9] exhibit paramagnetic resonance.

The formation of a paramagnetic species in these systems has been interpreted[1,7,9,10] as a one-electron oxidation to give the ion radical I.



I

(1) (a) Presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963; (b) part I, H. J. Shine and L. Piette, *J. Am. Chem. Soc.*, **84**, 4798 (1962); (c) part II, H. J. Shine, C. F. Dais, and R. J. Small, *J. Chem. Phys.*, **38**, 569 (1963); (d) supported by the Directorate of Chemical Sciences, Air Force Office of Scientific Research, grants AF-AFOSR-61-48 and AF-AFOSR-23-63, to whom we express our thanks.

(2) K. Fries and W. Vogt, *Ber.*, **44**, 756 (1911).

(3) K. Fries and W. Vogt, *Ann.*, **381**, 312 (1911).

(4) J. M. Hirshon, D. M. Gardner, and C. R. Fraenkel, *J. Am. Chem. Soc.*, **75**, 4115 (1953).

(5) J. E. Wertz and J. Vivo, *J. Chem. Phys.*, **23**, 2193 (1955).

(6) A. Fava, P. B. Sogo, and M. Calvin, *J. Am. Chem. Soc.*, **79**, 1078 (1957).

(7) W. C. Needler, Ph.D. thesis, University of Minnesota, August, 1961 [*Dissertation Abstr.*, **22**, 3873 (May, 1962)]. At the time of submission of our first papers in this series we were not aware of the work of Professor J. E. Werz and Dr. Needler. We wish to thank Dr. E. T. Kaiser, Washington University, for calling our attention to this thesis.

(8) M. Kinoshita and H. Akamatu, *Bull. Chem. Soc. Japan*, **35**, 1040 (1962).

(9) M. Kinoshita, *ibid.*, **35**, 1137 (1962).

(10) E. A. C. Lucken, *J. Chem. Soc.*, 4963 (1962).

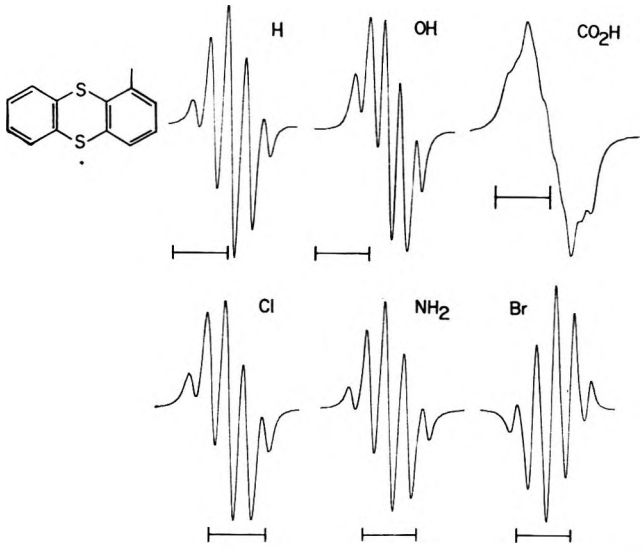


Fig. 1.—E.s.r. spectra of 1-substituted thianthrenes in 96% sulfuric acid. The scale calibration shown is 4 gauss. Field increases from right to left in each case.

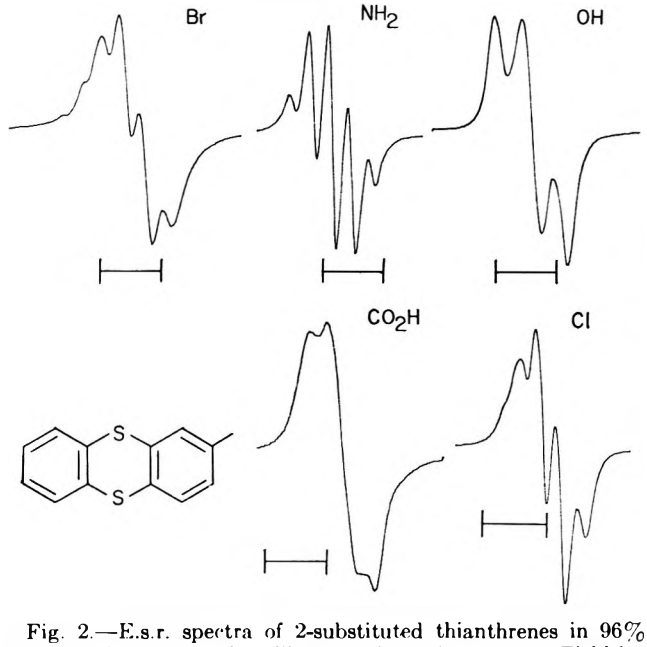


Fig. 2.—E.s.r. spectra of 2-substituted thianthrenes in 96% sulfuric acid. The scale calibration shown is 4 gauss. Field increases from right to left in each case.

Characteristic 5-line, 1:4:6:4:1, e.s.r. spectrum observed is consistent with the symmetrical radical I in which the spin coupling of only four of the protons is large enough to be observed. The four effective protons have been described as those in the 2-, 3-, 7-, and 8-positions.[1] As a test of this assignment a number of substituted thianthrenes were made and the spin and absorption spectra of their sulfuric acid solutions were recorded. The e.s.r. spectra of the 2,7-dimethyl- and 2,7-dichlorothianthrenes in sulfuric acid demonstrated the validity of the assignment.[1c,7] We now wish to report the spectral characteristics of a number of substituted thianthrenes, so that comparisons of 1-substituents with 2- and 2,7-substituents may be made.

Results and Discussion

E.s.r. Spectra.—With some exceptions the hyperfine structures of the e.s.r. spectra (Fig. 1–3) are clearly understandable on the basis of the assignments made previously.[1] Each of the 1-substituted thianthrenes has a 5-line spectrum, except the 1-carboxythianthrene. On the other hand, except for 2-aminothianthrene, substituents in the 2- and 2,7-positions cause marked changes from the 5-line pattern of the parent molecule. The spectra of the 2,7-dihydroxy- and 2,7-di-*t*-butylthianthrenes have hyperfine structures consistent with coupling with the 3,8-protons. The 3-line spectrum of 2,7-dichloro- and the 9-line spectrum of 2,7-dimethylthianthrene already have been discussed.[1c] The details of the variations in hyperfine structures of the 2-substituted thianthrenes are not explainable with certainty at this stage. The spectrum of 2-bromothianthrene shows marked lack of symmetry and this could not be removed by diluting or warming the solution in a capillary tube to about 60°. A similar, but less marked, dissymmetry is obtained with 2-chlorothianthrene. It is possible that these characteristics are due to *g*-anisotropy. The reasons for the 5-line pattern of 2-aminothianthrene and the pattern of the 1-carboxylic acid are also unknown. It is evident, however, that large distortions from the parent 5-line pattern occur mostly when substituents are placed in the 2- and 2,7-positions, and that this is what the earlier assignment[1] of proton coupling predicts.

The *g*-values and hyperfine splittings for the fifteen compounds are listed in Table I. It is seen that all of the *g*-values are larger than the free spin value of 2.0023. The substituents do not cause much variation in the *g*-values except in the case of the 2,7-dibromothianthrene. It is evident from the over-all splittings (about 4 to 13 gauss) that there is a larger spin density on the sufur atoms than on the other ring atoms. The *g*-values indicate also that, as with many other sulfur-containing radicals, spin-orbit coupling is occurring. It is possible that this is responsible for the rather large hyperfine line widths in the thianthrene cation radicals compared say, with those of the anthracene cation radical. This may also be the reason for the single broad line of the 2,7-dibromothianthrene cation radical.

TABLE I

ELECTRON SPIN RESONANCE SPECTRA

Thianthrene derivative	No. of lines	Hyperfine splitting[a]	Over-all splitting[a]	*g*-Values
Thianthrene	5	1.32	5.26	2.0081[d]
Monoxide	5	1.32	5.30	2.0081
1-NH_2	5	1.31	5.24	2.0081
2-NH_2	5	1.27	5.18	2.0080
1-Br	5	1.40	5.54	2.0081
2-Br	4[b]	[c]	6.7	2.0091
1-Cl	5	1.35	5.32	2.0081
2-Cl	3[b]	[c]	4.8	2.0079
1-OH	5	1.27	5.08	2.0081
2-OH	3	1.91	3.81	2.0077
1-COOH	[b]	[c]	5.6	2.0082
2-COOH	3[b]	[c]	3.6	2.0082
2,7-Me_2	9	1.65	13.2	2.0088
2,7-$(OH)_2$	3	1.90	3.79	2.0076
2,7-Cl_2	3	1.49	3.26	2.0083
2,7-Br_2	1	[c]	3.72	2.0101
2,7-(*t*-Bu)$_2$	3	1.60	3.21	2.0078

[a] In gauss. [b] Poorly resolved or unsymmetrical spectrum. [c] Not measurable. [d] Ref. 5 gives 2.0078, 2.0081; ref. 6 gives 2.009; ref. 8 gives 2.0083; ref. 9 gives 2.0080.

TABLE II

ABSORPTION SPECTRA IN THE VISIBLE AND ULTRAVIOLET OF SUBSTITUTED THIANTHRENES DISSOLVED IN 96% SULFURIC ACID

Substituent	Time[a]	λ, mμ	ε × 10⁻⁴	Time[a]	λ, mμ	ε × 10⁻⁴	λ, mμ	ε × 10⁻⁴
H	5 d	546	0.89	5 d	290	3.80	270	3.15
1-NH_2	30 m	539	0.52	70 m	290	2.61	271	2.45
	10 d	539	0.52	10 d	290	2.61	271	2.45
2-NH_2	10 m	531	0.62	25 m	290	3.88	274	3.05
	5 d	524	0.97	1 d	290	4.80	274	sh.[b]
	10 d	524	0.97	10 d	290	5.02	274	sh.[b]
1-OH	30 m	528	0.74	2 h	[c]		273	2.54
	5 d	515	0.77	1 d	[d]		[d]	
	10 d	515	0.77	10 d	[d]		[d]	
2-OH	30 m	597	1.08	2 h	291	6.90	[e]	
	5 d	592	1.01	1 d	291[f]	6.37	[e]	
	10 d	592	0.96	5 d	291[f]	5.50	[e]	
1-Cl	5 d	539	0.85	5 d	291[g]	2.84	274	3.10
	10 d	539	0.85	10 d	291[g]	2.84	274	3.10
2-Cl	5 d	572	1.09	5 d	294	4.91	274	3.13
	10 d	572	1.09	10 d	294	4.91	274	3.13
2-Br	5 d	584	1.18	5 d	295	5.23	275	3.23
	10 d	584	1.18	10 d	295	5.23	275	3.23
1-COOH	10 m	538	1.09	1 h	291	4.26	274	sh.[b]
	5 d	537	1.11	1 d	291	4.44	274	sh.[b]
	10 d	537	1.08	5 d	291	4.44	274	sh.[b]
2-COOH	15 m	539	0.72	1 h	300	3.97	[e]	
	5 d	534	0.96	1 d	300	4.30	[e]	
	10 d	534	0.96	10 d	300	4.63	[e]	
2,7-$(OH)_2$	5 m	604	1.15	1 h	333[h]	2.55	296[h]	3.60
	5 d	540	1.10	1 d	333	3.80	296	3.20
	10 d	540	1.10	10 d	333	5.37	296	2.55
2,7-$(Cl)_2$	6 d	585	1.20	6 d	297	4.80	276	2.62
	10 d	585	1.34	10 d	297	5.00	276	2.76
2,7-$(Br)_2$	14 d	600	[i]	14 d	300	[i]	277	[i]
2,7-$(Me)_2$	30 m	580	1.22	20 m	295	4.40	273	2.59
	4 d	580	1.22	4 d	295	4.40	273	2.59
2,7-(*t*-Bu)$_2$	1 d	585	1.28	1 d	296	4.53	273	2.82
	3 d	585	1.28	3 d	296	4.53	273	2.82

[a] From first contact of solute with acid in minutes (m), hours (h), or days (d). [b] Shoulder. [c] A broad band with broad maxima at 315 (ε 2.08 × 10⁴) and 295 mμ (1.88 × 10)⁴. [d] No maximum at 273 mμ; instead a broad band with maxima at 296 (ε 2.52 × 10⁴) and 281 mμ (2.32 × 10⁴). [e] No maxima in this region. [f] A new small peak appeared at 318 mμ (ε 2.60 × 10⁴). [g] Shoulder at 299 mμ (ε 2.50 × 10⁴). [h] The change in absorbance at these λ-values was accompanied by an isosbestic point at 305 mμ. [i] Compound too insoluble to determine reliably.

Electrolytic Oxidation.—The conclusion that the structure of the thianthrene positive ion radical was I suggested that anodic oxidation of thianthrene should give this radical. The oxidation was carried out[11] every elegantly chronopotentiometrically by Dr. J. D. Voorhies, using nitromethane as solvent and magnesium perchlorate as the supporting electrolyte. A red-violet color was obtained at the platinum anode and a value of $E^1/_4$ = 1.3 v. *vs.* a normal hydrogen electrode was obtained. The wave height was indicative of a one-electron oxidation. Since the thianthrene used in the anodic oxidation was from the same batch as was used for all of the sulfuric acid work,[1] there seemed to be no doubt that the electrolysis experiment had given the ion radical I. This was confirmed only recently when e.s.r. equipment became available in our own laboratory. Oxidation at a platinum electrode, carried out in a cell in the microwave cavity gave the result shown in Fig. 4.

Absorption Spectra in Sulfuric Acid.—Each of the thianthrenes dissolved in 96% sulfuric acid to give a colored solution, the colors varying from blue to wine red. The characteristics of the visible and ultraviolet spectra of the solutions are listed in Table II. The amino-, hydroxy-, carboxy-, and methylthianthrenes dissolved quickly so that their absorption spectra could be recorded fairly soon after making the necessary dilutions. Some of the spectra of this group of compounds changed with time. These changes were more pronounced in the ultraviolet than in the visible spectra. The most extensive changes occurred in the 2-amino, 1- and 2-hydroxy, and the 2,7-dihydroxy compounds. The 1-aminothianthrene solution was very stable. The behavior of 2,7-dihydroxythianthrene is most interesting. In the ultraviolet the initially predominant peak at 296 mμ decreased with time and the one at 333 mμ increased, the transition going through an isosbestic point at 305 mμ. This behavior is the *reverse* of what appears to be the characteristic behavior of the thianthrene oxides in 96% sulfuric acid.[1b,12] Thus, it seems that the 2,7-dihydroxythianthrene is undergoing disproportionation or rearrangement to a hydroxy oxide. The same diagnosis may be made from the change in the visible spectrum of this compound: from 604 to 540 mμ. Indications are present also in the spectra of 2-hydroxythianthene that a small amount of the hydroxy oxide may be forming. That is, a new peak appeared at 318 mμ after the solution was one day old, and there was an accompanying fall in

(11) In the laboratories of the American Cyanamid Co., Bound Brook, N. J.

(12) Part III, H. J. Shine and T. A. Bobinson, *J. Org. Chem.*, **28**, 2828 (1963).

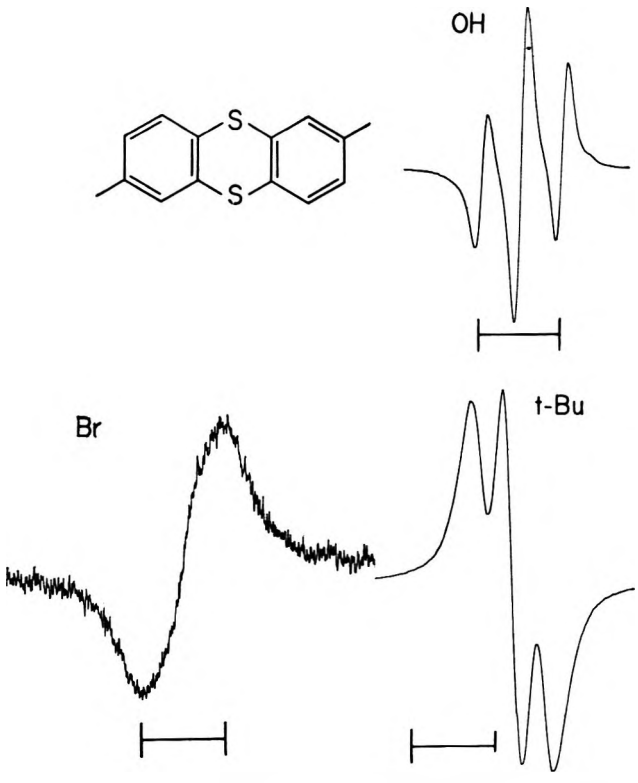


Fig. 3.—E.s.r. spectra of 2,7-disubstituted thianthrenes in 96% sulfuric acid. The scale calibration shown is 4 gauss. Field increases from right to left in each case.

absorbance at the maximum for the 2-hydroxythianthrene. The case of this compound and its oxide with λ_{max} at 319 mμ is discussed in the preceding paper.[12]

The remaining substituted thianthrenes dissolved in 96% sulfuric acid only slowly. The solutions were quite stable. The spectra of 1-chloro-, 2-chloro-, and 2-bromothianthrene were recorded at time intervals while these compounds were dissolving in stoppered cells. No differences were observed between the character of the visible and ultraviolet spectra recorded this way and the character of the spectra of solutions, used for absorbancy calculations, in which a known quantity of solute had taken several days to dissolve.

The spectra of all of the thianthrenes between 400 and 1200 mμ, when first recorded, had the same characteristics; that is, a large slender peak in the visible and two small bands in the near infrared, whose positions near 920 and 1050 mμ did not seem to differ much from one compound to another. On the other hand, the positions of the peaks in visible region clearly reflected the nature and positions of the substituents.

The λ_{max} of thianthrene in 96% sulfuric acid is 546 mμ. All of the 1-substituents cause a hypsochromic shift from 546 mμ, while most of the 2-substituents cause a bathochromic shift. The exceptions among the 2-substituents are the amino and carboxyl groups. Therefore, the transition from ground to excited state is facilitated by electron donors in the 2- and 7-positions, but it is adversely affected by all groups in the 1-position and the $-NH_3^+$ and $-C(OH)_2^+$ groups in the 2-position. It is evident, therefore, that the $\pi \rightarrow \pi^*$ transition occurring in the visible region is polarizing the ion radical along its long axis.

Molecular orbital calculations are being carried out both to define this transition exactly and to provide a clearer understanding of the e.s.r. spectra.

The ultraviolet spectrum of thianthrene in 96% sulfuric acid has maxima at 270 and 290 mμ. Most of the substituted thianthrenes have maxima in these regions. The positions of these maxima do not differ in most cases from those of thianthrene. The absorptivity in the region of 270 mμ does not change so much in going from one compound to another as the absorptivity in the region of 290 mμ. In this region the 2-substituted thianthrenes, with the exception of the 2-carboxy, have the larger absorptivities. Again, the precise analysis of these spectra must await a solution to the transitions which are occurring.

Experimental

Materials. Benzenesulfonyl Chlorides.—The following were obtained from Distillation Products: 2,5-dimethyl-, 2,5-dichloro-, 3,4-dichloro-, and *p*-bromobenzenesulfonyl chloride.

Thiols.—The following thiols were obtained from commercial sources: *p*-methylthiophenol and *p*-*t*-butylthiophenol (Distillation Products), *m*-methylthiophenol and *o*-methylthiophenol (Pitt-Consol Chemical Company). *p*-Bromothiophenol was prepared by the reduction of the corresponding benzenesulfonyl chloride with lithium aluminum hydride following the general procedure of Field and Greenwald,[13] m.p. 74.0–75.5° (lit.[14] 72–74°), after recrystallization from aqueous ethanol. All other thiols were prepared by the reduction of the corresponding benzenesulfonyl chlorides with zinc dust and sulfuric acid, following the general procedure of Vogel.[15] The resulting thiols were used without further purification.

Disulfides.—The general procedure was to dissolve the thiols in aqueous sodium hydroxide and oxidize with a solution of iodine in carbon tetrachloride. The resulting disulfides were recrystallized from ethanol ultraviolet spectra were of ethanol solutions): *p*-tolyldisulfide, m.p. 45.5–46.3° (lit.[16] 48°), λ_{max} 243 mμ; *o*-tolyl disulfide, m.p. 36.2–36.7° (lit.[17] 38–39°), λ_{max} 242 mμ; 4,4′-dibromodiphenyl disulfide, m.p. 93–93.5° (lit.[18] 92–94°), λ_{max} 249 mμ; 4,4′-di-*t*-butyldiphenyl disulfide, m.p. 88.0–88.6°, λ_{max} 243 mμ.

Anal. Calcd. for $C_{20}H_{26}S_2$: C, 73.12; H, 7.36; S, 19.51. Found: C, 73.38; H, 7.34; S, 19.20.

2,2′,5,5′-Tetramethyldiphenyl disulfide had m.p. 51.5–52.5°, λ_{max} 245 mμ.

Anal. Calcd. for $C_{16}H_{18}S_2$: C, 23.36. Found: S, 23.52.

Thianthrenes.—The following compounds were prepared as described by Gilman and Swayampati[19]: 1-aminothianthrene, m.p. 124–125° (lit. 120–121°); 1-chlorothianthrene, m.p. 84.5–85.5° (lit. 85–85.5°); 2-chlorothianthrene, m.p. 83.5–84.5° (lit. 84°); 1-carboxythianthrene, m.p. 228–228.8° (lit. 224–225°); 2-carboxythianthrene, m.p. 225–226° (lit. 227–228°). The 2-aminothianthrene, m.p. 158–159° (lit. 160°), and 2-bromothianthrene, m.p. 85–86° (lit. 88–89°), were prepared as described by Gilman and Swayampati.[20] 1-Bromothianthrene, m.p. 145–146.5° (lit.[21] 145°), was prepared from 1-aminothianthrene in a manner similar to the preparation of 1-chlorothianthrene. The 2-hydroxythianthrene, m.p. 143–144° (lit.[22] 145°), was prepared from 2-bromothianthrene by the procedure of Pützer and Muth.[22,23] 2,7-Dichlorothianthrene, m.p. 181.5–182° (lit.[24] 181.5°), was prepared by the procedure of Baw,

(13) L. Field and F. Greenwald, *J. Org. Chem.*, **16**, 946 (1951).
(14) L. Field, *J. Am. Chem. Soc.*, **74**, 394 (1952).
(15) A. Vogel, "A Textbook of Practical Organic Chemistry," Longmans Green and Co., New York, N. Y., 1954, p. 784.
(16) K. Slotta and W. Franke, *Ber.*, **63**, 681 (1930).
(17) F. Taboury, *Ann. Chim.* (Paris), **15**, 47 (1908).
(18) S. Wada, *Yakugaku Zasshi*, **79**, 88 (1959).
(19) H. Gilman and D. R. Swayampati, *J. Am. Chem. Soc.*, **79**, 211 (1957).
(20) H. Gilman and D. R. Swayampati, *ibid.*, **77**, 5947 (1955).
(21) H. Gilman and C. G. Stuckwisch, *ibid.*, **65**, 1461 (1943).
(22) B. Pützer and H. Muth, German Patent 606,350 (November, 1934).
(23) We are grateful to Mr. C. N. Sechrist, American Oil Co., Texas City, Tex., for carrying out the high-pressure hydrolysis.
(24) H. Baw, G. M. Bennett, and P. Dearns, *J. Chem. Soc.*, **680** (1934).

Bennett, and Dearns.[24] 2,7-Dimethylthianthrene and 2,7-dibromothianthrene were prepared by the same procedure and were recrystallized from ethanol. The 2,7-dimethylthianthrene had m.p. 117–118° (lit.[25] 117°). The 2,7-dibromothianthrene had m.p. 204–205°.

Anal. Calcd. for $C_{12}H_6S_2Br_2$: Br, 42.72. Found: Br, 42.44.

2,7-Di-*t*-butylthianthrene.—4,4′-Di-*t*-butyldiphenyl disulfide (3.2 g.) was mixed with 30 ml. of 96% sulfuric acid with shaking; 30 ml. of 30% fuming sulfuric acid was added to the shaking mixture in small portions. The color turned from green to wine red. After 1 hr. the reaction mixture was poured over ice, and the resulting brown solution was extracted with chloroform. The chloroform solution was washed with dilute sodium hydroxide solution and water, dried over anhydrous magnesium sulfate, filtered, and evaporated. A white solid was obtained, which was recrystallized from aqueous ethanol, m.p. 151–152°, 0.11 g. (3%).

Anal. Calcd. for $C_{20}H_{24}S_2$: C, 73.11; H, 7.36; S, 19.36. Found: C, 72.98; H, 7.50; S, 19.36.

2,7-Dihydroxythianthrene was prepared[23] by the hydrolysis of 2,7-dibromothianthrene using the procedure given[22] for 2-hydroxythianthrene. Recrystallization from aqueous methanol gave a product with m.p. 232–233°.

Anal. Calcd. for $C_{12}H_8O_2S_2$: C, 58.03; H, 3.25; S, 25.82. Found: C, 57.85; H, 3.51; S, 25.53.

Attempts to prepare 1,6-dimethyl-, 1,4,6,9-tetramethyl-, 1,4,6,9-tetrachloro-, and 2,3,7,8-tetrachlorothianthrene were unsuccessful.

Spectra.—The e.s.r. spectra were obtained with a Varian spectrometer using 100-kc. field modulation. Line calibrations were made by using potassium nitroso disulfonate in saturated sodium carbonate solution as a standard.[26] A Varian Associates V-4532 dual sample cavity was used. The standard solution was enclosed in a Pyrex capillary and modulated at 400 c.p.s. The thianthrene solutions were placed in Varian Associates flat quartz cells and modulated at 100 kc. A Varian Associates Model G-22 dual channel recorder was used to record standard and sample spectra simultaneously. The klystron frequency was measured with a Hewlett Packard Model 540-B transfer oscillator, in conjunction with a Model 524-C electronic counter, a Model 525-B frequency converter, and a Model X532-B frequency counter. The g-values were calculated from the dual recordings, using the value of 2.0057 for the standard.[26] Line splittings were measured as the distance between points on the derivative curves corresponding with the centers of absorption lines. The width of a hyperfine line was measured between the points on the derivative curve corresponding with points of maximum slope on the absorption curve.

The hyperfine splittings were found to be constant for all lines in those spectra whose shapes permitted splitting measurement. In some of these spectra, however, line widths were not constant.

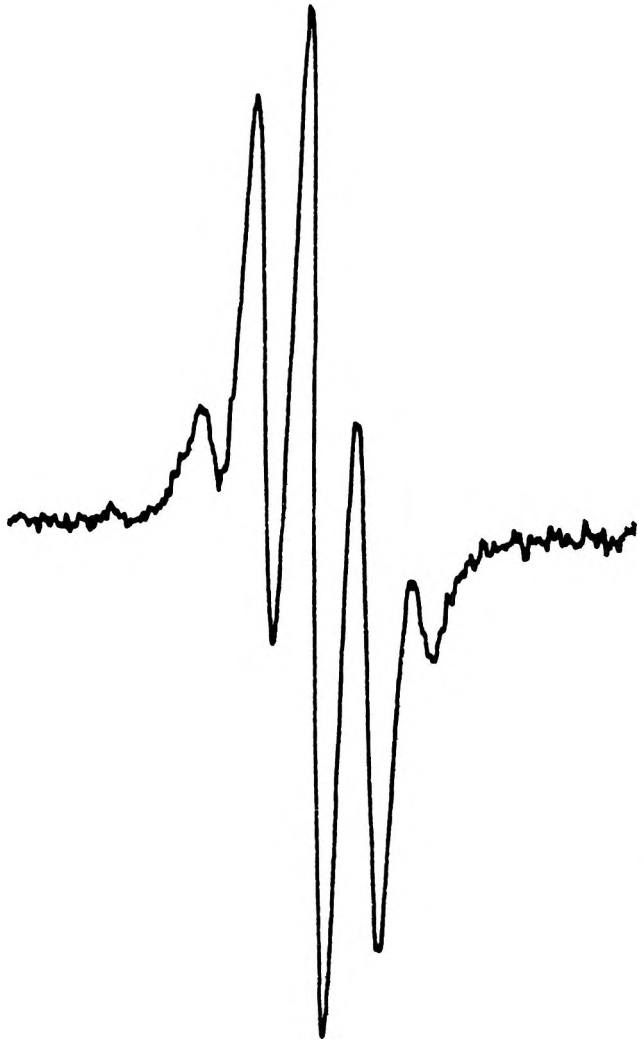


Fig. 4.—E.s.r. spectrum obtained from the anodic oxidation of thianthrene in nitromethane solution.

Line widths were constant in thianthrene (0.56), 1-bromo- (0.57), 1-chloro- (0.55), 2,7-dimethyl- (0.56), and 2,7-dihydroxythianthrene (0.63 gauss). In other cases the central lines were wider than the terminal. Thus, in 1-amino- and 2-aminothianthrene, the three central lines were 0.57 and the two terminals, 0.49 gauss. In 2,7-dichlorothianthrene, the center line was 0.98 and the terminals 0.90 gauss. The corresponding widths in 2,7-di-*t*-butylthianthrene were 0.94 and 0.86 gauss

(25) I. N. Tits-Skvortsova, A. I. Leonova, S. Ya. Levina, and E. A. Karaseva, *Sbornik Statei Obshchei Khim., Akad. Nauk SSSR*, **1**, 541 (1953).

(26) J. E. Wertz, D. C. Reitz, and F. Dravnieks, in "Free Radicals in Biological Systems," Academic Press, Inc., New York, N. Y., 1961, p. 186.

Homolytic Aromatic Substitution. III.[1,2] Meerwein Arylation of Anthracene. A General Route to 9-Aryl- and 9,10-Diarylanthracenes[2,3]

S. CARLTON DICKERMAN, ARTHUR M. FELIX, AND LEON B. LEVY

Department of Chemistry, New York University, New York 53, New York

Received July 17, 1963

Meerwein arylation of anthracene has been found to afford a general homolytic route to 9-aryl- and 9,10-diarylanthracenes. Synthetic applications are illustrated by the preparation of previously unknown nitro derivatives of 9-phenyl- and 9,10-diphenylanthracene. Factors controlling yields and the functions of the copper salts are discussed.

A recent investigation of the mechanism of the classical type of Meerwein arylation reaction[4] disclosed that substitution of chlorobenzene or nitrobenzene for the usual substrate, a monomer, resulted in the formation of mixtures of isomeric biaryls having compositions characteristic of homolytic aromatic substitution.[5] These observations not only confirmed a radical mechanism for the Meerwein reaction but also established a new method of accomplishing homolytic aromatic substitution.[6] Selection of anthracene as the substrate for this investigation was prompted by the absence of a homolytic route to arylanthracenes and by the possibility of eventually obtaining reactivity data for this typical polycyclic aromatic hydrocarbon.[7,8]

Although the low solubility of anthracene in aqueous acetone precluded concentrations much above 0.02 *M*, normal Meerwein reaction conditions were employed: an aqueous solution of the diazonium chloride was added to an acetone solution of anthracene and cupric chloride. Initial experiments with four representative diazonium cations demonstrated conclusively that both 9-aryl- and 9,10-diarylanthracenes are major products of Meerwein arylations of anthracene (Table I). Synthesis of the previously unknown 9-*p*-nitrophenylanthracene suggested similar experiments with the isomeric diazonium salts and these reactions afforded the first samples of 9-*o*- and 9-*m*-nitrophenylanthracenes (Table II). Finally, a particular Meerwein arylation reaction, *p*-nitrophenylation, was investigated in some detail (Table III). The variation in yield of 9-*p*-nitrophenylanthracene and 9,10-di-*p*-nitrophenylanthracene with initial concentrations of diazonium salt indicates that the former compound is an intermediate in the formation of the latter. Confirmatory evidence for the occurrence of consecutive reactions are the Meerwein syntheses of 9,10-diphenylanthracene and of 9-phenyl-10-*p*-nitrophenylanthracene from 9-phenylanthracene and the corresponding diazonium chlorides. All compounds prepared by the Meerwein reaction were identified by direct comparison with authentic samples or, for the nitro derivatives, by reduction and deamination to 9-phenyl- or 9,10-diphenylanthracene.

TABLE I

9-ARYL- AND 9,10-DIARYLANTHRACENES PREPARED FROM ANTHRACENE AND THE CORRESPONDING DIAZONIUM CHLORIDE BY MEERWEIN ARYLATION

Products (anthracenes)	Yield, %[a,b]
9-Phenyl-	(+)
9,10-Diphenyl-	(+)
9-*p*-Methoxyphenyl-	(+)
9,10-Di-*p*-methoxyphenyl-	18
9-*p*-Chlorophenyl-	(+)
9,10-Di-*p*-chlorophenyl-	37
9-*p*-Nitrophenyl-	11
9,10-Di-*p*-nitrophenyl-	62

[a] From 0.01 mole of anthracene and 0.10 mole of diazotized amine under standard reaction conditions; see Experimental section for details. [b] The (+) sign indicates that the specified compound was isolated.

TABLE II

9-NITROPHENYL- AND 9,10-DINITROPHENYLANTHRACENES PREPARED FROM ANTHRACENE AND THE CORRESPONDING DIAZONIUM CHLORIDE BY MEERWEIN ARYLATION

Products (anthracenes)	Yield, %[a,b]
9-*p*-Nitrophenyl-	21
9,10-Di-*p*-nitrophenyl	15
9-*m*-Nitrophenyl-	24
9,10-Di-*m*-nitrophenyl	11
9-*o*-Nitrophenyl-	(+)[b]
9,10-Di-*o*-nitrophenyl-	6

[a] From 0.01 mole of anthracene and 0.05 mole of diazotized amine under standard reaction conditions; see Experimental section for details. [b] Specified compound was isolated.

TABLE III

p-NITROPHENYLATION OF ANTHRACENE

Reactants, moles			Yield, %[a]	
Anthracene	*p*-Nitroaniline	$CuCl_2$	9-	9,10-
0.01	0.03	0.015	16	7
0.01	0.05	0.015	21	14
0.01	0.05	0.010	21	15
0.05	0.25	0.075	28	15
0.01	0.03	0.015		56,65
0.01	0.10	0.015	11	62,70

[a] Yields, based on anthracene, of 9-*p*-nitro- and 9,10-di-*p*-nitrophenylanthracenes.

Discussion

The mechanism suggested previously for the Meerwein arylation of monomers and simple arenes provides a basis for discussion of the present systems and an

(1) Paper II, S. C. Dickerman and G. B. Vermont, *J. Am. Chem. Soc.* **84**, 4150 (1962).

(2) Paper I, a preliminary report of some of these results, S. C. Dickerman, L. B. Levy, and A. W. Schwartz, *Chem. Ind.* (London), 360 (1958).

(3) Financial support in the form of Frederick Gardner Cottrell Grants from the Research Corporation is gratefully acknowledged.

(4) The Meerwein arylation reaction has been reviewed recently: C. S. Rondestvedt, Jr., *Org. Reactions*, **11**, 189 (1960).

(5) S. C. Dickerman and K. Weiss, *J. Org. Chem.* **22**, 1070 (1957).

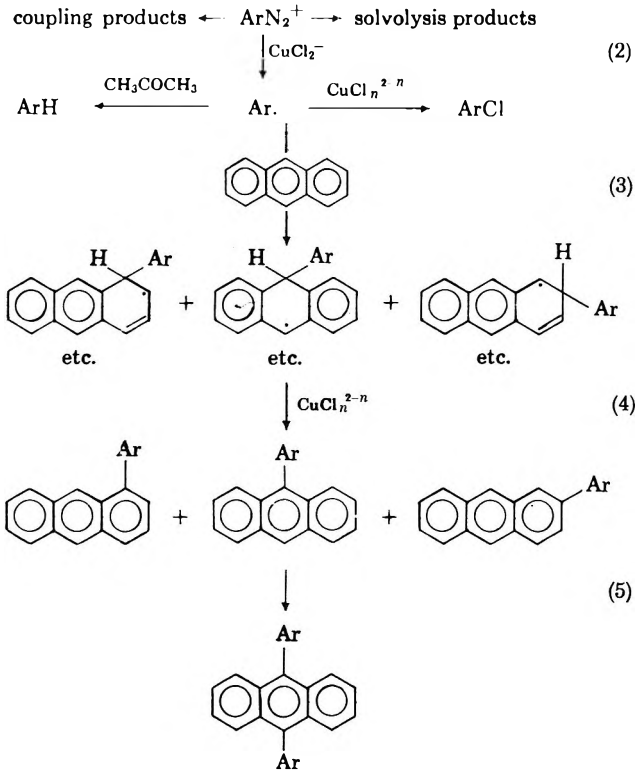
(6) For a comprehensive review of this subject, see G. H. Williams, "Homolytic Aromatic Substitution," Pergamon Press, New York, N. Y., 1960.

(7) A prior study of the arylation of anthracene by what is now termed Meerwein arylation or reactions closely related to it had given only 9,10-diaryl derivatives: A. Etienne and C. Degent, *Compt. rend.*, **236**, 92 (1953); **238**, 2093 (1954).

(8) Peroxide phenylation of anthracene had been reported to afford only benzoyloxy derivatives: I. M. Roitt and W. A. Waters, *J. Chem. Soc.*, 2695 (1952)

appropriate modification of that mechanism is presented in the accompanying equations.[9] The reagent responsible for the homolytic decomposition of the diazonium salt is a complex ion of cuprous chloride, probably the dichlorocuprate I anion, which is generated *in situ* from acetone and cupric chloride (eq. 1).[9,10] Furthermore, it is now generally recognized that the Meerwein and Sandmeyer reactions possess a common initiation step, *i.e.*, the formation of aryl radicals by an oxidation–reduction reaction involving cuprous chloride and the diazonium ion.[9-12]

$$2\ CuCl_2 + CH_3COCH_3 \rightarrow 2\ CuCl + ClCH_2COCH_3 + HCl \quad (1)$$



Solvolysis and coupling reactions, *e.g.*, formazan formation, compete with the electron-transfer reaction and may consume a significant fraction of certain diazonium salts. Once formed, the aryl radicals become involved in competitive reactions, *i.e.*, ligand transfer, hydrogen abstraction, and addition to arene or monomer. Obviously the yield in any Meerwein reaction is a complex function of a number of variables including the reactivity of the substrate. However, the yields of 9,10-diarylanthracenes under identical reaction conditions (Table I) parallel the effects of substituents on the rate of the initial electron-transfer reaction, *i.e.*, p-$NO_2 > p$-Cl $> p$-OCH_3.[13,14] This correlation indicates that the effects of substituents in the diazonium ion on the yields in these and other Meerwein arylations of a specific substrate are largely determined by the rate of formation of aryl radicals. If the electron-transfer reaction is rapid, *e.g.*, p-nitrobenzenediazonium ion, little diazonium salt is lost *via* coupling and solvolysis. Conversely, if aryl radical formation is inhibited by the substituent, *e.g.*, p-methoxy, diazonium salt will be consumed in side reactions.[15] The poor conversion of even the nitrobenzenediazonium salts to aryl- and diarylanthracenes is attributable to competing reactions involving the aryl radical and to the necessarily low concentration of anthracene in aqueous acetone.

Although 9-aryl- and 9,10-diarylanthracenes represent the major products of the reactions of aryl radicals with anthracene, the reactivity of this arene is not confined to the 9,10-positions. For example, the orientation pattern of anthracene in homolytic phenylation has been shown to comprise 84% 9, 14% 1, and 2% 2 isomer, respectively.[1] Furthermore, both o- and p-nitrophenylations of anthracene yield small amounts of the corresponding 1 and 2 isomers in addition to the 9-nitrophenylanthracene.[18] Thus, we infer that homolytic arylation of anthracene will in general afford isomeric arylanthracenes (eq. 3).

Participation by cupric copper in the reaction sequence leading to arylanthracene (eq. 4) is evidenced by the absence of detectable amounts of dimers (bianthryls) in Meerwein arylations and by previous observations that dimers are major products of the reactions of anthracene with 2-cyano-2-propyl,[19] methyl,[20] benzyl,[20] phenyl,[21] and "isocty" radicals,[22] all in the absence of copper salts. Significantly, the reactions of anthracene with phenyl radicals, generated from stabilized benzenediazonium salts with zinc dust (Waters reaction) in acetone has been reported to yield about equal amounts of 9,10-diphenylanthracene and 9,9′,10,10′-tetrahydro-10,10′-dipheny-9,9′-bianthryl; 9-phenylanthracene was not isolated although its presence during reaction was inferred from the formation of 9,10-diphenylanthracene.[21] The divergent results of Meerwein and Waters arylations of anthracene have been interpreted in terms of the nature of the metal salts present; *i.e.*, there is no evidence that zinc salts participate in either ligand or one electron-transfer reaction.[1] Therefore the concentration of intermediate and relatively stable radicals, *e.g.*, 9,10-dihydro-10-aryl-9-anthranyl, will build up to the point where dimerization and, possibly, disproportionation become important competing reactions. In the presence of cupric chloride these intermediate radicals become oxidized to the corresponding isomeric arylanthracene and thus to potential substrates for further arylation. Preferential formation of 9,10-diarylanthracenes by a repetition of the proposed sequence is

(9) S. C. Dickerman, K. Weiss, and A. K. Ingberman, *J. Org. Chem.*, **21**, 380 (1956); *J. Am. Chem. Soc.*, **80**, 1904 (1958).

(10) J. K. Kochi, *ibid.*, **77**, 5094, 5274 (1958).

(11) D. C. Nonhebel and W. A. Waters, *Proc. Roy. Soc.* (London) **A 242**, 16 (1957).

(12) The mechanism of the Sandmeyer and Meerwein reactions has been reviewed by H. Zollinger, "Diazo and Azo Chemistry," Interscience Publishers, Inc., New York, N. Y., 1961, pp. 162–168.

(13) W. A. Coudrey and D. C. Davies, *J. Chem. Soc.*, S 48 (1949).

(14) These 9,10-diarylanthracenes are virtually insoluble in the reaction medium.

(15) The effect of the p-methoxy group is interesting in that p-methoxybenzenediazonium ion undergoes electron-transfer,[13] solvolysis,[16] and coupling[17] reactions less readily than the unsubstituted diazonium cation. In Meerwein p-methoxyphenylations of anthracene the slow disappearance of the diazonium salt, about 48 hr., is accompanied by the formation of products that impart an intense red color to the solutions. Presumably, formazan and/or diazo resin are produced.

(16) M. L. Crossley, R. H. Kienle, and C. H. Benbrook, *J. Am. Chem. Soc.*, **62**, 1400 (1940).

(17) J. B. Conant and W. D. Peterson, *ibid.*, **52**, 1220 (1930).

(18) S. C. Dickerman and M. Klein, unpublished results.

(19) A. R. Bickel and E. C. Kooyman, *Rec. trav. chim.*, **71**, 1137 (1952).

(20) A. L. J. Beckwith and W. A. Waters, *J. Chem. Soc.*, 1008 (1956); 1001 (1957).

(21) R. O. C. Norman and W. A. Waters, *ibid.*, 167 (1958).

(22) A. L. J. Beckwith, *ibid.*, 2248 (1962).

a direct consequence of the initial orientation which strongly favors the 9 isomers.[23]

Although Meerwein arylation provides a general route to 9-aryl- and 9,10-diarylanthracenes, its synthetic utility is impaired by the concurrent formation of isomeric products. For this reason alone it does not present an attractive alternative for those compounds that have or may be prepared by classical methods, *e.g.*, the addition of organometallics to 9-anthrone or 9,10-anthraquinone followed by aromatization. However, homolytic arylation is at present the only route to mono- and dinitrophenyl derivatives of anthracene and, therefore, to a variety of previously unknown compounds.[24]

Experimental[25]

Reagents.—Eastman Kodak anthracene (480), Aldrich 9-phenylanthracene, and Merck alumina were used.

General Procedure for Meerwein Arylation of Anthracene.—A solution of 1.78 g. (0.01 mole) of anthracene and 2.55 g. (0.015 mole) of cupric chloride dihydrate in a mixture of 400 ml. of acetone and 40 ml. of water was prepared in a three-necked flask fitted with a sealed stirrer, a condenser, and a pressure-equalizing addition funnel. The condenser was attached to a simple gas buret and the apparatus was flushed with nitrogen or carbon dioxide. A solution of the diazonium salt, prepared from 0.05 mole of amine, 0.05 mole of sodium nitrite in 15 ml. of water, and 25 ml. of 6 *N* hydrochloric acid and filtered when necessary, was added rapidly and with vigorous stirring to the contents of the flask. The evolution of nitrogen varied from rapid and virtually quantitative for the nitrobenzenediazonium chlorides to slow and incomplete for diazotized *p*-anisidine. In any event, the reaction mixture was maintained at about 35° until the evolution of nitrogen ceased. After refrigeration overnight, any precipitate of diarylanthracene was collected by filtration and the filtrate was steam distilled. Experiments that involved smaller or larger amounts of diazonium salts were modified so that the total volume of water was 100 ml. for the former and 100–120 ml. for the latter. Reactions with larger amounts of anthracene represent simple multiples of these "standard conditions."

Phenylation of Anthracene.—The addition of 0.01 mole of diazotized aniline failed to yield a precipitate and the residue from steam distillation was dissolved in benzene. This extract was washed with dilute sodium hydroxide and water, dried, and chromatographed on alumina. The first five fractions off the column were combined and fractionally recrystallized from 1:1 benzene–ethanol to yield 9,10-diphenylanthracene of m.p. 244–248° (lit.[26] 249–250°). Addition of authentic 9,10-diphenylanthracene did not depress the melting point and the infrared spectra of the two samples were essentially identical.

The various solids and mother liquors from the fractional crystallization were combined and the solvents were removed under reduced pressure. The residue was dissolved in hexane chromatographed on alumina using hexane as developer and eluent. Fraction 3 off the column was recrystallized from ethanol and the first crop of crystals, mostly anthracene, was discarded. The second crop of crystals was recrystallized three times from ethanol and afforded 9-phenylanthracene, m.p. 149.5–150.5° (lit.[27] 152–153°). Addition of authentic 9-phenylanthracene did not depress the melting point and the infrared spectra of the two samples were virtually identical.

p-**Methoxyphenylation of Anthracene.**—Decomposition of the diazonium salt from 0.10 mole of diazotized *p*-anisidine gave 0.72 g. (18%) of product. Several recrystallizations from benzene afforded a sample of 9,10-di-*p*-methoxyphenylanthracene, m.p. 282–284° (lit.[26] 282°). Addition of authentic 9,10-di-*p*-methoxyphenylanthracene (m.p. 285–286°), prepared by the procedure of Ingold and Marshall,[26] did not depress the melting point and the infrared spectra of the two samples were virtually identical.

The residue after steam distillation was chromatographed in benzene on alumina and the colorless solids off the column were rechromatographed using hexane and alumina. The middle fraction off the column afforded a solid which was recrystallized several times from ethanol to give 9-*p*-methoxyphenylanthracene, m.p. 168–169° (lit.[28] 168.0–168.5°). Addition of authentic 9-*p*-methoxyphenylanthracene, prepared from 9-anthrone and *p*-methoxyphenyl lithium, did not depress the melting point and the infrared spectra of the two samples were identical.

p-**Chlorophenylation of Anthracene.**—Decomposition of the diazonium chloride from 0.01 mole of *p*-chloroaniline gave 1.46 g. (37%) of pale yellow needles, m.p. 288–305°. Several recrystallization from benzene–ethanol raised the melting point to 313–314° (lit.[26] 311°). Addition of an authentic sample of 9,10-di-*p*-chlorophenylanthracene[28] did not depress the melting point and the infrared spectra of the two samples were virtually identical.

Chromatography of the tarry residue from the steam distillation in hexane on alumina gave anthracene followed by colorless crystals, m.p. 168–174°. Recrystallization from a 4:1 mixture of acetone and water afforded 9-*p*-chlorophenylanthracene, m.p. 176.5–178.5° (lit.[29] 179–180°). Addition of authentic 9-*p*-chlorophenylanthracene, prepared from 9-anthrone and *p*-chlorophenylmagnesium bromide, did not depress the melting point and the infrared spectra of the two samples were essentially identical.

p-**Nitrophenylation of Anthracene.**—Addition and decomposition of a solution of *p*-nitrobenzenediazonium chloride from 0.10 mole of amine gave 2.17 g. (62%) of yellow solid. After recrystallization from pyridine, 9,10-di-*p*-nitrophenylanthracene was isolated as yellow needles, m.p. >400°, with decomposition (lit.[7] 457°).

Steam distillation of the reaction mixture followed by chromatography of the residue on alumina in a 1:1 mixture of hexane–benzene yielded 9-*p*-nitrophenylanthracene contaminated with *p*-chloronitrobenzene. Sublimation removed the latter compound leaving 0.320 g. (11%) of product. An analytical sample, bright yellow plates, m.p. 229–230°, was prepared by recrystallization from 1:1 benzene–ethanol.

Anal. Calcd. for $C_{20}H_{13}NO_2$: C, 80.25; H, 4.38; N, 4.68. Found: C, 80.29; H, 4.76; N, 4.57.

m-**Nitrophenylation of Anthracene.**—Decomposition of 0.05 mole of diazotized *m*-nitroaniline followed by concentration of the reaction mixture to three-quarters of the original volume gave 0.457 g. (11%) of pale yellow solid, m.p. 320–330°, with decomposition. Recrystallization from pyridine afforded 9,10-di-*m*-nitrophenylanthracene as off-white microcrystals, m.p. 344–345°.

Anal. Calcd. for $C_{26}H_{16}N_2O_4$: C, 74.28; H, 3.84; N, 6.66. Found: C, 74.05; H, 4.16; N, 6.91.

The remainder of the reaction mixture was processed in the usual manner and yielded 0.712 g. (24%) of 9-*m*-nitrophenylanthracene. Two recrystallizations from ethanol afforded an analytical sample of yellow plates or needles, m.p. 158–159°.

Anal. Calcd. for $C_{20}H_{13}NO_2$: C, 80.25; H, 4.38; N, 4.68. Found: C, 80.41; H, 4.43; N, 4.98.

o-**Nitrophenylation of Anthracene.**—Addition and decomposition of a solution of *o*-nitrobenzenediazonium chloride prepared from 0.05 mole of amine gave 0.257 g. (6%) of precipitate. After recrystallization from pyridine, 9,10-di-*o*-nitrophenylanthracene was isolated as yellow plates, m.p. 400°, with decomposition (lit.[7] 425°).[30]

Chromatography of the residue from steam distillation on alumina using 1:1 hexane–benzene gave a mixture of compounds

(23) Small amounts of what appear to be isomeric di-*p*-nitrophenylanthracenes and of a tri-*p*-nitrophenylanthracene have been isolated from Meerwein *p*-nitrophenylation of anthracene: S. C. Dickerman and A. A. Felix, unpublished results.

(24) For example, all structurally isomeric 9,10-dinitrophenylanthracenes and 9-methoxyphenyl-10-nitrophenylanthracenes have now been synthesized by Meerwein arylation: S. C. Dickerman, M. Klein, and G. B. Vermont, unpublished results.

(25) All melting points below 350° are corrected. The infrared spectra were determined with a Baird Model 4-55 spectrophotometer using potassium bromide wafers. The microanalyses were performed by the Schwartzkopf Microanalytical Laboratory, Woodside 77, N. Y.

(26) C. K. Ingold and P. G. Marshall, *J. Chem. Soc.*, 3080 (1926).

(27) P. L. Julian, W. Cole, G. Diemer, and J. G. Schafer, *J. Am. Chem. Soc.*, **71**, 2060 (1949).

(28) C. K. Bradsher and E. Faye Sinclair, *J. Org. Chem.*, **22**, 79 (1957).

(29) C. K. Bradsher and F. A. Vingiello, *J. Am. Chem. Soc.*, **71**, 1434 (1949).

(30) It is presumed that 9,10-di-*o*-nitrophenylanthracene can exhibit configurational isomerism due to restricted rotation. However, the configuration of the isolated compound has not been established.

from which 9-*o*-nitrophenylanthracene was isolated as yellow coralloid crystals or needles, m.p. 150–151°, by repeated recrystallizations from cyclohexane.

Anal. Calcd. for $C_{20}H_{13}NO_2$: C, 80.25; H, 4.38; N, 4.68. Found: C, 80.45; H, 4.42; N, 4.79.

Reduction and Deamination of Nitrophenylanthracenes and Dinitrophenylanthracenes.—A solution or a suspension of 0.150 g. (0.005 mole) of the nitro or 0.210 g. (0.005 mole) of the dinitro compound in glacial acetic acid was treated with 0.791 g. or 1.582 g. of stannous chloride dihydrate and 0.5–1.0 ml. of concentrated hydrochloric acid. The mixture was heated on the steam bath with stirring until the characteristic yellow color of the nitro compound disappeared and then was concentrated under reduced pressure. The residue was digested with 5–10 ml. of concentrated hydrochloric acid and the solid was removed by filtration and diazotized in 5–10 ml. of 50% hypophosphorous acid.[31] After standing overnight, the reaction mixture was extracted with benzene and the extracts were concentrated and dried by distillation. Chromatography on alumina using hexane or a mixture of hexane and benzene gave the corresponding hydrocarbon. The yields of 9-phenylanthracene were 26% for the *ortho* isomer, 56% for the *meta*, and 15% for the *para* isomer while the yields of 9,10-diphenylanthracene amounted to 6%, 64% and 57% for the *ortho*, *meta*, and *para* isomers, respectively. After a single recrystallization, identity was established by mixture melting points and by comparison of the infrared spectra of authentic 9-phenyl- and 9,10-diphenylanthracene with those of the experimental samples.

Phenylation of 9-Phenylanthracene.—Ten milliliters of an aqueous solution of benzenediazonium chloride prepared in the usual manner from aniline (0.700 g., 0.0075 mole) was added with stirring to a solution of 0.254 g. (0.001 mole) of 9-phenylanthracene and 0.170 g. (0.001 mole) of cupric chloride dihydrate in 40 ml. of acetone. Decomposition of the diazonium salt was accompanied by precipitation of a crystalline solid. After 2 hr. at 35°, the reaction mixture was cooled and 0.083 g. (25%) of 9,10-diphenylanthracene, m.p. 246–248° (lit.[26] 249–250°), was isolated by filtration. Identity was confirmed in the manner described previously.

***p*-Nitrophenylation of 9-Phenylanthracene.**—An aqueous solution of *p*-nitrobenzenediazonium chloride, prepared in the usual manner from 4.14 g. (0.03 mole) of *p*-nitroaniline and diluted with water to a volume of 100 ml., was added with stirring to 2.54 g. (0.01 mole) of 9-phenylanthracene and 2.55 g. (0.015 mole) of cupric chloride dihydrate dissolved in 400 ml. of acetone. Decomposition of the diazonium salt afforded 2.04 g. (54%) of yellow solid, m.p. 282–290°. Recrystallization from benzene–ethanol gave yellow plates of 9-*p*-nitrophenyl-10-phenylanthracene, m.p. 296–297°.

Anal. Calcd. for $C_{26}H_{17}NO_2$: C, 83.18; H, 4.57; N, 3.73. Found: C, 83.01; H, 4.67; N, 3.59.

Reduction, diazotization, and deamination of 0.300 g. (0.001 mole) of 9-*p*-nitrophenyl-10-phenylanthracene by the procedure described afforded 0.118 g. (58%) of 9,10-diphenylanthracene, m.p. 250–252° (lit.[26] 249–250°). Identity was confirmed by the usual methods.

(31) N. Kornblum and D. C. Iffland, *J. Am. Chem. Soc.*, **71**, 2137 (1949).

Rearrangement of the 1,2,2-Triphenylethyl Radical

WILLIAM A. BONNER AND FRANK D. MANGO[1]

Department of Chemistry, Stanford University, Stanford, California

Received July 22, 1963

2,3,3-Triphenylpropionaldehyde has been prepared by the lithium aluminum hydride reduction of *N*-(2,3,3-triphenylpropionyl)azridine. The *t*-butyl peroxide-catalyzed decarbonylation of this aldehyde in *o*-dichlorobenzene solvent at 155–185° yielded monomeric products (15%), consisting of 1,1,2-triphenylethane (95%) and triphenylethylene (5%), and a dimeric product (85%) whose infrared and n.m.r. spectra were in accord with those of 1,1,2,3,4,4-hexaphenylbutane. When the decarbonylation was conducted in the presence of thiophenol the yield of monomeric products increased to 37% and that of the dimeric product decreased to 22%. Uniquely labeled 2,3,3-triphenylpropionaldehyde-2-C^{14} was decarbonylated under similar conditions (thiophenol) and at several temperatures. Permanganate oxidation (not attended by subsequent phenyl migration) of the labeled 1,1,2-triphenylethane products afforded benzophenone samples whose radioactivity assays indicated that the intermediate 1,2,2-triphenylethyl radical had undergone 5% phenyl migration during decarbonylation at 155–165° and 14% at 176–184°. Subjection of 1,2,2-triphenylethane-1-C^{14} to the conditions of decarbonylation at 155–165° and 176–184° yielded samples of starting material, oxidative degradation of which indicated that 2.1% phenyl migration had occurred at the lower and 2.5% at the higher temperature. The oxidation of 1,2,2-triphenylethane-1-C^{14} to benzophenone using chromic oxide was attended by about 10% phenyl migration. Application of this degradation to the labeled 1,1,2-triphenylethane and 1,1,2,3,4,4-hexaphenylbutane products from the decarbonylation of 2,3,3-triphenylpropionaldehyde-2-C^{14} afforded benzophenone samples having identical radioactivity assays, suggesting that equivalent extents of phenyl migration had attended the oxidation of each hydrocarbon. The observed phenyl 1,2-rearrangement in the 1,2,2-triphenylethyl radical provides the second example of a radical 1,2-shift which is *not* accompanied by the formation of a more stable radical intermediate or by the relief of steric compression on the carbon atom adjacent to the radical site. The application of these techniques to the question of nonclassical, bridged radical intermediates is discussed.

Intramolecular rearrangements during free-radical reactions are neither so plentiful nor so extensively studied as those occurring during carbonium ion reactions. Several investigators have documented the tendency of 2-arylethyl radicals to undergo varying extents of aryl 1,2-migration, whether the radicals were produced by the action of cobaltous chloride and Grignard reagents on β-arylalkyl halides,[2-4] by the peroxide-catalyzed decarbonylation of β-arylpropionaldehydes,[5-11] by the thermal decomposition of 2-arylethylazo derivatives,[12,13] during the addition of thiol com-

(1) The authors are indebted to the National Science Foundation for a grant (G9479) which supported a portion of this investigation.

(2) W. H. Urry and M. S. Kharasch, *J. Am. Chem. Soc.*, **66**, 1438 (1944).

(3) W. H. Urry and N. Nicolaides, *ibid.*, **74**, 5163 (1952).

(4) W. B. Smith and J. D. Anderson, *ibid.*, **82**, 656 (1960).

(5) S. Winstein and F. M. Seubold, Jr., *ibid.*, **69**, 2916 (1947).

(6) D. Y. Curtin and M. J. Hurwitz, *ibid.*, **74**, 5381 (1952).

(7) F. M. Seubold, Jr., *ibid.*, **75**, 2532 (1953).

(8) L. M. Slaugh, *ibid.*, **81**, 2262 (1959).

(9) D. Y. Curtin and J. C. Kauer, *J. Org. Chem.*, **25**, 880 (1960).

(10) J. W. Wilt and M. Philip, *ibid.*, **25**, 891 (1960).

(11) C. Rüchardt, *Ber.*, **94**, 2609 (1961).

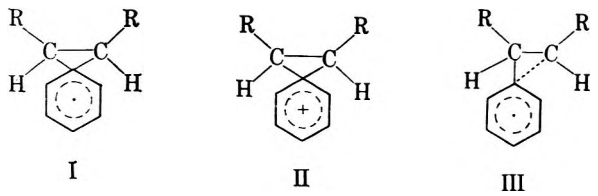
(12) C. G. Overberger and H. Gainer, *J. Am. Chem. Soc.*, **80**, 4556, 4561 (1958).

(13) D. Y. Curtin and T. C. Miller, *J. Org. Chem.*, **25**, 885 (1960).

pounds to α-arylalkenes,[14] by the peroxide-catalyzed β-hydrogen abstraction from alkylbenzenes,[15] during the high-pressure thermal alkylations of monoalkylbenzenes with olefins,[16] or by heating alkylbenzenes with halogen- or sulfur-containing promotors.[17] Aryl migrations involving 1,5-[18,19] and 1,6-interactions[19] also have been reported. Analogous alkyl 1,2-shifts have apparently never been clearly observed,[20] and hydrogen 1,2-shifts have been shown specifically not to occur in systems involving 2-arylethyl[8,9,20] as well as other[21-23] radical intermediates.

All but one of the reported 2-arylethyl radical rearrangements have involved systems where the rearranged radical is more stable than its unrearranged precursor, or where steric compression on the β-carbon is relieved during the migration process. That such factors are not prerequisites for aryl migration, however, has been convincingly demonstrated by Slaugh,[8] who found that the 2-phenylethyl-1-C^{14} radical rearranged to the 2-phenylethyl-2-C^{14} radical to the extent of 2.3–5.1% before its final conversion to ethylbenzene. Here the rearranged radical and its precursor have identical steric and stability features, and the phenyl migration must be determined only by the intrinsic tendency of the 2-phenylethyl radical to rearrange and by its lifetime as an intermediate. That 2-alkylethyl radicals fail to rearrange[3,6,20] further supports the contention that steric and stability factors alone are not definitive in engendering such 1,2-migrations.

The exclusive occurrence of aryl (as opposed to alkyl) 1,2-rearrangements of radicals has been explained by several investigators[3,4,7,8,10-12,15,17] in terms of resonance-stabilized bridged radical intermediates such as I, analogous to the widely postulated "symmetrical phenonium ion" (II). Overberger and Gainer,[12] studying neophyl radicals generated from azo compounds, provided evidence against phenyl participation in the rate-determining step of radical formation. Seubold[7] has argued against bridged radicals on grounds that the phenyl migration observed during decarbonylation of β-phenylisovaleraldehyde increased under conditions of dilution with an inert[24] solvent. Smith and Anderson,[4] on the other hand, proposed the intervention of unsymmetrically bridged 2-phenylethyl radicals (III, analogous, presumably, to "unsymmetrical phenonium ions")[25-27] in their studies with 2-phenylethyl-1-C^{14} radicals generated by action of Mg–$CoCl_2$ on 2-phenylethyl-1-C^{14} bromide, and Rüchardt[11] has argued for bridged intermediates to rationalize relative migration tendencies within *p*-substituted neophyl radicals. A recent physical organic textbook[28] argues in favor of bridged radical intermediates, and it has been recently stated[4] that "Until the appearance of. . .(stereoselectivity). . .data the question of a bridged free radical must be considered unsolved."



I II III

Some time ago we examined certain solvolytic[29] and deamination[30] reactions of 1,2,2-triphenylethyl derivatives to test the general concept of bridged phenonium ions in carbonium ion reactions. Using double-labeling techniques, it was found that cationic processes in this system proceeded *via* equilibrating classical carbonium ions (IV) and not through bridged phenonium ions of type II (R = Ph), despite the marked stereoselectivity[31,32] observed in many of these reactions. The nonambiguity of the double-labeling criterion compared

$$Ph_2CH-\overset{\oplus}{C}HPh \rightleftharpoons \overset{\oplus}{P}hCH-CHPh_2$$

IV

with the stereochemical criterion for bridged intermediates has suggested the desirability of investigating the possible existence of bridged 1,2,2-triphenylethyl radicals (I, R = Ph) by similar techniques. Preliminary studies in this direction are described subsequently.

Discussion

In view of the wide applicability of aldehyde decarbonylation as a means of generating free radicals, the decarbonylation of 2,3,3-triphenylpropionaldehyde appeared potentially capable of providing the desired 1,2,2-triphenylethyl radical intermediate. This aldehyde, m.p. 109–111°, proved accessible from the known[33,34] 2,3,3-triphenylpropionic acid *via* the sequence of reactions[35]: 2,3,3-triphenylpropionyl chloride (m.p. 96–98°) + ethyleneimine → *N*-(2,3,3-triphenylpropionyl)aziridine (m.p. 186.5–187.5°) $\xrightarrow{LiAlH_4}$ 2,3,3-triphenylpropionaldehyde. Furthermore, since the uniquely labeled 2,3,3-triphenylpropionic-2-C^{14} acid can be readily prepared,[34] a precursor was available for the synthesis of 2,3,3-triphenylpropionaldehyde-2-C^{14}, a labeled analog potentially capable of generating the 1,2,2-triphenylethyl-1-C^{14} radical (Va), whose possible rearrangement (eq. 1) might be studied by previously employed techniques.

(14) J. Weinstock and S. N. Lewis, *J. Am. Chem. Soc.*, **79**, 6243 (1957).
(15) H. Pines and C. N. Pillai, *ibid.*, **81**, 3629 (1959); **82**, 2921 (1960).
(16) H. Pines and J. T. Arrigo, *ibid.*, **79**, 4958 (1957).
(17) L. H. Slaugh and J. H. Raley, *ibid.*, **82**, 1259 (1960); **84**, 2640 (1962).
(18) D. F. DeTar and A. Hlynsky, *ibid.*, **77**, 4411 (1955).
(19) S. Winstein, R. Heck, S. Lapporte, and R. Baird, *Experientia*, **12**, 138 (1956).
(20) C. Walling, "Molecular Rearrangements. Part I," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 417 ff.
(21) N. Kornblum and E. P. Oliveto, *J. Am. Chem. Soc.*, **71**, 226 (1949).
(22) N. Kornblum and H. E. De La Mare, *ibid.*, **74**, 3079 (1952).
(23) H. C. Brown and G. A. Russel, *ibid.*, **74**, 3995 (1952).
(24) E. R. Bell, J. H. Raley, F. F. Rust, F. H. Seubold, Jr., and W. E. Vaughan, *Discussions Faraday Soc.*, **No. 10**, 242 ff. and 315 (1951).
(25) J. D. Roberts and C. M. Regan, *J. Am. Chem. Soc.*, **75**, 2069 (1953).
(26) S. Winstein, M. Brown, K. C. Schreiber, and A. H. Schlesinger, *ibid.*, **74**, 1140 (1952).
(27) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *ibid.*, **74**, 1113 (1952).
(28) J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 482.
(29) W. A. Bonner and C. J. Collins, *ibid.*, **75**, 5372 (1953); **78**, 5587 (1956); C. J. Collins and W. A. Bonner, *ibid.*, **77**, 92 (1955).
(30) W. A. Bonner and C. J. Collins, *ibid.*, **78**, 5587 (1956); W. A. Bonner and T. A. Putkey, *J. Org. Chem.*, **27**, 2348 (1962).
(31) C. J. Collins, W. A. Bonner, and C. T. Lester, *J. Am. Chem. Soc.*, **81**, 466 (1959).
(32) C. J. Collins, J. B. Christie, and V. F. Raaen, *ibid.*, **83**, 4267 (1961).
(33) E. P. Kohler and G. Heritage, *Am. Chem. J.*, **33**, 156 (1905).
(34) W. A. Bonner, *J. Am. Chem. Soc.*, **81**, 1181 (1959).
(35) H. C. Brown and A. Trukamoto, *ibid.*, **83**, 4549 (1961).

$$\underset{\text{Va}}{Ph_2CH-{}^{14}\dot{C}HPh} \xrightarrow{Ph\sim} \underset{\text{Vb}}{Ph\dot{C}H-C^{14}HPh_2} \quad (1)$$

When 2,3,3-triphenylpropionaldehyde was decarbonylated by heating (170°) in *o*-dichlorobenzene solvent in the presence of *t*-butyl peroxide, gas was evolved and two crystalline substances were obtained by chromatographic separation of the crude reaction product. The minor product (15%) proved to be a mixture of monomeric derivatives, 1,1,2-triphenylethane (VI, *ca.* 95%) and triphenylethylene (*ca.* 5%). The major product (85%) had the constitution of a "dimeric" hexaphenylbutane derivative, and its infrared and n.m.r. spectra were consistent with the 1,1,2,3,4,4-hexaphenyl isomer (VII).

$$\underset{\text{VI}}{Ph_2CH-CH_2Ph} \qquad \underset{\text{VII}}{Ph_2CH-\overset{Ph}{\overset{|}{C}}H-\overset{Ph}{\overset{|}{C}}H-CHPh_2}$$

The results of the decarbonylation may be interpreted in terms of the following steps[36] (eq. 2–9).

$$t\text{-}Bu_2O_2 \longrightarrow 2t\text{-}BuO\cdot \quad (2)$$

$$t\text{-}BuO\cdot \longrightarrow Me\cdot + Me_2CO \quad (3)$$

$$RCH{=}O + t\text{-}BuO\cdot \longrightarrow R-\dot{C}{=}O + t\text{-}BuOH \quad (4)$$

$$RCH{=}O + Me\cdot \longrightarrow R-\dot{C}{=}O + CH_4 \quad (5)$$

$$R-\dot{C}{=}O \longrightarrow R\cdot + CO \quad (6)$$

$$R\cdot + RCH{=}O \longrightarrow VI + R-\dot{C}{=}O \quad (7)$$

$$2R\cdot \longrightarrow VI + Ph_2C{=}CHPh \quad (8)$$

$$2R\cdot \longrightarrow VII \quad (9)$$

$$R = Ph_2CH-\overset{|}{C}HPh$$

The low yield of monomeric hydrocarbon VI was somewhat surprising, suggesting a high activation energy for step 7 and indicating that the majority of acyl radicals must here be formed by steps 4 and 5.

In view of this low yield of monomeric product VI and our inability (see following) to find a means of degrading the dimeric product VII without further phenyl rearrangement, we sought a means of increasing the yield of VI. The ability of mercaptans to catalyze aldehyde decarbonylations was first demonstrated by Waters,[37] who rationalized this observation in terms of the chain sequence 10, 11, and 12.

$$R'S\cdot + RCH{=}O \longrightarrow R'SH + R-\dot{C}{=}O \quad (10)$$

$$R-\dot{C}{=}O \longrightarrow R\cdot + CO \quad (11)$$

$$R\cdot + R'SH \longrightarrow RH + R'S\cdot \quad (12)$$

Additionally, chain transfer constants for mercaptans[38,39] in the polymerization of styrene are much greater than those for aldehydes,[40] suggesting that mercaptans donate hydrogen to free radicals (eq. 12) more readily than do aldehydes. While this latter factor is capable of reducing the lifetime of free-radical intermediates and hence curtailing aryl 1,2-migration,[8] decarbonylation in the presence of mercaptans nevertheless appeared promising as a means of increasing the yield of 1,1,2-triphenylethane in the present case. When 2,3,3-triphenylpropionaldehyde was decarbonylated in the presence of benzyl mercaptan (5 mole %) the yield of monomeric hydrocarbons increased 3-fold and the yield of the dimeric product VII decreased from 73 to 22%. An even greater enhancement of monomer yield (37%) occurred using thiophenol. Variation in aldehyde concentration had little effect on monomer yield (37–42%), and 1,1,2-triphenylethane again proved to be the principal component (*ca.* 75%) of the monomer mixture.

To assay phenyl migration in the 1,2,2-triphenylethyl radical, a means for degrading the hydrocarbon products VI and VII into benzophenone without subsequent rearrangement was required. Direct oxidation of VI with potassium permanganate has been shown to proceed without rearrangement.[34] Permanganate oxidation of the dimeric product VII, however, proved ineffectual, as did several other degradative techniques. Oxidation of VII with chromic oxide–acetic acid afforded benzophenone in low yield, but was found to proceed with 10% phenyl migration when applied to 1,1,2-triphenylethane-2-C^{14}. Our studies of the phenyl migration occurring prior to the formation of VII accordingly have an uncertainty due to possible phenyl rearrangement during its subsequent degradation to benzophenone.

The decarbonylation in the presence of thiophenol of 2,3,3-triphenylpropionaldehyde-2-C^{14} afforded the usual mixture of hydrocarbon products (Chart I). The

CHART I

$$Ph_2CH-C^{14}H-CH{=}O$$
$$\overset{|}{Ph}$$
1.201 ± 0.008 mc./mole

$Ph_2C^{14}H-C^{14}H_2Ph$	$Ph_2C^{14}H-C^{14}H(Ph)-C^{14}H(Ph)-C^{14}HPh_2$
1.163 ± 0.006 mc./mole[a]	2.42 ± 0.05 mc./mole[a]
1.178 ± 0.008 mc./mole[b]	2.43 ± 0.02 mc./mole[b]

[a] Experiment 1 [b] Experiment 2.

slight difference (*ca.* 3%) in the specific radioactivities of the monomeric hydrocarbon product and the starting aldehyde suggest a normal isotope effect during the abstraction step (12). Oxidation with permanganate of the 1,1,2-triphenylethane products from similar decarbonylations afforded benzophenone derivatives whose radioactivity assays indicated (Table I) that 4.9% (corrected, following) phenyl migration had occurred during the lifetime of the intermediate triphenylethyl radical when the decarbonylation was conducted at 155–165°, and 13.9% (corrected) rearrangement had occurred at 176–184°. We have no similar data regarding concomitant hydrogen migration within the present 1,2,2-triphenylethyl radical, but on the basis of earlier studies[8,9,21–23] we assume it is negligible in the present case. 1,1,2-Triphenylethane-2-C^{14} itself, when subjected to these conditions of the decarbonylation, was found to undergo 2.1% rearrangement at the lower temperature and 2.5% at the higher temperature. This phenyl migration, which has been subtracted from the total in the figures quoted earlier, apparently re-

(36) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 278, 469.
(37) E. F. P. Harris and W. H. Waters, *Nature*, **170**, 211 (1952).
(38) C. Walling, *J. Am. Chem. Soc.*, **70**, 2561 (1948).
(39) R. A. Gregg, F. R. Alderman, and F. R. Mayo, *ibid.*, **70**, 3740 (1948).
(40) R. A. Gregg and F. R. Mayo, *ibid.*, **75**, 3530 (1953).

sults from the generation of 1,2,2-triphenylethyl radicals by a displacement reaction involving either RS· or *t*-BuO· radicals (eq. 13). A similar displacement

$$Ph_2CHCH_2PH + RS\cdot \text{ (or } t\text{-BuO}\cdot) \longrightarrow Ph_2\dot{C}HCHPh + RSH \text{ (or t-BuOH)} \quad (13)$$

reaction has been reported by Wang and Cohen.[41] Our finding of up to 14% phenyl migration, even in the presence of thiophenol,[8] in the case of the 1,2,2-triphenylethyl radical confirms the disclosure of Slaugh[8] that radical stability factors and relief of steric strain are not uniquely important in determining free radical rearrangements. It is interesting that our rearrangement involved a more stable and presumably longer lived secondary benzyl radical, whereas Slaugh's example involved a less stable, shorter lived primary 2-phenylalkyl radical. The greater extent of phenyl migration in our radical intermediate appears to be a logical consequence of its longer lifetime.

Degradation (chromic oxide–acetic acid) of the dimeric hexaphenylbutane products (VII) from similar decarbonylations of 2,3,3-triphenylpropionaldehyde-2-C^{14} revealed similar extents of phenyl migration to those observed when the monomeric products from the same reactions were similarly degraded (Table III). If one assumes identical extents of phenyl migration (and, therefore, lifetimes) for 1,2,2-triphenylethyl radicals following either the dimerization path (eq. 9), the disproportionation path (eq. 8), or hydrogen abstraction paths (eq. 7, 12), these results suggest that the chromic oxide–acetic acid oxidations of both hydrocarbons VI and VII were attended by identical extents of subsequent phenyl rearrangement. We are aware of no other reported instances of phenyl migration during a chromic oxide–acetic acid oxidation.

Having now established the occurrence of significant phenyl 1,2-migration during the lifetime of the 1,2,2-triphenylethyl radical, we presently hope to examine the possibility of nonclassical bridged radical intermediates in this system by employing our previous double-labeling techniques.

Experimental

2,3,3-Triphenylpropionic Acid.—The crude acid was prepared *via* the action of phenylmagnesium bromide on methyl α-phenylcinnamate in the manner previously described,[34] m.p. 212–214°, lit.[34] m.p. 220.5°.

2,3,3-Triphenylpropionyl Chloride.—A mixture of thionyl chloride (200 g.), benzene (25 ml.), and the prior 2,3,3-triphenylpropionic acid (20 g.) was heated under reflux for 1 hr., then stripped of volatile components under reduced pressure. The resulting pale yellow oil crystallized on standing and was recrystallized from hexane to yield 17 g. (80%) of rectangular prisms. Three additional recrystallizations afforded the pure acid chloride, m.p. 96–98°.

Anal. Calcd. for $C_{21}H_{17}OCl$: C, 78.62; H, 5.34. Found: C, 78.46; H, 5.38.

N-(2,3,3-Triphenylpropionyl)aziridine.—The procedure employed was adapted from that of Brown and Trukamoto.[35] The prior acid chloride (2.83 g.) in benzene (50 ml.) was stirred dropwise over a period of 30 min. into an ice-cooled ether–benzene (1:1, 50 ml.) solution of triethylamine (1.8 ml.) and ethyleneimine (1.0 ml.). Stirring was continued at 0° for 30 min., then at room temperature for 30 min., whereupon the amine hydrochloride precipitate was filtered and washed with hot acetone. Solvent evaporation from the combined filtrates and washings yielded 3.2 g. of white solid. A portion (1 g.) of the crude product was chromatographed on 50 g. of acid-washed silica, using ether–hexane (1:10) as eluent. Evaporation of the of eluent left 0.54 g. of white solid, fraction A. The n eluent yielded 0.37 g. of white solid, fraction B.

The infrared spectrum of fraction A showed a sharp bending frequency at 1474 cm.$^{-1}$, characteristic of azir. derivatives.[42] The spectrum showed no N–H stretching quencies expected for primary and secondary amides (310 3600 cm.$^{-1}$),[43] but displayed a strong carbonyl absorption band a 1676 cm.$^{-1}$. The n.m.r. spectrum of fraction A showed a octet of bands centered at 1.85, a quartet of bands (4.4 4.65, 4.76 and 5.95) centered at 4.95, and a complex bands between 7.0 and 7.5 p.p.m. Their relative intensities were consistent with the *N*-(2,3,3-triphenylpropionyl)-aziridine structure, octet–quartet–complex (2:1:8). After two recrystallizations from a mixture of benzene and pentane, pure *N*-(2,3,3-triphenylpropionyl)aziridine was obtained, m.p. 186.5–187.5°.

Anal. Calcd. for $C_{23}H_{21}ON$: C, 84.37; H, 6.47. Found: C, 84.56; H, 6.70.

The infrared spectrum of fraction B showed a sharp absorption at 3310, the N–H stretching frequency, and a strong carbonyl band at 1646, the secondary amide region of the spectrum, as well as a strong peak at 661 cm.$^{-1}$, the organo-halogen region of the spectrum.[44] A positive halogen test was observed on sodium fusion. The compound appeared to be *N*-(2-chloroethyl)-2,3,3-triphenylpropionamide, arising from the reaction of the acid chloride with 2-chloroethylamine, formed in turn by the action of the hydrochloric acid by-product on ethylenimine.[42]

The yields of the desired aziridine were improved in subsequent preparations by using a greater excess of triethylamine. It was found that the aziridine need not be isolated and purified, but could be converted in its crude form directly into 2,3,3-triphenylpropionaldehyde as described subsequently.

2,3,3-Triphenylpropionaldehyde.—The following procedure was adapted from that of Brown and Trukamoto.[35] An ether suspension (100 ml.) containing 200% excess of lithium aluminum hydride was stirred dropwise over a period of 30 min. into an ice-cooled ether–benzene (200 ml., 1:1) solution of crude *N*-(2,3,3-triphenylpropionyl)aziridine prepared from 5.14 g. of 2,3,3-triphenylpropionyl chloride. Stirring at 0° was continued for 30 min., whereupon the excess hydride was destroyed by cautious addition of chilled 5 *N* sulfuric acid. The organic layer was separated and processed as usual, being washed with dilute sodium bicarbonate. Solvent evaporation afforded 4.54 g. (99%) of thick sirup. This was chromatographed on 300 g. of acid-washed silica with benzene as eluent. Evaporation of the first 600 ml. of eluent left 2.2 g. (48% based on acid chloride) of white solid which proved homogeneous in thin layer chromatography. Pure 2,3,3-triphenylpropionaldehyde, m.p. 109–111° was obtained after two recrystallizations from a mixture of hexane and benzene.

Anal. Calcd. for $C_{21}H_{18}O$: C, 88.08; H, 6.33. Found: C, 88.11; H, 6.34.

The 2,4-dinitrophenylhydrazone was prepared in the usual way and recrystallized three times from a mixture of hexane and benzene, m.p. 230–232°.

Anal. Calcd. for $C_{27}H_{22}N_4O_4$: C, 69.51; H, 4.75; N, 12.01. Found: C, 69.27; H, 4.96; N, 12.03.

The 2,3,3-triphenylpropionaldehyde-2-C^{14} employed in the following experiments was prepared by application of the former sequence of reactions to 2,3,3-triphenylpropionic-2-C^{14} acid.[34]

The Decarbonylation of 2,3,3-Triphenylpropionaldehyde.—The procedure employed was adapted from that described by Slaugh.[8] A solution of this aldehyde (1.00 g.) and freshly distilled *t*-butyl peroxide (0.15 ml., 20 mole %) in *o*-dichlorobenzene (5.0 ml.) was immersed in an oil bath preheated to 170° and fitted with a steam condenser to allow for escape of volatile reaction products. The gases evolved were collected in a graduated cylinder inverted over a brine solution. After gas evolution had subsided, the reaction mixture was quickly cooled to room temperature, treated with additional fresh peroxide (0.15 ml.), and again heated to 170°. This procedure was repeated three times, yielding a total of 84 ml. (98% based on carbon monoxide)

(41) C. H. Wang and S. G. Cohen, *J. Am. Chem. Soc.*, **79**, 1924 (1957).

(42) R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," Interscience Publishers, Inc., New York, N. Y., 1960, p. 7.

(43) A. D. Cross, "Introduction to Practical Infrared Spectroscopy," Butterworths Scientific Publications, London, 1960, pp. 57–75.

(44) N. R. Jones and C. Sandorfy, "Techniques of Organic Chemistry," Vol. IX, W. West, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, pp. 564–580.

of gas. The major portion of the solvent was removed by evaporation at reduced pressure and the residual crude product was chromatographed on 100 g. of alumina using hexane as eluent. Evaporation of the first 150 ml. of eluent yielded a viscous oil, 0.119 g., fraction A, which partially crystallized on standing for 1 week. Evaporation of the last 500 ml. of eluent (enriched in benzene) yielded 0.674 g. of white solid, fraction B.

Thin layer chromatographic investigation of fraction A revealed the presence of two components whose R_f values and spot colors were identical with those of authentic 1,1,2-triphenylethane and triphenylethylene. Mixtures of these hydrocarbons behaved similarly to fraction A upon thin layer chromatography on alumina using a variety of eluents. Fraction A was recrystallized three times from methanol to yield a white solid, m.p. 54.5–55.5°, whose infrared spectrum was superimposable on that of authentic 1,1,2-triphenylethane with reported m.p. 55–55.5°.[34] The mixture of the two monomers, 1,1,2-triphenylethane and triphenylethylene, constituted a 15% yield from the starting aldehyde.

Fraction B was recrystallized three times from hexane–benzene, affording white crystals, m.p. 210–213°. Their infrared spectrum was generally similar to that of 1,2,2-triphenylethane, although characteristic methylene C–H stretching bands (2940–2915, 2870–2845 cm.$^{-1}$)[43] were seemingly absent. Only two relatively weak bands appeared in these regions of the spectrum (2900 and 2930), in contrast to three stronger bands at 2880, 2925, and 2939 and a weak band at 2859 cm.$^{-1}$ present in the spectrum of 1,2,2-triphenylethane. The n.m.r. spectrum of the solid contained two overlapping bands at 4.14 and 4.17 and a complex of bands between 6.5 and 7.5 p.p.m. The ratio of integrated band intensities was consistent with a hexaphenylbutane structure, aromatic (complex)–aliphatic (doublet) 15:2.

Anal. Calcd. for $C_{40}H_{34}$: C, 93.34; H, 6.66; mol. wt., 514.7. Found: C, 93.31; H, 6.78; mol. wt. (Rast), 484.

The structure most consistent with the previous data appeared to be 1,1,2,3,4,4-hexaphenylbutane. The absence of methylene absorption bands in the infrared spectrum, we believe, makes other hexaphenylbutane isomers less likely, in that each of these contains a methylene group. The hydrocarbon, $C_{40}H_{34}$, was the principal product of the decarbonylation reaction (75% based on aldehyde, Table I).

The aldehyde decarbonylation was repeated in the same solvent under a variety of reaction conditions, results of which are shown in Table I.

TABLE I

THE DECARBONYLATION OF 2,3,3-TRIPHENYLPROPIONALDEHYDE

Aldehyde (molality)	*t*-Butyl peroxide (mole %)	Temp., °C.	Gas evolved (% of theoretical amount of CO)	Hydrocarbon yield, % Monomeric	Hydrocarbon yield, % Dimeric	Hydrocarbon yield, % Total
0.074	39	153	102			71
.128	20	165	95			72
.538	20	170	98	15	75	90
.250	15	180	85	1	58	59
.192	15	180	114	11	62	73

The Mercaptan-Catalyzed Decarbonylation of 2,3,3-Triphenylpropionaldehyde.—The procedure for the decarbonylation of the aldehyde in the presence of mercaptans was similar to that described earlier. A mixture of 2,3,3-triphenylpropionaldehyde (0.55 g.), freshly distilled *t*-butyl peroxide (40 mg.), and benzyl mercaptan (13 mg., 5 mole %) in *o*-dichlorobenzene solvent (0.75 ml.) was placed in a bath preheated at 180°. Decarbonylation was vigorous, yielding 48 ml. (114% based on carbon monoxide) of gas. The monomer and dimer hydrocarbon products were separated chromatographically as before. The mixture of monomers (166 mg., 33%) was further separated by gas chromatography (silicone rubber column, 250°), and found to consist of 1,1,2-triphenylethane (29%, based on aldehyde) and triphenylethylene (4%). The dimeric hydrocarbon product was obtained in 32% yield. The decarbonylation was repeated under similar reaction conditions employing thiophenol as catalyst. The results of these experiments are listed in Table II. In each case 1,1,2-triphenylethane represented the principal component (*ca.* 74%) of the monomer mixture.

TABLE II

DECARBONYLATION OF 2,3,3-TRIPHENYLPROPIONALDEHYDE IN THE PRESENCE OF THIOPHENOL

Aldehyde (molality)	*t*-Butyl peroxide (mole %)	Thiophenol (mole %)	Temp., °C.	Gas evolved (% of theoretical amount of CO)	Hydrocarbon yield, % Monomeric	Hydrocarbon yield, % Dimeric
0.190	5.6	6.2	185	122	37	22
.075	30	8.1	185	172	41	29
.075	30	16.5	180	195	42	21

Oxidation of 1,1,2-Triphenylethane-2-C^{14}.—1,2,2-Triphenylethanol-1-C^{14} was converted by the action of Raney nickel in refluxing ethanol into 1,1,2-triphenylethane-2-C^{14}.[34] This was recrystallized from methanol to give a pure sample, m.p. 55–56°, specific activity 1.90 ± 0.07 mc./mole, which was employed in the following oxidation experiments.

A. With Chromic Oxide.—A solution of the previous hydrocarbon (121 mg.) in acetic acid (5 ml.) was treated with a solution of chromic oxide (600 mg.) in water (1 ml.) and the mixture was heated on the steam bath for 19 hr., then was cooled, made alkaline with sodium hydroxide, and extracted thoroughly three times with ether. The extract was washed, dried, and stripped of solvent to yield a neutral oil, thin layer chromatography of which revealed no starting material. The oil was converted in the usual way to benzophenone 2,4-dinitrophenylhydrazone (180 mg., 106%) which, on recrystallization from dioxane, had m.p. 243–244° and specific activity of 0.193 mc./mole. Thus *ca.* 10% phenyl migration accompanied the oxidative degradation of 1,1,2-triphenylethane with chromic oxide.

B. With Potassium Permanganate.—The previous hydrocarbon was oxidized with potassium permanganate as previously described,[34] affording a sample of benzophenone whose purified 2,4-dinitrophenylhydrazone, m.p. 240–242°, was void of radioactivity. This degradation, involving no subsequent molecular rearrangement, was thus deemed suitable for assessing rearrangement in the 1,1,2-triphenylethane fraction from decarbonylation reactions.

Degradation of 1,1,2,3,4,4-Hexaphenylethane.—A variety of techniques was attempted to find satisfactory conditions for the degradation of the dimeric hydrocarbon (IX) from the decarbonylation reaction. These included attempts at preliminary dehydrogenation using chloranil, preliminary halogenation with N-bromosuccinimide, and direct oxidation (as before) with potassium permanganate. All of these methods failed, and the only applicable degradation proved to be direct oxidation with chromic oxide in acetic acid, as before. Since this oxidation proceeded with 10% molecular rearrangement in the case of 1,1,2-triphenylethane, and since benzophenone yields were quite low (20–25%) and benzoic acid yields negligible in the present case, it was apparent that any estimates of the extent of rearrangement during the formation of the dimeric decarbonylation product could only be approximate.

Effect of Decarbonylation Conditions on 1,1,2-Triphenylethane-2-C^{14}.—The conditions in the following experiment were maintained as close to those of the previous decarbonylation as possible. A solution of 1,1,2-triphenylethane-2-C^{14} (930 mg., m.p. 55–56°, specific activity 0.645 ± 0.005 mc./mole), freshly distilled *t*-butyl peroxide (400 mg.), and thiophenol (148 mg.) in *o*-dichlorobenzene (18 ml.) was divided into two equal portions. Using the previous decarbonylation apparatus, each portion was inserted into its bath, preheated to 160° and 182°, respectively. After 45 min. the flasks were cooled, additional peroxide (200 mg.) was added, and the reactants were again heated at their prescribed temperatures. After a total reaction time of 2 hr. and a second intermittent addition of fresh peroxide, the reactions were stopped, and the products were isolated as before. The crude triphenylethane chromatography fraction (830 mg., 89.5%) contained approximately the same per cent of triphenylethylene (*ca.* 8%) as did that from the decarbonylation. Portions of each triphenylethane sample were converted *via* permanganate oxidation as described into benzophenone 2,4-dinitrophenylhydrazone, which was purified and assayed for radioactivity. The benzophenone derivative from the experiment conducted at 154–159° had a specific activity of 0.0135 mc./mole (2.09%

TABLE III

THIOPHENOL-CATALYZED DECARBONYLATIONS OF 2,3,3-TRIPHENYLPROPIONALDEHYDE-2-C^{14}

Starting aldehyde (A)					
Sp. act., mc./mole	1.365[a]	1.365[a]	1.201[b]	1.201	1.201[b]
Concn., *M*	0.51	0.51	0.50	0.50	0.50
Temperature, °C.	155–165	176–184	155–158	155–158	174–178
t-Bu_2O_2, mole % of A	30	30	31	31	31
Thiophenol, mole % of A	14	14	11	11	11
VI, sp. act., mc./mole			1.163[b]	1.178[b]	1.18[a]
VII, sp. act., mc./mole			2.42[c]	2.43[c]	
Oxidant for degradation	$KMnO_4$	$KMnO_4$	CrO_3	CrO_3	CrO_3
Ph_2CO from VI, mc./mole	0.0949[b]	0.224[d]	0.143[d]	0.147[d]	0.189[d]
Phenyl migration in VI, %	6.9[e]	16.4[e]	11.9[f]	12.2[f]	15.7[f]
Ph_2CO from VII, mc./mole			0.141	0.147	
Phenyl migration in VII, %			11.7[f]	12.2[f]	

[a] ±0.010 to 0.015. [b] ±0.006 to 0.008. [c] ±0.05. [d] ±0.0007 to 0.0015. [e] Not to be compared with figures in columns 3 and 5, respectively, due to differences in the experimental conditions of the decarbonylation and degradation. [f] Including rearrangement caused by oxidative degradation.

rearrangement). That from the experiment conducted at 178–184° had a specific activity of 0.0159 mc./mole (2.46% rearrangement).

Decarbonylation of 2,3,3-Triphenylpropionaldehyde-2-C^{14}.—The previous labeled aldehyde was decarbonylated in *o*-dichlorobenzene solvent in the manner described for the unlabeled analog, each reaction mixture being divided into several equal portions for decarbonylations at different temperatures. The decarbonylation products were isolated as before, assayed, and then degraded by either permanganate or chromic oxide oxidation. The final benzophenone 2,4-dinitrophenylhydrazone from each experiment was assayed to determine the extent of phenyl migration during each decarbonylation. The results of these experiments are summarized in Table III.

Nitrogen Analogs of Ketenes. VI.[1] Dehydration of Amides

CALVIN L. STEVENS AND GOPAL H. SINGHAL[2]

The Department of Chemistry, Wayne State University, Detroit, Michigan

Received August 12, 1963

A novel method for the preparation of nitrogen analogs of ketenes has been developed which involves direct linear dehydration of the corresponding amides.

Ketenimines were first prepared in 1921 by Staudinger in unspecified yield by the interaction of a phosphinimine and a ketene,[3] and more recently Backer has successfully prepared several ketenimines by the reaction of diazomethane with negatively substituted nitriles.[4] Over the past decade this laboratory has sought more general and convenient methods for the synthesis of these interesting compounds. Two methods were developed which involved (1) the dechlorination of α-chloroimino chlorides with sodium iodide in acetone,[5a] and (2) the dehydrochlorination of imino chlorides with a tertiary amine.[5b] This paper reports a third new and general method for the facile preparation of ketenimines by the direct linear dehydration of N-monosubstituted amides.

Although the linear dehydration of N-monosubstituted amides for the preparation of nitrogen analogs of ketenes is not known, dehydration of amides to form nitriles is well known.[6] Some of the common dehydrating agents are phosphorus pentoxide, phosphorus oxychloride, phosphorus pentachloride, thionyl chloride, polyphosphoric acid, and phthalic anhydride. Phosphorus pentoxide is preferred for the dehydration of unsaturated amides where the use of dehydrating agents such as phosphorus pentachloride may give halogen-containing products.

Scheibler and co-workers[7] used phosphorus pentoxide in combination with a tertiary amine to dehydrate an acid-sensitive amide. From diethoxy acetamide they obtained diethoxyacetonitrile in 30% yield with phosphorus pentoxide and quinoline. In the same reaction, McElvain and co-workers[8] employed N-hexylpiperidine and triethylamine as tertiary bases with phosphorus pentoxide and obtained yields of 45% and 80%, respectively, of diethoxyacetonitrile. In the case of N-substituted amides, cyclic dehydration is the basis of the Bischler–Napieralski reaction.[9] Thus, β-phenethylamides on cyclic dehydration lead to 3,4-dihydroisoquinolines and Itoh and Sugasawa[10] used phosphorus pentoxide mixed with dry sand and pyridine to obtain isoquinoline derivatives in excellent yields.

In the present work, exploration of the dehydration of N-monosubstituted amides was initiated using various tertiary amines in combination with a five- to

(1) The previous paper of this series was by C. L. Stevens and M. E. Munk, *J. Am. Chem. Soc.*, **80**, 4069 (1958).

(2) Abstracted in part from the dissertation of Gopal H. Singhal in partial fulfillment of the requirement for the degree of Doctor of Philosophy, Wayne State University, 1962. This work was supported by Grant No. CY3772 from the National Institutes of Health.

(3) H. Staudinger and E. Hauser, *Helv. Chim. Acta*, **4**, 887 (1921).

(4) R. Dijkstra and H. J. Backer, *Rec. trav. chim.*, **73**, 575, 695 (1954).

(5) (a) C. L. Stevens and J. C. French, *J. Am. Chem. Soc.*, **75**, 657 (1953); (b) **76**, 4398 (1954).

(6) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 596–598; see also R. E. Kent and S. M. McElvain, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 493.

(7) H. Scheibler, *et al.*, *Ber.*, **67**, 1513 (1934).

(8) S. M. McElvain and Robert L. Clarke, *J. Am. Chem. Soc.*, **69**, 2659 (1947).

(9) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **6**, 99 (1951).

(10) N. Itoh and S. Sugasawa, *Tetrahedron*, **1**, 45 (1957).

TABLE I

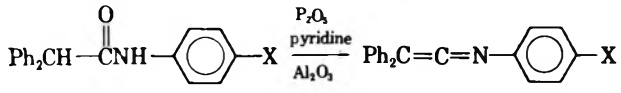
PROPERTIES OF KETENIMINES

Ketenimine	M.p. or b.p. (mm.), °C.	Yield, %	Recrystg. solvent	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Diphenylketene-N-(*p*-tolyl)imine[a] (I)	82–84	87	Petr. ether						
Diphenylketene-N-(*p*-bromophenyl)imine (II)	78–80	69	Hexane	68.98	4.05	4.02	69.21	4.02	3.97
Diphenylketene-N-(*p*-anisyl)imine (III)	83–85	69	Petr. ether	84.24	5.69		84.30	5.81	
Diphenylketene-N-(*p*-methylthiophenyl)imine (IV)	82–83	75	Pentane	80.00	5.40	[b]	79.96	5.63	
Diphenylketene-N-(*o*-tolyl)imine (VII)	71–72	84	Petr. ether	89.00	6.05	4.94	89.01	5.95	4.84
Diphenylketene-N-(*o*-anisyl)imine (VIII)	90–92	67	Hexane	84.24	5.69	4.68	84.46	5.82	4.71
Diphenylketene-N-(*n*-butyl)imine[a] (IX)	150–153 (16)	50							
Diphenylketene-N-(*p*-methylsulfonylphenyl)imine (VI)	137–139	30	Ether	72.59	4.93	4.03	72.44	4.97	4.00
4,4′-Dithiobis[N-(diphenylvinylidine)aniline] (XII)	103–104	27	Benzene–pentane	79.98	4.67	[c]	80.00	4.85	
4,4′-Methylenebis[N-diphenylvinylidine)aniline] (XI)	122–123	84	Hexane	89.44	5.49		89.46	5.78	
Ethyl-*n*-butylketene-N-(*p*-tolyl)imine (X)	119 (0.3)	19		83.74	9.70		83.50	9.92	

[a] Ref. 5a. [b] Calcd.: S, 10.06. Found: S, 10.32. [c] Calcd.: S, 10.67. Found: S, 10.75.

tenfold excess of phosphorus pentoxide as the dehydrating agent. The reaction mixture, however, was difficult to stir and the reaction rate, as followed by infrared measurements[11] was very slow. The utilization of sand, Florisil, or alumina facilitated stirring and reduced markedly the time of reaction. In general, pyridine was found to be the most suitable base and served as the reaction medium as well. With the higher boiling 2,3,6-collidine, more polymeric byproducts resulted, whereas, with triethylamine, the reactions proceeded very slowly.

Diphenylketene *p*-substituted phenylimines, in which the *p*-substituent was CH_3, CH_3O, Br, or SCH_3, could be prepared by this method in 69–87% yield from the corresponding amides. Since the amides could be prepared in excellent yield from the acids, these ketemimines are now available in reasonable quantity by simple synthetic operations.



I, X = CH_3
II, X = Br
III, X = OCH_3
IV, X = SCH_3
V, X = NO_2
VI, X = SO_2CH_3

The scope of the dehydration does not include the preparation of the diphenylketene *p*-nitrophenylimine (V). Attempted preparation of the ketenimine (V) from the corresponding amide using the conditions successful for I–IV gave 80% of the starting material from the reaction mixture. Increasing the time of reaction until the amide had reacted gave only polymeric material. The *p*-nitrophenylketenimine (V) was made by dehalogenation of the α-chloroimino chloride[5a] and subjected to the condition of the attempted preparation. Under these conditions the ketenimine was shown to be unstable, only decomposition material being recovered.

The failure of the dehydration reaction with the strongly electronegative *p*-nitro-substituted amide suggested that the scope of the reaction might be limited and exclude a group such as a *p*-sulfone substituent. However, diphenylketene N-(*p*-methylsulfonyl)imine(VI) could be prepared by the linear dehydration of the corresponding amide, although the yield was lowered to 30%.

Two substituted phenylimines (VII and VIII) were prepared in good yield from the amides (see Table I). A straight-chain aliphatic substitution on the nitrogen of the amide did not limit the synthesis of the ketenimine.

Diphenylketene N-butylimine (IX) could be prepared in 50% yield. However, the corresponding *t*-butyl amide gave 69% nitrile and no ketenimine. An all aliphatic ketenimine could not be made by this method. *n*-Butylethylketene N-butylimine was not formed from the corresponding amide in pyridine with phosphorus pentoxide. When the liquid amide was distilled from phosphorus pentoxide, only the nitrile was isolated in 64% yield.

An example of an aliphatic ketene–aromatic imine was the synthesis of X. The yield was low at 19% but 35% of amide was recovered.

Two bisymmetrical ketenimines (XI and XII) were prepared by this method. The synthesis of the 4,4′-methylenebis[N-(diphenylvinylidine)aniline] (XI) was straightforward and XI was isolated in 84% yield. The disulfide ketenimine (XII) required Florisil as the inert ingredient and the yield was markedly lower (27%).

The sulfur-containing ketenimines (IV, VI, and XII) were made from *p*-aminothiophenol. When the thiophenol was treated with one mole of diphenylacetyl chloride, a mixture of products resulted although some of the desired N-(*p*-mercaptophenyl)diphenylacetamide was isolated. The *p*-aminothiophenol could be air oxidized in an alcoholic ammonium hydroxide solution at room temperature to *p*-aminophenyl disulfide in 89% yield.[12] Treatment of the latter with diphenylacetyl chloride formed 4,4-dithiobisdiphenylacetanilide (XXI) in 86% yield. The disulfide could be readily cleaved to the hydrosulfide with sodium borohydride and methylated with methyl iodide to form N (*p*-methylthiophenyl)diphenylacetamide (XXII) in 92% yield. It also was found that the latter compound could be prepared in 80% yield directly from *p*-aminophenyl disulfide without isolation of the intermediate disulfide. The thioether, upon treatment with hydro-

(11) The N-substituted amides absorb at 5.9 to 6.0 μ while the ketenimine products possess an intense absorption band at 4.9 to 5.0 μ.

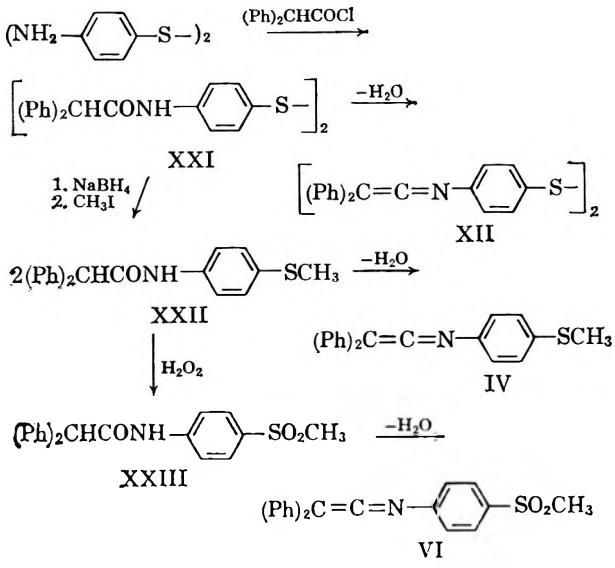
(12) E. C. Hornung, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 86, and reference thereto.

TABLE II

PROPERTIES OF STARTING AMIDES

Amide	M.p., °C.	Yield, %	Recrystg. solvent	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
N-(*p*-Tolyl)diphenylacetamide[a] (XIII)	179–180	90	Toluene						
N-(*o*-Tolyl)diphenylacetamide (XIV)	148	93	Ethanol–water	83.65	6.35	4.65	83.49	6.65	4.41
N-(*p*-Anisyl)diphenylacetamide (XV)	188–189	95	Ethyl acetate–petr. ether	79.45	6.03		79.19	5.88	
N-(*o*-Anisyl)diphenylacetamide (XVI)	150–151	85	Ethyl acetate–petr. ether	79.45	6.03	4.42	79.56	6.21	4.50
N-(*p*-Bromophenyl)diphenylacetamide (XVII)	203–205	85	Ethyl acetate–petr. ether	65.58	4.40		65.36	4.34	
N-(*n*-Butyl)diphenylacetamide[a] (XVIII)	93–94	70							
N-(*p*-Tolyl)-α-ethylcaproamide (XIX)	112–114	92	Ethyl acetate–hexane	77.26	9.94	6.00	77.41	9.87	6.20
4,4′-Methylenebisdiphenylacetanilide (XX)	265–267	76	Pyridine	83.93	5.84	4.78	84.08	5.79	4.85
4,4′-Dithiobisdiphenylacetanilide (XXI)	262–264	86	Pyridine–hexane	75.39	5.06	*b*	75.32	5.14	
N-(*p*-Methylthiophenyl)diphenylacetamide (XXII)	183–184	92	Ethyl acetate–hexane	*c*					
N-(*p*-Methylsulfonylphenyl)diphenylacetamide (XXIII)	212–214	83	Acetone–water	69.02	5.24	3.83	68.95	5.31	5.74

[a] Ref. 5a. [b] Calcd.: S, 10.06. Found: S, 9.99. [c] Calcd.: S, 9.62. Found: S, 9.43.



gen peroxide, gave the desired N-(*p*-methylsulfonylphenyl)diphenylacetamide (XXIII) in 83% yield.

Experimental

Preparation of N-Substituted Amides.—Amides were prepared from the acid chlorides and the corresponding primary amine. Yields are based on the acid used. Unless otherwise stated, the procedure employed is similar to that for N-(*p*-tolyl)diphenylacetamide (XIII) as reported by Stevens and French,[5a] and the properties of the amides are listed in Table II. The experimental procedures for the sulfur-containing amides are described separately.

4,4-Dithiobisdiphenylacetanilide (XXI).—Air was bubbled through a solution of 15.0 g. of *p*-aminothiophenol in 300 ml. of an equivolume mixture of ethanol, concentrated ammonia, and water for 24 hr. The resulting crystalline yellow precipitate of *p*-aminophenyl disulfide was filtered, washed with water, and dried to constant weight, 13.3 g. (89%), m.p. 76–78°.[12]

A portion (4.96 g.) of the disulfide was dissolved in 200 ml. of benzene containing 5.05 g. of triethylamine. To this solution was added, with stirring, a solution of 4.71 g. of diphenylacetylchloride in 120 ml. of benzene, the temperature being kept at 25° or below. The reaction mixture was heated to reflux for 2 hr.; 300 ml. of water was added with stirring, and the reaction mixture was allowed to stand overnight. The resulting white solid was filtered, washed with water and a little ether, and dried to give 11.1 g. (86%) of 4,4-dithiobisdiphenylacetanilide, m.p. 259–261°. Two recrystallizations from pyridine–hexane gave an analytical sample, m.p. 262–264°.

N-(*p*-Methylthiophenyl)diphenylacetamide (XXII). A. From XXI.—A suspension of 1.8 g. of sodium borohydride in 30 ml. of absolute alcohol was added with stirring and cooling to a solution of 3.18 g. of disulfide XXI in 30 ml. of pyridine. When the reaction had subsided, a solution of 5.0 g. of methyl iodide in 95% ethanol was added to the reaction mixture through a dropping funnel. The mixture was stirred for 45 min. and 200 ml. of water was added. The mixture was then allowed to stand for 30 min. and filtered. The precipitate was washed with water and a little petroleum ether and dried to give 3.05 g. (92%) of white solid, m.p. 180–182°. Two recrystallizations from ethyl acetate–hexane gave an analytical sample, m.p. 183–184°.

It was found that this compound could be prepared in 80% yield directly from *p*-aminophenyl disulfide without isolation of intermediates. In this case, pyridine was employed instead of triethylamine in the acylation step.

B. From *p*-Nitrothioanisole.—To 10.0 g. of *p*-nitrothioanisole (m.p. 70°) were added 30.0 g. of iron dust, 10 drops of concentrated hydrochloric acid, and 200 ml. of water. The mixture was stirred at 85–90° for 14 hr. The cooled mixture was made alkaline with sodium carbonate and filtered. The filtrate was extracted well with benzene to dissolve the oil, and the iron residue was extracted four times with hot benzene. The benzene was removed in major part by distillation and the last traces were removed *in vacuo*. The resulting *p*-aminothioanisole was obtained as an oil, 7.5 g. (91%). The oil and 6.0 g. of triethylamine were dissolved in 200 ml. of benzene to which was added 12.5 g. of diphenylacetylchloride in 170 ml. of benzene over a 10-min. period. The reaction mixture was refluxed and stirred for 4 hr. and filtered to remove triethylamine hydrochloride. The salt was washed with benzene and the benzene was removed by distillation and vacuum treatment. The residual crystalline mass of XXII was recrystallized from acetone–pentane to give 16.4 g. (92%) of a white crystalline solid, m.p. 181–183°, undepressed upon admixture with a sample from procedure A.

N-(*p*-Methylsulfonylphenyl)diphenylacetamide (XXIII).—To a solution of 1.1 g. of N-(*p*-methylthiophenyl)diphenylacetamide (XXII) in 15 ml. of glacial acetic acid was added 3 ml. of 40% hydrogen peroxide. The mixture was refluxed for 2 hr. The clear solution was cooled and poured with stirring into 300 ml. of cold water. The precipitate was filtered, washed well with water, and dried to give 1.0 g. (83%) of product, m.p. 206–209°.[14] One recrystallization from acetone–water raised the melting point to 212–214°.

Preparation of Kenenimines. Apparatus and Reagents.—The apparatus was flame-dried before use. The tertiary amines were distilled from phosphorus pentoxide and stored over potassium hydroxide or phosphorus pentoxide. Ether, petroleum ether (b.p. 30–60°), and benzene were dried over sodium, distilled, and stored over sodium. Alumina, Florisil, and sand were dried in

an oven at 150° for 2 days. The particle size of these inert ingredients did not appear to be critical.

The preparation of diphenylketene-*p*-tolylimine (I) represents a general procedure for the preparation of ketenimines. Modifications, where used, are noted.

Diphenylketene-*p*-tolylimine (I).—To a stirred solution of 10.0 g. of N-(*p*-tolyl) diphenylacetamide (XIII) in 300 ml. of dry pyridine were added 25.0 g. of phosphorus pentoxide, 50.0 g. of alumina, and 200 ml. of pyridine. The mixture was refluxed for 7 hr., then allowed to cool, and filtered. The residue was leached with pyridine and the pyridine was evaporated under reduced pressure from the combined filtrates. The crystalline mass was dissolved in dry petroleum ether, filtered, concentrated, and allowed to crystallize. Bright yellow stout needles of ketenimine (I), 8.2 g. (87%), m.p. 82–84°,[5a] were obtained.

The replacement of alumina with Florisil or sand yielded approximately the same results. In the absence of these materials the reaction was very slow, although an 80% yield was obtained.

The *o*-methoxyketenimine (VIII) was prepared using Florisil instead of alumina. The *p*-bromoketenimine (II) was prepared in the stated yield with no inert ingredients added; using alumina in the dehydrating mixture lowered the yield to 26%.

In the preparation of the aromatic ketene aliphatic imine (IX), triethylamine was preferred to pyridine. In the preparation of the aliphatic ketene aromatic imine (X), 2,4,6-collidine was the preferred base. In the preparation of *p*-methylthiophenyl compound (IV), 10 equivalents of phosphorus pentoxide instead of the usual 5 equivalents were required to obtain 75% yield.

Hydrolysis of Ketenimines.—For proof of structure, all the ketenimines were hydrolyzed to the starting amides.[5b] For this purpose, 200 mg. of the ketenimine was dissolved in 10 ml. of acetone and 1 ml. of 4 *N* hydrochloric acid was added. The solution was allowed to stand until the characteristic yellow color of the ketenimine was discharged. The reaction mixture was made turbid by the addition of water, if necessary, and allowed to stand overnight. The resulting solid was filtered and recrystallized from the proper solvent. The yield of recrystallized amide in all cases was over 75%. Mixture melting points with the original amide were undepressed in all cases.

Asymmetric Reductions. XI. The Grignard Reagent from (+)-1-Chloro-2-phenylbutane[1]

J. S. BIRTWISTLE, KELVIN LEE, JAMES D. MORRISON,[2] W. A. SANDERSON, AND HARRY S. MOSHER

The Department of Chemistry, Stanford University, Stanford, California

Received July 24, 1963

Reduction of a series of alkyl phenyl ketones by the optically active Grignard reagent from (+)-1-chloro-2-phenylbutane in ether at room temperature has produced the corresponding alkylphenylcarbinols with the following optical purities: methyl, 37%; ethyl, 52%; isobutyl, 53%; isopropyl, 82%; and *t*-butyl, 14%. These per cent asymmetric reductions parallel, but, with the exception of the *t*-butyl case, are much higher than those observed when the same ketones were reduced with the Grignard reagent from (+)-1-chloro-2-methylbutane. The use of tetrahydrofuran instead of ether solvent reduced the stereoselectivity from 82 to 75% at 35°. The effect of a 66° variation in temperature on this reaction in tetrahydrofuran was to increase the per cent asymmetric reduction from 69% at 66° to 78% at 0°; however, the difference in free energy of activation, $\Delta\Delta F^*$, did not vary over this range. The 82% asymmetric reduction of the isoproply phenyl ketone (which corresponds to the production of 91% *l*-, 9% *d*-carbinol ($\Delta\Delta F^* = 1.45$ kcal./mole) is the highest asymmetric synthesis reported for a reagent containing a single asymmetric center. The factors contributing to this high stereoselectivity and the surprisingly low value obtained in the phenyl *t*-butyl case are discussed.

With the specific purpose of finding variations which will lead to stereoselectivities approaching those of enzyme systems, we have continued our studies on the asymmetric Grignard reduction reaction. The highest asymmetric reductions which we observed with the Grignard reagent from (+)-chloro-2-methylbutane were 24% in the reduction of isopropyl ketone and 25% in the reduction of cyclohexyl phenyl ketone.[3,4]

Vavon and Angelo[5] reported a 72% asymmetric synthesis in the reduction of *t*-butyl phenyl ketone using the Grignard reagent from "pinene hydrochloride." The reducing agent in this case (isobornylmagnesium chloride) has three asymmetric centers and after the hydrogen is transferred the olefin formed (bornylene) still retains two of these three centers and is optically active. The reduction of 1-deuteriobenzaldehyde with isobornyloxymagnesium in a Meerwein–Ponndorf type reaction by Streitwieser and Wolfe[6] produced optically active 1-deuteriobenzyl alcohol which has been assumed to approach optical purity.[7] In this case the reducing agent has three asymmetric centers, only one of which is lost during the reduction.

The reduction of methyl *t*-butyl ketone by "diisopinocamphenylborane," prepared from diborane and α-pinene, carried out by Brown and Bigley,[8] has given methyl-*t*-butylcarbinol of 35% optical purity, and hydroboration of *cis*-2-butene followed by peroxide oxidation has given 2-butanol of better than 90% optical purity.[9] Again, this has been brought about with a reagent containing multiple asymmetric centers which are not destroyed in the reaction.

We believe that in a properly designed system containing only one asymmetric center the difference in the energies of activations between the *d*- and *l*-transition states may be sufficient to permit asymmetric reductions approaching 100%. In order to elucidate further the effect of structural variations in the Grignard reagent upon the degree of asymmetric reduction we have investigated the reduction of some alkyl phenyl

(1) We acknowledge with gratitude support of these investigations by the U. S. Public Health Service (RG-5248) and the National Science Foundation (GF-955).

(2) National Science Foundation Post Doctoral Fellow, 1962.

(3) R. MacLeod, F. J. Welch, and H. S. Mosher, *J. Am. Chem. Soc.*, **82**, 876 (1960).

(4) E. P. Burrows, F. J. Welch, and H. S. Mosher, *ibid.*, **82**, 880 (1960).

(5) G. Vavon and B. Angelo, *Compt. rend.*, **224**, 1435 (1947).

(6) A. Streitwieser, J. R. Wolfe, Jr., and W. D. Schaeffer, *Tetrahedron*, **6**, 340 (1959).

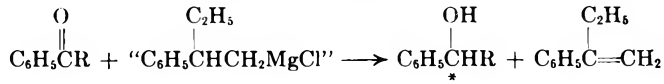
(7) In a preliminary investigation [H. S. Mosher, and V. Althouse, paper presented at the 140th National Meeting of the American Chemical Society Chicago, Ill., September, 1961] it was reported that reduction of 1-deuteriobenzaldehyde by actively fermenting yeast produced 1-deuteriobenzyl alcohol with a rotation 2.2 times that obtained from the isobornylmagnesium reduction. This case is still under investigation by the present authors and by Dr. Streitwieser (private communication.)

(8) H. C. Brown and D. B. Bigley, *J. Am. Chem. Soc.*, **83**, 3166 (1961).

(9) H. C. Brown and G. Zweifel, *ibid.*, **83**, 486 (1961).

TABLE I

ACTIVE PHENYLALKYLCARBINOLS FROM GRIGNARD REDUCTIONS

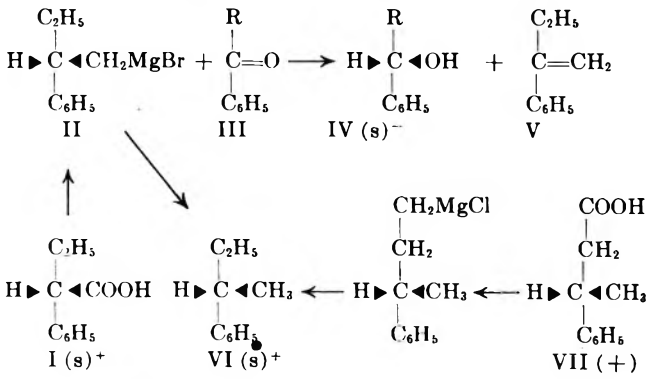


Alkyl group, R	Solvent (T, °C.)	Carbinol yield,[a] %	Minimum carbinol purity,[b] %	Rotation observed,[c] $[\alpha]_D$, deg. (T, °C.)	Specific rotation corrected[d] $[\alpha]_D$, deg.	Maximum lit. rotation[e] $[\alpha]_D$, deg. (T, °C.)	Asymmetric reduction,[f] %	$\Delta\Delta F^*$,[g] kcal./mole
Me	Ether (25)	19	98	−19.86 (28)[h]	−20.6[o]	43.6 (25)	47.2	0.606
Et	Ether (25)	89	95	−14.65 (27)[h]	−15.2[p]	29.1 (27)	52.2	0.686
i-Bu	Ether (25)	63	98	−6.34 (28)[i]	−17.2[p]	32.3 (26)	53.2	0.729
i-Pr	Ether (25)	69	97	−3.67 (27)[j]	−39.2[p]	47.7 (20)	82.1	1.446
i-Pr	THF (66)	44	99	−3.06 (28)[k]	−32.9[q]	47.7 (20)	69.1	1.148
i-Pr	THF (35)	48	97	−2.98 (27)[l]	−35.7[r]	47.7 (20)	74.8	1.147
i-Pr	THF (0)	45	99	−3.58 (28)[m]	−37.4[q]	47.7 (20)	78.4	1.146
t-Bu	Ether (25)	77	99	−1.05 (27)[n]	−5.72	36.2 (20)	15.8	0.189

[a] Based on gas chromatographic analysis after simple distillation. [b] Estimated from the gas chromatograms of the products after purification *via* preparative gas chromatography (Beckman Megachrom). [c] All rotations were taken in center filled tubes with the zero reading determined without altering the caps and are to 0.03° or better, usually 0.01°. [d] The corrected specific rotations are for the same temperatures as the observed rotations and were calculated by correcting for the per cent purity of the carbinol, assuming that the impurities (mostly ketone) were optically inactive and correcting for the optical purity of the chloride used for the Grignard preparation. The optical purity of the chloride was based on a value of $[\alpha]^{27}D$ 5.95° for optically pure 1-chloro-2-phenylbutane. [e] See ref. 3 and 4. Concentrations and solvents were comparable to those reported for the maximum literature values. [f] The per cent asymmetric reduction is defined as 100 × $[\alpha]$ corrected/$[\alpha]$ maximum. [g] $\Delta\Delta F^*$ is calculated from $\Delta\Delta F^* = -RT \ln k_l/k_d$. [h] Neat liquid, l = 1. [i] *n*-Heptane solvent, c 19.00, l = 2. [j] Ether solvent, c 5.30, l = 2. [k] Ether solvent, c 4.965, l = 2. [l] Ether solvent, c 4.473, l = 2. [m] Ether solvent, c 5.010, l = 2. [n] Ether solvent, c 9.49, l = 2. [o] Optical purity of chloride used for Grignard reagent, 98.5%. [p] Optical purity of chloride, 97.7%. [q] Optical purity of chloride, 93.3%. [r] Optical purity of chloride, 93.6%.

ketones with the Grignard reagent from (+)-1-chloro-2-phenylbutane.

The Grignard reagent (II) from (+)-1-chloro-2-phenylbutane was prepared from (+)-2-phenylbutanoic acid (I) by the sequence illustrated. The resolved 2-phenylbutanoic acid was 97.3% optically pure based on the maximum values reported.[10] That the sequence of reactions went without significant racemization was verified by decomposing an aliquot of the Grignard reagent (II) with water to give (+)-2-phenylbutane (VI) which had a rotation that was 97.7% of the value reported by Cram[11] who prepared it by a similar sequence of reactions, but started from resolved 3-phenylbutyric acid (VII). Furthermore, this sequence of reactions interrelates 2-phenylbutyric (I) and 3-phenylbutyric (VII) acids and verifies the consistency of the assigned[11,12] configurations as shown.



The Grignard reagent (II) was treated with each of the alkyl phenyl ketones listed in Table I with the results shown. In each case the preponderant alkylphenylcarbinol isomer was levorotatory and thus had the absolute s configuration[13] as represented by IV. From a consideration of the cyclic transition state mechanism for the hydrogen transfer process in which the interactions of the two phenyl groups are minimized by occupying unopposed positions, as in VIII, one predicts the s configuration (IV) for these products as observed. Thus the predictive value of these assumptions from a configurational standpoint is verified in spite of the fact that this must represent an oversimplification of the problem.

From a quantitative standpoint, the results in Table I can be compared to those obtained with the Grignard reagent from (+)-1-chloro-2-methylbutane[3] where a methyl group is substituted for the phenyl group in the Grignard reagent of the present investigation. One would predict that the greater steric requirement imposed on the transition state resulting from the incorporation of the more bulky phenyl group would lead to greater stereoselectivity. This also has been verified, and in a dramatic fashion, in the case of isopropyl phenyl ketone where 82% asymmetric reduction was observed with the Grignard reagent from (+)-1-chloro-2-phenylbutane as compared to 25% asymmetric reduction with the Grignard reagent from (+)-1-chloro-2-methylbutane.

It is thus seen that a *single* asymmetric center in the reducing agent is capable of inducing a rather high order of asymmetry in the product. The 82% asymmetric reduction using diethyl ether solvent at 35° represents the production of 91% of the s isomer and 9% of the R isomer and corresponds to a difference in the free energies of activation ($\Delta\Delta F^*$) of the competing transition states of about 1.45 kcal./mole at 25°.

(10) (a) K. Petterson, *Arkiv. Kemi*, **10**, 283 (1956); (b) M. Delépine and F. Larèze, *Bull. soc. chim. France*, [5] **22**, 104 (1955); (c) B. Sjöberg, *Acta Chem. Scand.*, **14**, 273 (1960); (d) P. A. Levene, L. A. Mikeska, and K. Passoth, *J. Biol. Chem.*, **88**, 27 (1930).

(11) D. J. Cram, *J. Am. Chem. Soc.*, **74**, 2137 (1952). The values for the asymmetric reductions reported in Table I have been corrected on the basis of a value of $[\alpha]^{25}D$ 5.95° as the rotation of optically pure 1-chloro-2-phenylbutane.

(12) Cram used the (−) isomer of VII and obtained the (−) enantiomorph of VI opposite to that represented here.

(13) The configurational assignments have been discussed in previous papers in this series, ref. 3 and 4.

This represents a fourfold increase in the $\Delta\Delta F^*$ value (0.35 kcal./mole at 25°) for the asymmetric reduction of the same ketone by the previous Grignard reagent from (+)-chloro-2-methylbutane.

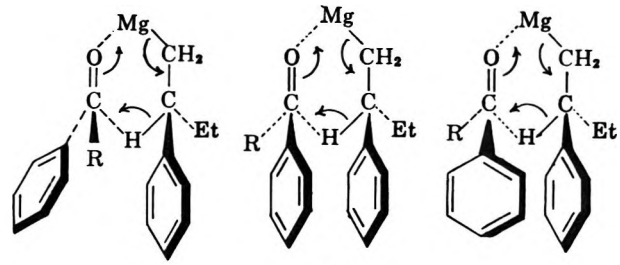
A large gap still exists between these values and the *total* asymmetric synthesis of enzyme systems; nevertheless, these results clearly indicate that the steric requirements at the immediate site of reaction are of utmost importance in the organic chemical reaction and, by inference, in biochemical enzyme processes dealing with low molecular weight substrates as well.

Of special interest in the experiments using the present Grignard reagent (II) is the dramatic drop in stereoselectivity in going from isopropyl phenyl ketone (82%) to more hindered *t*-butyl phenyl ketone (16%). A decrease, but of a smaller amount, of from 25% to 16% was previously noted[3] for the asymmetric reduction of the same two ketones by the less hindered Grignard from (+)-1-chloro-2-methylbutane; thus the trend is confirmed, although greatly magnified, in the present case. From a purely steric interpretation one would conclude that the phenyl group is much larger than the tertiary butyl group, although it is not obvious that this should be so. It is recognized under the same conditions of solvent and temperature that there are at least three major factors contributing to the over-all extent of asymmetric reduction: steric, electronic, and rate.

In a study of the rate of reduction of a series of alkyl phenyl ketones by sodium borohydride, Brown and Ichikawa[14] observed that the relative rates of reduction of alkyl phenyl ketones was in the order: methyl, 0.136; ethyl, 0.076; isopropyl, 0.071; isobutyl, 0.011; and *t*-butyl, 2.47. The fact that the rate of reduction of the highly hindered *t*-butyl phenyl ketone increased instead of decreased was attributed to the large steric strain which forced the phenyl group out of coplanarity with the carbonyl group and thus allowed the former to exert its natural inductive effect without resonance interaction. The inhibition of resonance interactions between the carbonyl and phenyl groups has been independently demonstrated on spectroscopic grounds.[15]

The same factors must be operative on the Grignard reduction reaction although the steric requirements for the Grignard reagent must be much greater than those for the borohydride reagent. It may be reasoned than that the decrease in stereoselectivity has its origin in either the noncoplanar conformation of the *t*-butyl phenyl ketone or in the enhanced rate of reduction which this noncoplanarity allows. It is difficult to evaluate properly this role of coplanarity in the transition state under consideration but a study of models in which only steric considerations are evaluated seems to indicate that noncoplanarity should lead to enhanced steric interactions and, therefore, greater stereoselectivity contrary to what is observed. On the other hand, a faster over-all rate of reduction should result in decreased stereoselectivity.

In the transition states of the reactions being considered, that one leading to the predominant alcohol of the S configuration may be represented by VIII and that leading to the less favored enantiomorph by IX. It is the difference in energies of activation ($\Delta\Delta F^*$) of these two transition states which is responsible for the asymmetric reduction observed. The transition of the carbonyl carbon atom of the ketone from trigonal to tetrahedral, and the concomitant reverse transition of the carbon atom attached to the phenyl group of the Grignard reagent from tetrahedral to trigonal as the reaction proceeds, will tend to increase the planarity of the cyclic transition states and will tend to bring the two phenyl groups face to face in the nonpreferred transition state IX. The electronic repulsions of these two phenyl rings, which are minimized in VIII, rather than steric interactions may be the factor accounting for the high stereoselectivity in this series.



VIII IX X

In the case of the extreme steric effect of the *t*-butyl group, which reduces the coplanarity of the phenyl group attached to the carbonyl carbon atom, the nonpreferred transition state may be represented as X. Although this conformation apparently increases the steric interactions, it may decrease the electronic repulsions even more and at the over-all expense of stereoselectivity.

It is difficult to assess the relative importance of these factors. In addition, no absolute rate data are available in order to evaluate this additional variable. Investigations on further examples in which the steric and electronic factors may be separated are in progress.

Experimental

Materials.—The alkyl phenyl ketones were distilled under nitrogen before use, and their purity verified by gas–liquid chromatography using a Wilkens Model A-90 Aerograph fitted with a 10% Ucon Polar column. Tetrahydrofuran was purified by allowing it to stand over potassium hydroxide for 24 hr., refluxing with lithium aluminum hydride for 3 hr., and finally distilling. It was stored over sodium wire.

Resolution of 2-Phenylbutanoic Acid.—The procedure of Levene, Mikeska, and Passoth[10d] was followed. From 400 g. of racemic acid was obtained, after five crystallizations, 143.1 g. of (+)-2-phenylbutanoic acid, $[\alpha]^{26}D$ +93.2° (neat, l = 1), b.p. 126–127° (2 mm.). On the basis of the maximum value in the literature[10a] of $[\alpha]^{23}D$ −95.8°, this acid is 97.3% optically pure.

Reduction of (+)-2-Phenylbutanoic Acid.—To lithium aluminum hydride (37.3 g., 0.98 mole) in anhydrous ether (400 ml.) was added (+)-2-phenylbutanoic acid (143.1 g., 0.87 mole, $[\alpha]^{26}D$ +93.2, neat, l = 1) dissolved in 100 ml. of ether. After addition was complete, the mixture was refluxed for 4.5 hr. A small amount of ice was added to decompose the excess lithium aluminum hydride, and the reaction mixture was hydrolyzed with 10% sodium hydroxide solution. Ether extracts of the aqueous basic solution were dried over anhydrous magnesium sulfate and distilled to yield (+)-2-phenylbutanol, 119.6 g., b.p. 94–96° (2 mm.), $[\alpha]^{25}D$ +16.5° (neat, l = 1). V.p.c. failed to detect the presence of any impurities.

(+)-1-Chloro-2-phenylbutane.—To 119.6 g. (0.81 mole) of (+)-2-phenylbutanol, $[\alpha]^{25}D$ +16.5° (neat), in 121.5 g. (1.5 mole) of dry pyridine was added slowly 152 g. (1.3 mole) of thionyl chloride with stirring at 0–10°. The resulting thick mixture was stirred for 4 hr. at 0–10° and then warmed. At approxi-

(14) H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **84**, 373 (1962).
(15) G. D. Hedden and W. G. Brown, *ibid.*, **75**, 3744 (1953).

mately 70° a vigorous evolution of gas was observed and after heating for 17 hr. at 90°, the reaction mixture was cooled, and the excess thionyl chloride was decomposed with ice. The upper layer was separated and combined with ether extracts of the lower layer, washed successively with cold saturated sodium bicarbonate solution (three times) and with water (once), dried over anhydrous magnesium sulfate, and distilled to give (+)-1-chloro-2-phenylbutane, b.p. 74–75° (4 mm.), 110.4 g. (81%), $[\alpha]^{25}D$ +5.75 ± 0.01° (neat, l = 1), 97.7% optically pure based on its conversion to (+)-2-phenylbutane.

Asymmetric Reductions.—The Grignard reagent was prepared under purified nitrogen from (+)-1-chloro-2-phenylbutane in anhydrous ether (or tetrahydrofuran) in the usual manner[3,4] using highly purified magnesium.[16] An aliquot of this Grignard solution (about 0.06 mole of an 0.2 *M* solution) was added dropwise with stirring to the solution of alkyl phenyl ketone (about 0.06 mole in 25 ml. of ether or tetrahydrofuran) maintained in water bath at the specified temperature. The runs reported in Table I in ether solvent, with the exception of the first, used (+)-1-chloro-2-phenylbutane described earlier, $[\alpha]^{28}D$ +5.75° (neat, l = 1). The runs in tetrahydrofuran were made with a sample of (+)-1-chloro-2-phenylbutane with $[\alpha]^{27.5}D$ +5.55°. A suitable correction for the optical purity of the Grignard reagent, as determined by conversion to the (+)-2-phenylbutane, is made in the calculated per cent asymmetric reduction. After 18 hr., the reaction mixture was hydrolyzed with an ice-cold ammonium chloride solution. The ether layer was combined with several ether extracts of the aqueous layer and dried over magnesium sulfate. The ether extracts were fractionated through a short column, and the fractions were analyzed with an Aerograph A-90 vapor phase chromatograph. The carbinol fraction was then purified on a Beckman Megachrom preparative gas chromatograph fitted with a 12-ft. 10% Ucon Polar column, using helium as the carrier gas. Under a vacuum of less than 1 mm. the carbinol was distilled from the collection trap into a specially designed centrifuge tube. The purity of the alcohol was then established on an Aerograph A-90 gas chromatograph. The results are summarized in Table I.

(+)-2-Phenylbutane.—An aliquot of the prepared Grignard reagent from (+)-1-chlorophenylbutane (0.04 mole) was added to an ice-cold solution of ammonium chloride, and the mixture extracted with ether. The ether extracts were washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled to give (+)-2-phenylbutane, b.p. 31–33° (4 mm.), 4.11 g., $[\alpha]^{26}D$ +23.76 ± 0.02° (neat, l = 1).[17] Analysis by gas chromatography failed to detect any impurity.

Acknowledgment.—We are indebted to Professor Kurt Mislow for valuable discussions concerning these experiments.

(16) We gratefully acknowledge a gift from Dow Chemical Co. of sublimed magnesium with the following upper limits of elemental impurities in parts per million: Al, 1; Cu, 1; Fe, 4; Mn, 2; Ni, 4; Pb, 10; Si, 10; Sn, 10; Zn, 100; Ba, 1; Ca, 18; K, 5; Na, 6; Sr, 1.

(17) This value is 97.7% of the maximum value of $[\alpha]^{24}D$ 24.3° (neat, l = 1) reported by Cram.[11] Based on this hydrocarbon value the Grignard reagent and the chloride from which it was prepared will be considered 97.7% optically pure.

Alicyclic Syntheses. I. The Diels–Alder Reaction of 2-Phenylbutadiene with Citraconic Anhydride and 5-*p*-Tolylthiotoluquinone

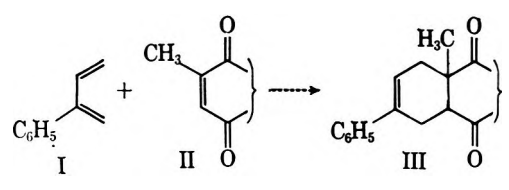
V. GEORGIAN[1] AND J. LEPE M.

The Department of Chemistry, Northwestern University, Evanston, Illinois

Received October 24, 1962

The identity of the adduct of 2-phenyl-1,3-butadiene and citraconic anhydride has been established as *cis*-1-methyl-4-phenyl-1,2,3,6-tetrahydrophthalic acid (IV), contrary to what would have been predicted from a consideration of polar factors. The significance of this and related Diels–Alder reactions is discussed and a mechanism to account for the results is propounded. The stereochemical configurations of the hydrogenation products VII and IX of the adduct IV and of its *trans* isomeride VIII, respectively, have been assigned on the basis of a conformation analytical argument. Use of an arylthiotoluquinone X has been made in an analogous addition to phenylbutadiene to force the generation of angularly methylated decalin systems XI, XII, XIII. Substance XI was desulfurated and reduced in one operation with zinc–acetic acid. Substances XII and XIII were desired as models in the synthesis of steroids lacking ring B.

It was desired to acquire an understanding of the mode of addition of 2-phenyl-1,3-butadiene to unsymmetrical dienophiles of the type II as an introduction to projected syntheses of substances incorporating



I II III

part structure III. Such structures bearing a 1,4-arylmethyl relationship were desired in projected syntheses[2] of 19-nor steroidal compounds lacking ring B.

Subsequent to the inception of this work, there have appeared disclosures of similar activity from other laboratories aimed at the synthesis of such substances,[3] and one case, that of estrone and estradiol lacking ring B,[4] was shown to possess considerable estrogenic activity.

2-Phenyl-1,3-butadiene[5] was treated with citraconic anhydride, and the product was isolated in good yield more conveniently as the diacid. The orientation of the angular methyl group and the identity of the adduct as *cis*-1-methyl-4-phenyl-1,2,3,6-tetrahydrophthalic acid (IV) were established as follows.

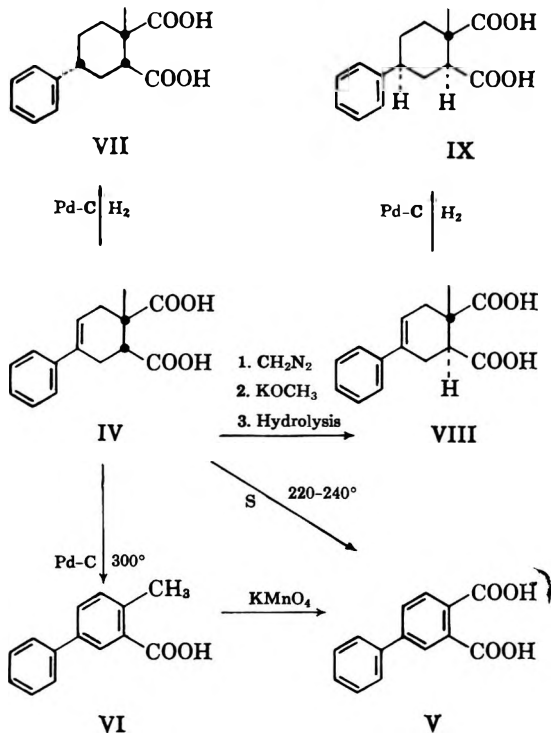
(1) Department of Chemistry, Tufts University, Medford 55, Mass.

(2) Additionally, polycyclic substances containing styryl moieties and available by Diels–Alder reactions were desired to test the acid-catalyzed benzyl hydroperoxide transformation of such to oxo derivatives in another synthetic problem. The facile conversion of α-methylstyrene or the derived tertiary alcohol or chloride therefrom to phenol and acetone by Kharasch and co-workers, *J. Org. Chem.*, **15**, 748 (1950), and later papers [see also H. Kwart and R. T. Keen, *J. Am. Chem. Soc.*, **81**, 943 (1959), for a related transformation] suggested the possibility of utilizing such a sequence in synthetic work to introduce carbonyl groups at sites suitably earmarked initially as styryl functions. This scheme, an additional portion of which is presented in paper II of this series, V. Georgian and J. Lepe M., *J. Org. Chem.* **29**, 45 (1964), is under investigation.

(3) A. J. Birch, E. Pride, and H. Smith *J. Chem. Soc.*, 4688 (1958); R. H. Jaeger, *Tetrahedron*, **2**, 326 (1958).

(4) F. C. Novello, U. S. Patent 2,886,589 (May 12, 1959).

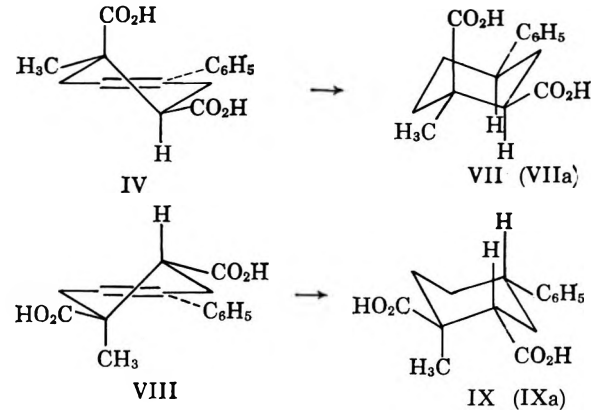
(5) C. C. Price, F. L. Benton, and C. J. Schmidle, *J. Am. Chem. Soc.*, **71**, 2810 (1949).



The Diels–Alder product as the free acid, when dehydrogenated with sulfur at 220–240°, was found to have lost the angular methyl group with the production of 4-phenylphthalic acid (V).[6] The methyl group was retained, however, when the dehydrogenation was conducted at 300° over 10% palladium–charcoal,[7] and a phenyltoluic acid of m.p. 211–212° was obtained. This was not identical with the known 2-methyl-4-phenylbenzoic,[6] which would have arisen had the diene addition proceeded in the alternative manner. The structure VI for this acid was confirmed on conversion to 4-phenylphthalic acid (V) by permanganate oxidation.

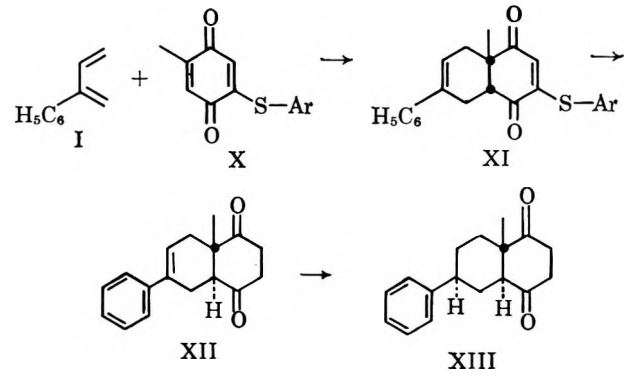
In addition to the correspondence of structure IV to partial structure III, another desirable feature of the former is its ability to be transformed to a *trans* oriented diacid, which could serve as a point of departure in syntheses of steroidal models lacking ring B and requiring *trans* C/D (homo) ring fusion. Indeed, the dimethyl ester of IV was isomerized on being refluxed with potassium methoxide,[8] and subsequently hydrolyzed to yield about 70% of the *trans*-1-methyl-4-phenyl-1,2,3,6-tetrahydrophthalic acid (VIII). Approximately 20% of the *cis* compound (IV) was recovered.

Each of the unsaturated acids IV and VIII was hydrogenated over palladium–charcoal to the corresponding methylphenylhexahydrophthalic acids VII and IX. Although no rigorous proof is available for the stereochemical configurations of the hydrogenation products, those depicted in formulas VII (VIIIa) and IX (IXa) are suggested as reasonble and are derived from a consideration in each case of the most favorable conformation offering least steric hindrance to the catalyst surface. For the cyclohexene systems, the minimum energy half-chair conformations[9] are selected bearing the smallest number of axial substituents (other than hydrogen) with catalyst approach from the least hindered side.[10]



To approach closer to the objectives set forth earlier in this paper, attention was next focused on an addition of 2-phenylbutadiene to a dienophile of an analogous electronic and geometric character to citraconic anhydride but containing a preformed carbocyclic ring system. A toluquinone, of such substitution as to force formation of an angular methylated adduct with the diene, was the required precursor, and specifically a 5-(or 6-)arylthiolated toluquinone was considered to fulfill the added requirement of affording an adduct, permitting easy removal of the protecting group.

A *p*-tolylthiotoluquinone X (Ar = *p*-C_7H_7), most likely bearing the sulfur substitution at position 5, was



prepared from *p*-toluenethiol and excess toluquinone,[11] and caused to undergo addition with 2-phenylbutadiene. An adduct resulted which is represented as XI by analogy on the one hand to the known course of diene addition to the electronically similar 5-methoxytolu-

(6) K. v. Auwers and W. Jülicher, *Ber.* **55**, 2167 (1922).

(7) For examples of decarboxylation–dehydrogenation of α-methylcycloalkanoic acids see: W. E. Bachmann and J. M. Chemerda, *J. Am. Chem. Soc.*, **70**, 1468 (1948); A. Butenandt, H. A. Weidlich, and H. Thompson, *Ber.*, **66**, 601 (1933); J. Heer and K. Miescher, *Helv. Chim. Acta*, **31**, 219, 229 (1948); J. Alder, J. Haydn, and B. Krüger, *Ber.*, **86**, 1372 (1953).

(8) W. Hückel and E. Goth, *ibid.*, **58**, 447 (1925); J. Heer and K. Miescher, *Helv. Chim. Acta*, **32**, 1572 (1949).

(9) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956).

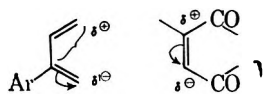
(10) The transition states thus may be envisioned as incorporating no 1,3-nonbonded diaxial interactions between any of the substituents (other than hydrogen) on the cyclohexene ring and catalyst-H, considered as an axial substituent in the transition state. Inspection of the half-chair conformations alternate to those shown previously will reveal such diaxial interferences.

(11) For analogous quinone–sulfide formations see: T. Posner, *Ann.*, **336**, 85 (1904); J. M. Snell and A. Weissberger, *J. Am. Chem. Soc.*, **61**, 450 (1939); A. Schöberl and A. Wagner, "Methoden der Organischen Chemie," Vol. 9, Houben-Weyl, Ed., 4th Ed., Georg Thieme Verlag, Stuttgart, 1955, p. 130. For the ensuing purposes of our *p*-tolylthiotoluquinone the exact position, 5 or 6, of sulfide substitution is not critical.

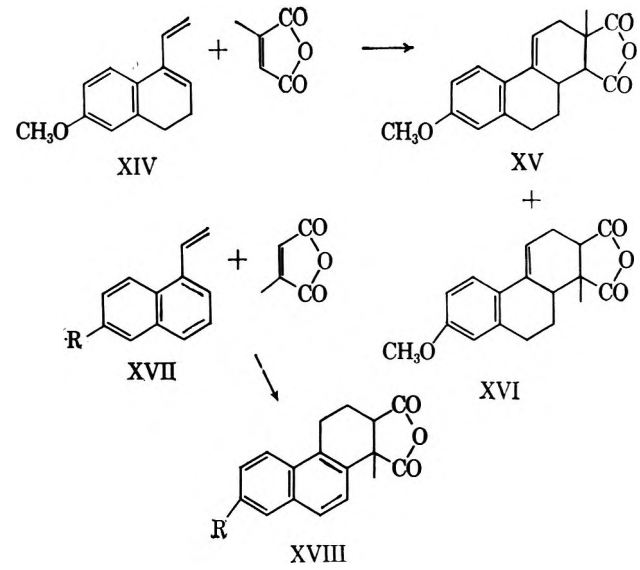
quinone on the methylated side,[12] and on the other hand to the course of addition of phenylbutadiene with citraconic anhydride established previously. Such an assignment is available from a more detailed study of Diels–Alder additions of alkylthiotoluquinones.[13] Adduct XI was isolated only in a noncrystalline condition, but after desulfuration–reduction a crystalline substance XII was afforded albeit in small over-all yield from components I and X.

The usual Raney nickel desulfuration method failed in the latter transformation as erratic over reductions ensued. A new method, though probably unique for the system in XI, consisted in refluxing XI with zinc dust in acetic acid for a few hours.[13] The *trans* ring juncture in XII is postulated on the basis of the investigations of Robins and Walker[14] on the course of zinc–acetic acid reductions of Diels–Alder products from quinone. Prolonged treatment together with heating results in the reduction of the dioxoethylenic system concomitant with isomerization of the initially produced *cis* ring juncture to *trans*. The conditions of our desulfuration–reduction are those which almost certainly ensure the more stable *trans* ring fusion in XII.[15] Compound XII was readily reduced to XIII by means of hydrogenation over palladium–charcoal, this result being in contradistinction to a comparable situation elsewhere.[16] The stereochemical representation of XIII is the reasonable one resulting from catalyst-H approach from the least hindered side, *vide supra* for representation of the analogous hydrogenation process (VIII → IX).

Note on the Orientational Course of the Diels–Alder Addition.—We wish to draw attention to two points on the orientational aspects of the Diels–Alder reaction observed herein, which are germane to the methanistic considerations of this reaction. (a) The diene addition leading to IV has proceeded *contrary to the direction predictable purely on electrostatic grounds.*



(b) There is a variation in the methyl–phenyl relationship in the adducts resulting from the additions of citraconic anhydride to dienes of the phenylbutadiene type, *e.g.*, phenylbutadiene (I), 1-vinyl-6-methoxy-3,4-dihydronaphthalene (Dane's diene[17] XIV), and 1-vinylnaphthalenes (XVII, R = H or OCH_3), in which the phenylbutadiene moiety is incorporated in a dialin and a naphthalene ring system, respectively. It has been shown[18] that Dane's diene (XIV) yields a portion



of adduct XVI (1-3 methyl-"phenyl" orientation) in addition to adduct XV[19] (1-4 methyl-"phenyl" orientation). However, the vinylnaphthalenes (XVII, R = H or OCH_3) gave good yields of only adducts XVIII (R = H, OCH_3) (1-3 methyl-"phenyl" orientation).[20] These results show a definite transition from the 1-4 methyl-phenyl orientation observed as the preponderant if not sole course of our addition, *viz.* IV, with phenylbutadiene itself.[21] We feel this variation as well as the orientational course of our diene addition are readily explicable on the basis of the theory for the Diels–Alder reaction[22,23a] propounded by Woodward.

The transition state leading to the establishment of the initial bond[23b] (in a two-step process) between the termini of unsymmetrical addends will control the gross structure of the adduct. The transition state of lowest energy will be determined by the extent of electron delocalization and a cogent argument may be made in favor of that transition state among the various ones *a priori* possible that avails as sites for electron delocalization in decreasing order of stability: benzyl or α to center of polarizable electrons > tertiary >

(12) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. MacLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952); M. Orchin and L. W. Butz, *J. Org. Chem.*, **8**, 509 (1943).

(13) V. Georgian and L. L. Skaletzky, *J. Org. Chem.*, **29**, 51 (1964). Additional examples of such additions are also to be found in paper II of this series.

(14) P. A. Robins and J. Walker, *J. Chem. Soc.*, 642, 1612 (1952); 3960 (1954).

(15) This point is proved definitely in the study on the simpler system resulting from butadiene and quinone X: L. L. Skaletzky, Ph.D. dissertation, Northwestern University (1959); paper III of this series; *cf.* also R. H. Baker, L. S. Minckler, and A. S. Hussey, *J. Am. Chem. Soc.*, **81**, 2379 (1959), and paper II of this series.

(16) A. J. Birch, E. Pride, and H. Smith, *J. Chem. Soc.*, 4688 (1958).

(17) E. Dane and J. Schmitt, *Ann.*, **537**, 246 (1939).

(18) W. E. Bachmann and J. M. Chemerda, *J. Am. Chem. Soc.*, **70**, 1468 (1948); J. Heer and K. Miescher, *Helv. Chim. Acta*, **31**, 219 (1948).

(19) Isomeric adducts with the same gross structure as XV and XVI, but with the double bond in the 4a,10a-position in the hexahydrophenanthrene skeleton, were obtained [W. E. Bachmann and J. Controulis, *J. Am. Chem. Soc.*, **73**, 2636 (1951)], but the argument presented subsequently with respect to the orientational course of these Diels–Alder reactions is not changed, inasmuch as the double bond isomers are transformation products subsequent to the original diene addition.

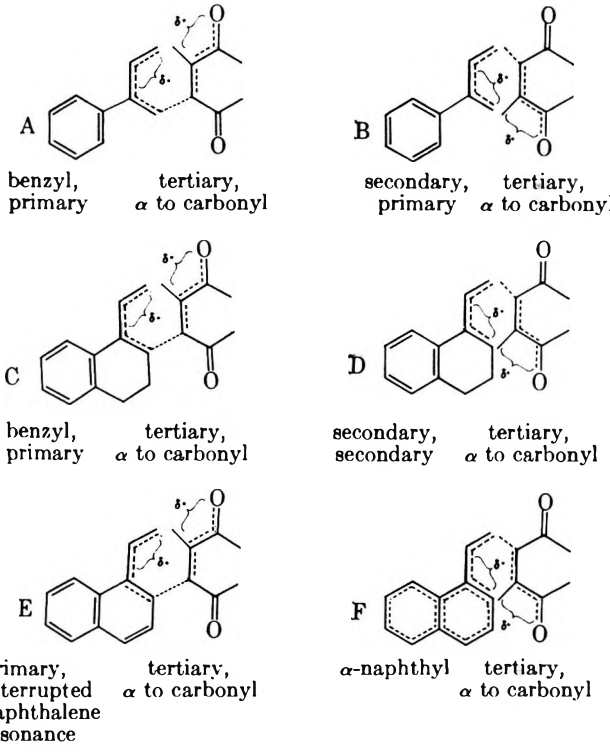
(20) W. E. Bachmann and L. B. Scott, *ibid.*, **70**, 1462 (1948), who also observed that mesaconic acid gave adducts of the type XVIII, *trans* carboxyls.

(21) For an extensive study on the Diels–Alder reaction between unsymmetrical addends consult the series of papers by K. Alder and coworkers: *Ann.*, **564**, 79, 109, 120 (1949); **570**, 201, 214, 230 (1950); **571**, 157 (1951); *Ber.*, **86**, 1302, 1312, 1364, 1372 (1953). In a related study, J. S. Meek, R. T. Merrow, D. E. Ramey, and S. J. Cristol, *J. Am. Chem. Soc.*, **73**, 5563 (1951), showed that the addition of 2-phenyl-1,3-butadiene to monosubstituted ethylenic dienophiles yielded 1,4-disubstituted adducts as major products. See also E. Buchta and G. Satzinger, *Ber.*, **92**, 449 (1959), for a study of the addition of 2-phenyl-1,3-butadiene to substituted acrylic acids.

(22) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

(23)(a) Significant observations and predictive suggestions also have been recorded by C. Walling and J. Peisach, *J. Am. Chem. Soc.*, **80**, 5819 (1958); J. A. Berson, R. D. Reynolds, and W. M. Jones, *ibid.*, **78**, 6049 (1956); and G. Stork, S. S. Wagle, and P. C. Mukharji, *ibid.*, **75**, 3197 (1953). In footnote 2 of the later reference there is formulated in canonical form an electron delocalized single-bonded intermediate for the diene addition process. (b) For recent suggestions that the Diels–Alder reaction may involve transient intermediates in which one bond has formed, see R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959); C. Walling and J. Peisach, *J. Am. Chem. Soc.*, **80**, 5819 (1958); and R. P. Lutz and J. D. Roberts, *ibid.*, **83**, 2198 (1961).

SCHEME I
TRANSITION STATES



secondary > primary. We may thus postulate as transition states for the cases under discussion those depicted in Scheme I.

In Scheme I only those forms are considered for the dienophilic moiety which involve a tertiary center clearly in preference to the alternate secondary one (each, of course, α to carbonyl). With respect to the diene it may be seen that form A, with electron delocalization involving the aromatic ring, would be of lower energy than B and the product may reasonably be expected to be IV. Similarly, F will be recognized as being of lower energy than E and the product here is solely XVIII. With respect to the situation obtaining in the case of the dialin XIV, transition state C represents the controlling force leading to XV, but now state D, which has an electron (or fraction thereof) delocalized at two secondary sites, represents an energetically more favorable situation than that prevailing in the hypothetical state B, and it may be expected that some product of the 1-3 methyl-"phenyl" orientation, *i.e.*, XVI, would appear as has been observed.[18]

Conformational specificity, obviously important in the more detailed stereochemistry of the polycyclic phenanthrenoid cases XV, XVI and XVIII controlling *exo* or *endo* addition, is neglected in the discussion at hand since it bears no significance to the constitution of the products resulting from the Diels–Alder reaction with 2-monosubstituted butadiene. Attention here has been limited solely to the disposition of methyl and aryl groups in the transition state. It is, of course, understood that the other auxiliary factors characteristic of and contributing to the diene addition process, *e.g.*, cisoid conformation of the diene, parallel biplanar approach of the addends (not shown in perspective in Scheme I), and the electrorestrictive forces leading to a highly circumscribed transition state,[24] will obtain in the present cases also.

Attention was called in the preceding to an apparently "wrong" interplay of polar factors in influencing the orientational course of the Diels–Alder reaction leading to IV (also in the case of XVII → XVIII). Many previously recorded cases involving unsymmetrical addends[21] conform to this same ostensible anomaly. Accordingly, it has proved fruitful in accounting for and predicting products, to treat such cases, even those wherein polar factors[25] appear to suffice, in terms of the single electron delocalization particularized as in Scheme I.

Experimental[26]

2-Phenyl-1,3-butadiene.—The pyrolysis of 4-acetoxy-2-phenyl-1-butene to produce 2-phenyl-1,3-butadiene was conducted essentially as described in the method of Price, Benton, and Schmidle.[5]

***cis*-1-Methyl-4-phenyl-1,2,3,6-tetrahydrophthalic Acid (IV).**—Citraconic anhydride[27] (103 g.) was added to a solution of 120 g. of 2-phenyl-1,3-butadiene in 500 ml. of thiophene-free anhydrous benzene. An exothermicity and the appearance of a yellowish color were noted at this point. After being refluxed for 24 hr., the reaction solution was concentrated by distillation and ultimately was heated at 140° (7–8 mm.) to remove any excess citraconic anhydride. The residual oil was taken up in a solution of 75 g. of sodium hydroxide in 250 ml. of water and extracted twice with ether. The alkaline solution was acidified and the product, *cis*-1-methyl-4-phenyl-1,2,3,6-tetrahydrophthalic acid (IV), separated as a thick oil which soon crystallized. It was filtered, washed with water, and air-dried, yielding 158 g. (66%), m.p. 158–162 (gas evolution). It could be recrystallized (90% recovery) from dilute ethanol, m.p. 174–176° (gas evolution).

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.20; H, 6.15. Found: C, 69.17; H, 6.56.

4-Phenylphthalic Acid (V) from Sulfur Dehydrogenation of Adduct IV.—*cis*-1-Methyl-4-phenyl-1,2,3,6-tetrahydrophthalic acid (IV, 3 g.) was mixed with sulfur (1.5 g.) and heated 25 min. at 220–240°. Water and hydrogen sulfide were evolved, and the dark residue was then taken up in hot potassium carbonate solution, filtered (Norit), and extracted twice with ether. Acidification, extraction with ether, and evaporation of the washed and dried ether solution afforded 4-phenylphthalic acid (V), which was recrystallized from acetone–cyclohexane, yielding 580 mg., m.p. 196–197°, lit.[6] 194°.

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.42; H, 4.13. Found: C, 69.82; H, 4.51.

The **anhydride of 4-phenylphthalic acid** was prepared from the acid by treatment with acetyl chloride for 60 hr. at room temperature. It was recrystallized from benzene–cyclohexane, m.p. 140–142°, lit.[7] m.p. 135–136°.

Anal. Calcd. for $C_{14}H_8O_3$: C, 75.00; H, 3.57. Found: C, 74.87; H, 3.58.

2-Methyl-5-phenylbenzoic Acid (VI) from Pd–C Dehydrogenation of Adduct IV.—A mixture of *cis*-1-methyl-4-phenyl-1,2,3,6-tetrahydrophthalic acid (IV, 2.6 g.) and 10% palladium–charcoal (500 mg.) was heated under an initial nitrogen cover at 300° for 30 min. Ether extraction, water washing, drying over sodium sulfate (Norit), and evaporation yielded 2-methyl-5-phenyl-

(24) Including the coupling of the spins of the electrons involved[22] and overlap of unsaturated centers. For evidence against triplet biradical intermediates in Diels–Alder reactions see N. J. Turro and G. S. Hammond, *J. Am. Chem. Soc.*, **84**, 2841 (1962).

(25) For further discussion eliminating polar structures from consideration as intermediates in the Diels–Alder reaction between the neutral components, diene and dienophile, see C. Walling and J. Peisach, *ibid.*, **80**, 5819 (1958). The startling accelerations of some diene additions between anthracene and dienophiles of the maleic anhydride and quinone types imparted by aluminum chloride present in *one and two molar equivalents* and observed recently by P. Yates and P. Eaton, *J. Am. Chem. Soc.*, **82**, 4436 (1960), may very well be due to an altered nature of one or both components and may not necessarily be used as an argument either supporting or negating the intermediacy of polar structures in the reactions between the noncatalytically (Lewis acids) perturbed components.

(26) All melting points and boiling points are uncorrected. Microanalyses were performed at Northwestern University by Miss Joyce Sorenson.

(27) R. L. Shriner, S. G. Ford, and L. J. Roll, in "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 140.

benzoic acid (VI, 810 mg.), m.p. 175–205°, recrystallized from dilute ethanol, m.p. 211–212°.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.24; H, 5.66. Found: C, 79.58; H, 5.85.

Permanganate Oxidation of 2-Methyl-5-phenylbenzoic Acid (VI).—The palladium–charcoal hydrogenation product VI of m.p. 200–211° (780 mg.) was refluxed for 3 hr. with a solution of 3.5 g. of potassium permanganate in 75 ml. of water containing 1 ml. of 10% alkali. The excess permanganate and manganese dioxide were reduced with sodium bisulfite, and the filtered solution was acidified and extracted exhaustively with ether. Solvent removal left 200 mg. of 4-phenylphthalic acid, m.p. 195–197°, undepressed by a sample prepared previously in the sulfur hydrogenation of IV.

***trans*-1-Methyl-4-phenyl-1,2,3,6-tetrahydrophthalic Acid (VIII).**—A suspension of 12 g. of *cis*-1-methyl-4-phenyl-1,2,3,6-tetrahydrophthalic acid (IV) in 200 ml. of ether was treated with an ether solution of diazomethane (prepared from 7 g. of nitrosomethylurea[28]). The excess diazomethane was boiled off after 10 min., the ether solution was washed with bicarbonate solution, water to neutrality, and saturated sodium chloride solution, and dried over magnesium sulfate. After evaporation of the ether, the remaining oil was taken up in dry benzene and boiled down to ensure dryness; the last traces were removed *in vacuo*.

The residual dimethyl ester of acid IV was refluxed 72 hr. in a solution of 1.0 g. of potassium metal in 200 ml. of absolute methanol. Then a solution of 5.0 g. of sodium hydroxide in 250 ml. of water was added and refluxing was continued for 4 hr. The alkaline solution, after being extracted with ether, was acidified and extracted exhaustively with ether. The ether solution was processed in the usual manner after partial evaporation of the ether. Addition of cyclohexane and storage overnight in the cold yielded 8.3 g. (70%) of *trans*-1-methyl-4-phenyl-1,2,3,6-tetrahydrophthalic acid (VIII), m.p. 216–221°. A second fraction, 2.0 g. (17%), m.p. 174–176°, proved to be recovered *cis* diacid IV, and a third fraction, 1.0 g., had m.p. 155–160°. Recrystallization of the *trans* diacid VIII from acetone–cyclohexane raised the melting point to 229–231°.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.23; H, 6.15; neut. equiv., 130. Found: C, 69.69; H, 6.31; neut. equiv., 136.

***cis-syn*-1-Methyl-4-phenylhexahydrophthalic Acid (VII).**—Three grams of 1-methyl-4-phenyl-1,2,3,6-tetrahydrophthalic acid in 50 ml. of absolute ethanol was hydrogenated over 150 mg. of 5% palladium–charcoal. During 1 hr. 280 ml. of hydrogen was absorbed (theoretical, 300 ml.). The catalyst was filtered off and the product, *cis-syn*-1-methyl-4-phenylhexahydrophthalic acid (VII), was crystallized from dilute ethanol, yielding 2.5 g. (83%), m.p. 188.5–189.5°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.70; H, 6.87. Found: C, 69.20; H, 7.01.

***trans-syn*-1-Methyl-4-phenylhexahydrophthalic Acid (IX).**—One and one-half grams of *trans* diacid VIII was hydrogenated in 50 ml. of absolute ethanol over 150 mg. of 5% palladium–charcoal. The uptake of hydrogen, 148 ml. (theoretical, 144 ml.), required 20 min. After the usual work-up, there was isolated 1.3 g. of *trans-syn*-1-methyl-4-phenylhexahydrophthalic acid (IX), m.p. 215–225° (acetone–cyclohexane). One more recrystallization (acetone–cyclohexane) afforded 1.10 g. of IX (74%), m.p. 243–245°.

(28) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons Inc., New York, N. Y., 1946, p. 166.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.70; H, 6.78. Found: C, 68.36; H, 7.06.

5(or 6?)-*p*-Tolylthiotoluquinone (X, Ar = *p*-C_7H_7).—*p*-Toluenethiol (31 g.) was added in one portion to a magnetically stirred suspension of 61 g. of toluquinone in 100 ml. of absolute ethanol. A clear dark red solution soon resulted with the evolution of some heat. The reaction was cooled to and maintained at room temperature overnight. The product, 5(6?)-*p*-tolylthiotoluquinone (X, Ar = *p*-C_7H_7), was filtered, washed with ligroin (b.p. 86–100°), and recrystallized from benzene–ligroin twice to yield 20 g. of bright orange crystals, m.p. 151.5–153°. The analytical sample had m.p. 154.7–155.6°.

Anal. Calcd. for $C_{14}H_{12}O_2S$: C, 69.00; H, 4.97; S, 13.15. Found: C, 69.40; H, 5.00; S, 13.16.

***trans*-1,4-Dioxo-6-phenyl-8a-methyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene (XII).**—A solution of 5.2 g. of freshly distilled 2-phenylbutadiene and 9.7 g. of 5-(or 6?)*p*-tolylthiotoluquinone (X, Ar = *p*-C_7H_7) in 250 ml. of toluene was refluxed for 17 hr. The initially dark red solution gradually lightened in color to orange. Much of the toluene was removed *in vacuo* and the residue was diluted with 300 ml. of ether. This solution was then extracted with alternate portions of 10% sodium hydroxide solution and sodium hydrosulfite solution until no more color was removed in the washings. These were followed by washing with water until neutral and then with saturated sodium chloride solution; the organic layer was dried over magnesium sulfate and solvents were evaporated. The oily residue was kept under vacuum on the steam bath until no further change in weight. Approximately 15 g. of a thick yellow oil remained, and this corresponds to adduct XI.

The reaction concentrate obtained was taken up in 300 ml. of glacial acetic acid, 40 g. of zinc dust was added, and the mixture was refluxed with magnetic stirring for 8 hr. The cooled reaction was filtered and the zinc and salts were washed with acetone. The volatile matter was removed under aspirator vacuum on the steam bath, and the residue was taken up in ether, and washed several times with 5% sodium hydroxide solution until no more coloration to the wash liquors. After being washed with water and saturated sodium chloride solution until neutral, the ether solution was dried over magnesium sulfate and evaporated, and the product was distilled evaporatively at 0.2 mm. with a short path distillation apparatus at an oil bath temperature of 210–215°. A distillate of 6.4 g. was obtained which crystallized and was recrystallized from ethanol to yield XII, 4.8 g., m.p. 128–129° (after vacuum drying).

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.46; H, 7.31.

1,4-Dioxo-6-phenyl-8a-methyldecahydronaphthalene (*cis*-6,4a, *trans*-4a,8a, XIII).—A solution of 500 mg. of XII in 20 ml. of reagent ethyl acetate was hydrogenated over 50 mg. of 5% Pd–C at near atmospheric pressure. The theoretical uptake of hydrogen required only 20 min., and the reaction was worked up in the usual way to yield 420 mg. of the dioxophenylmethyldecahydronaphthalene XIII, m.p. 149–150°. The analytical sample was recrystallized from ethanol, m.p. 152–153°.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.44; H, 7.71.

Acknowledgment.—We wish to express our gratitude to the Research Corporation for financial assistance in support of this and related researches on alicyclic syntheses.

Alicyclic Syntheses. II. Diels–Alder Adducts Derived from 1-(α-Styryl)cyclohexene and 3-(α-Styryl)-Δ²-cyclohexenone

V. GEORGIAN[1a] AND J. LEPE M.

The Department of Chemistry, Northwestern University, Evanston, Illinois

Received October 26, 1963

The synthesis of 1-(α-styryl)cyclohexene (XII) and 3-(α-styryl)-Δ²-cyclohexenone (VII) and the Diels–Alder reactions of these dienes with a variety of dienophiles, maleic and citraconic anhydrides, and quinone, are described. Of particular interest is the reaction with 5-*p*-tolylthiotoluquinone (XXI). Angularly methylated polycarbocyclic systems have been stereospecifically obtained as models for steroid synthesis. The stereochemistry of the various adducts and their transformation products is discussed.

In our initial publication[1b] in this series of studies on the use of the Diels–Alder reaction in the synthesis of angularly methylated polycarbocyclic ring systems approaching steroid proportions, we presented our general theme on the potential utility of incorporating styryl moieties in an alicyclic system at the site(s) of potential oxygen functions. The general purpose of this diene addition scheme, as well as the orientational course of the reaction with unsymmetrical addends of the types necessary to the proposed scheme, was studied earlier in the simpler systems of 2-phenyl-1,3-butadiene (I) and citraconic anhydride (II) yielding *cis*-1-methyl-4-phenyl-1,2,3,6-tetrahydrophthalic acid anhydride (III).[1b]

We now wish to report on an extension of this approach to larger size ring systems in both the diene and the dienophilic components.

The possibility of employing a system such as 3-(α-styryl)-Δ²-cyclohexenone (VII) as the diene appeared initially attractive, since Diels–Alder products therefrom could be envisioned as models for C-ring oxygenated steroids. Cyclohexenones of the general type VII are readily available as shown by the work of Woods on the reaction of phenylmagnesium bromide on dihydroresorcinol enol ethers.[2] More recently announcements from three laboratories, those of Eschenmoser,[3] Nazarov,[4] and Normant,[5] report the successful addition of acetylene and the vinyl Grignard reagent[6] to the enol ethers of dihydroresorcinols affording 3-ethinyl- or 3-vinyl-Δ²-cyclohexenones. In strict analogy, α-styrylmagnesium bromide (IV)[7] was treated with dihydroresorcinol methyl ether (V) followed by acid hydrolysis of the reaction intermediate VI to produce the desired dienone VII, albeit in a yield reduced considerably by resinification. In fact, although an adduct, 8-oxo-4-phenyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylic acid (VIII), was obtained from VII and maleic anhydride, further attempts to utilize VII in additions with citraconic anhydride (II) and 5-methoxytoluquinone[8] (X) were fruitless as a result of its extreme instability under the more drastic and driving conditions required generally in Diels–Alder reactions with the methylated dienophiles. Such sensitivity was noted also for the related vinyl cyclohexenones cited previously.[4] Although it was possible to obtain a yellow dinitrophenylhydrazone derived from structure VIII, mixtures of dinitrophenylhydrazones were obtained varying in color from yellow to reddish orange indicating considerable mobility of the styryl double bond (β,γ to the carbonyl) into conjugation with the carbonyl. Such facile isomerization contraindicated the desirability of further preoccupation with structures of the type VIII for our intended purposes, requiring the preservation of the styryl function. Concerning the stereochemical configuration of adduct VIII, *vide infra.*

Attention was next directed at the desoxo system, 1-(α-styryl)cyclohexene, to ascertain whether or not the geometrical factors obtaining in a bulky diene of this degree of substitution were still compatible with successful addition to dienophiles of the citraconic and, ultimately, a blocked toluquinone type. Considerably more success was achieved along these lines.

The addition of α-styrylmagnesium bromide (IV) to cyclohexanone afforded 1-(α-styryl)cyclohexanol (XI) in satisfactory yield, but attempts to dehydrate the latter by azeotropic distillation of water formed by mild oxalic acid or iodine[9] catalysis did not meet with complete success. More vigorous conditions employing thionyl chloride and pyridine resulted in a product contaminated with halogen-containing material.[10] Dehydration of the carbinol XI to 1-(α-styryl)cyclohexene (XII) ultimately was accomplished successfully by heating with fused potassium bisulfate.

The diene XII was induced to react with a variety of dienophiles, including maleic anhydride, citraconic anhydride, and *p*-benzoquinone. The adduct from maleic anhydride, XIII, was characterized additionally as the diacid 4-phenyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylic acid (XIIIa), and that from citraconic anhydride was best characterized as 1-methyl-4-phenyl-1,2.3.5,6,7,8,8a-octahydronaphthalene 1,2-dicarboxylic acid (XVI) (concerning the position of the methyl group *vide infra*). Quinone yielded the adduct 1,4-dioxo-9-phenyl-1,4,4a,4b,5,6,7,8,10,10a-decahydrophenanthrene (XVIII).

Concerning the stereochemistry of the Diels–Alder adducts described herein, the following discussion is

(1)(a) Department of Chemistry, Tufts University, Medford 55, Mass.; (b) V. Georgian and J. Lepe M., paper I of this series, *J. Org. Chem.*, **29**, 40 (1964).

(2) G. F. Woods, *J. Am. Chem. Soc.*, **69**, 2549 (1947); G. F. Woods and I. W. Tucker, *ibid.*, **70**, 2174 (1948).

(3) A. Eschenmoser, J. Schreiber, and S. A. Julia, *Helv. Chim. Acta*, **36**, 482 (1953).

(4) I. N. Nazarov, I. V. Torgov, and G. P. Verkholetova, *Dokl. Akad. Nauk SSSR*, **112**, 1067 (1957); *Chem. Abstr.*, **51**, 14, 647 (1957).

(5) C. Crisan and H. Normant, *Bull. soc. chim. France*, 1451 (1957).

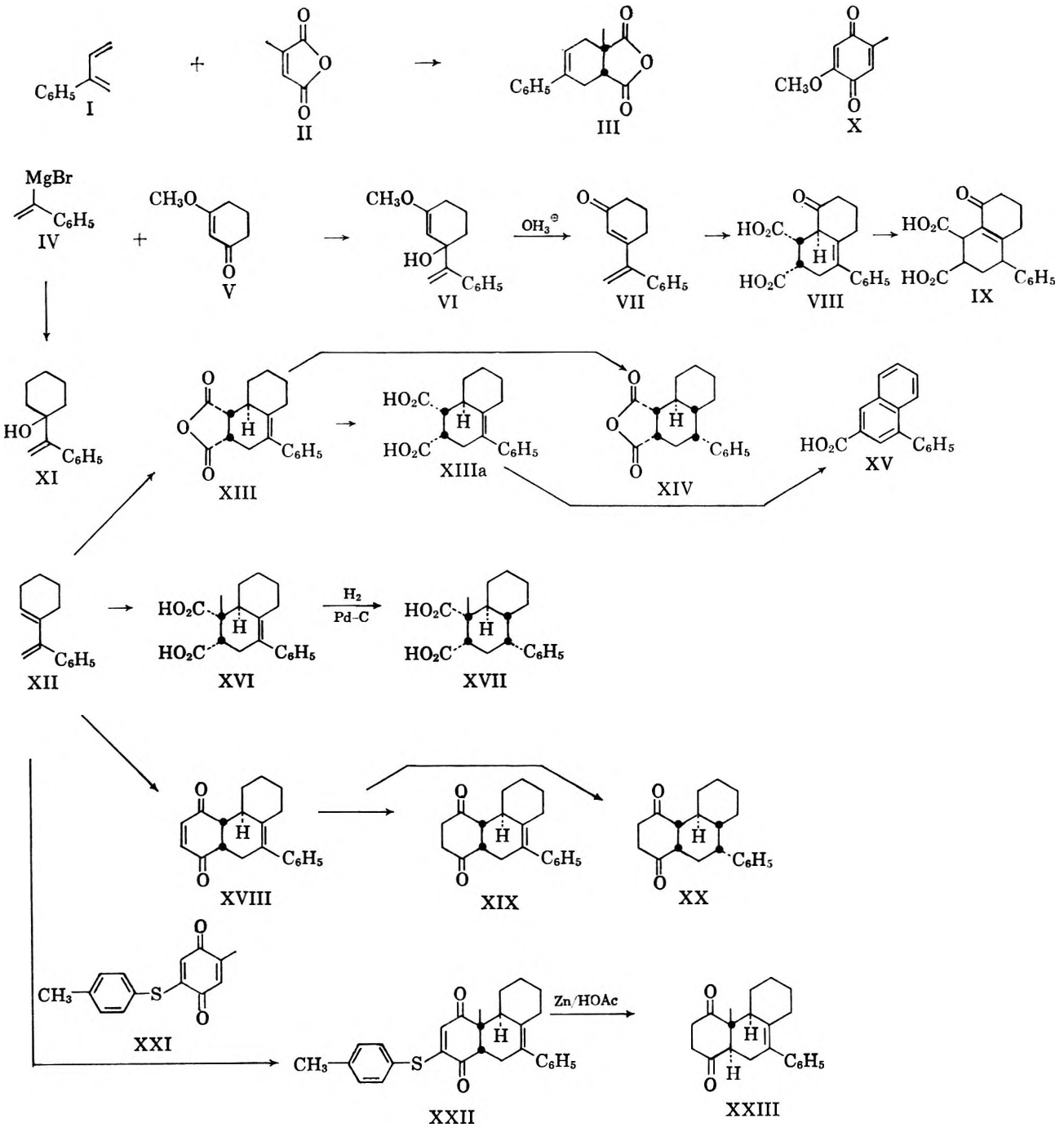
(6) For a general review with collection of references on the vinyl Grignard in synthesis, see H. Normant, *ibid.*, 1764 (1959).

(7) For an earlier application of this Grignard reagent, see K. Alder and J. Haydn, *Ann.*, **570**, 201 (1950).

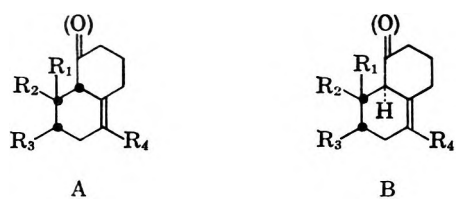
(8) Kindly supplied by Dr. W. S. Knowles, Monsanto Chemical Co., St. Louis, Mo.

(9) H. Hibbert, *J. Am. Chem. Soc.*, **37**, 1748 (1915); P. A. Robins and J. Walker, *J. Chem. Soc.*, 3249 (1956); 177 (1957).

(10) K. Alder and J. Haydn[7] successfully converted an α-styryl *sec*-carbinol to the corresponding chloride with hydrochloric acid.



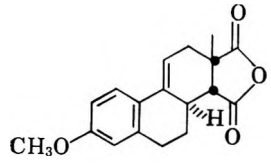
germane. In strict compliance with the Alder–Stein rules,[11] a *cis–syn* configuration, represented in A, would have to be assigned, arising from *endo* addition accounted for by maximum accumulation of unsaturation in the transition state of the Diels–Alder complex.[12]



However, the situation at hand has been rendered sufficiently complicated by the forcing reaction conditions (higher reaction temperatures, prolonged heating periods, lower yields than those obtaining in cleaner-cut cases unencumbered by geometrical factors) as to warrant a reappraisal of such an assignment. Thus, Ansell and Brooks[13] assigned a *cis–syn* configuration to the adduct from maleic anhydride and 1-(1-acetoxyvinyl)cyclohexene (A, R_1 = H; R_2, R_3 = anhydride; R_4 = OAc), which was obtained under *mild* conditions (room temperature) and which obviously differed from a liquid adduct obtained in addition thereto by Nazarov[14] under more forcing conditions (8 hr., boiling benzene) to which the latter investigator assigned a *cis–anti* configuration (B, R_1 = H; R_2, R_3 = anhydride; R_4 = OAc). This case is quite closely comparable with our own. Similar results have been encountered with 1-vinylcyclohexene and maleic anhydride. Cook

(11) K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937).
(12) See also R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).
(13) M. F. Ansell and G. T. Brooks, *J. Chem. Soc.*, 4518 (1956).
(14) I. N. Nazarov, V. F. Kucherov, V. M. Andreyev, and G. M. Segal, *Dokl. Akad. Nauk SSSR*, **104**, 729 (1955); *Chem. Abstr.*, **50**, 11, 304 (1956).

and Lawrence[15] obtained an adduct under mild conditions (in solvent, room temperature) undoubtedly of *cis–syn* configuration (A, $R_1 = R_1 = H$; R_2, $= R_3 =$ anhydride), whereas Nazarov[16] using somewhat more forcing conditions (exothermicity of reaction without solvent, or low temperature and long reaction time) obtained the *cis–syn* adduct and an isomeric one as well, undoubtedly the *cis–anti* adduct (B, $R_1 = R_1 = H$; $R_2 = R_3 =$ anhydride). Moreover, the former substance was isomerized to the latter on heating. While assigning a *cis–syn* configuration to their acetoxyvinylcyclohexene–maleic anhydride adduct, Ansell and Brooks[13] were careful to consider the possibility of a departure from the *endo* addition principle in their diene addition of acetoxyvinylcyclohexene and 2,6-xyloquinone, which was conducted under more strenuous conditions (*i.e.*, 21 hr., boiling benzene or ethanol). Perhaps even more closely related to our case at hand is that of the addition of citraconic anhydride to 1-(1-acetoxyvinyl)cyclohexene which required rather elevated temperatures and which was shown to yield a *cis–anti* adduct (B, $R_1 = CH_3$; $R_2 = R_3 =$ anhydride; $R_1 = OAc$).[17a] Finally, it may be recalled that Heer and Meischer[17b] established that one of the adducts from citraconic anhydride and 6-methoxy-1-vinyl-3,4-dihydronaphthalene under not especially forcing conditions (overnight, cold and short heating period) had a *cis–anti* configuration. The foregoing examples make



it abundantly obvious that whereas the Alder–Stein rule for *endo* addition may be applied with confidence in those cases where low temperatures and not too long reaction periods are employed, quite clearly an opportunity is presented for *exo* addition where forcing conditions obtain. We feel that this latter qualification more accurately represents the situation prevailing in our case at hand and suggest tentatively that a *cis–anti* configuration, *viz.*, B, is possessed by our initially isolated adducts.

Hydrogenation of the styryl function in substances XIII and XVI was smoothly effected over palladium–charcoal to yield XIV and XVII, respectively, and, in the case of XVIII, a di- as well as a tetrahydro derivative was obtained, XIX and XX. The configurational assignment at the newly established ring junctures in these hydrogenation products will be discussed subsequently.

Although the anhydride XIII did not yield any recognizable product on palladium–charcoal dehydrogenation, the dimethyl ester of XIIIa afforded, after dehydrogenation and saponification, a monocarboxy-4-phenylnaphthalene of m.p. 261–263°. This acid is not 4-phenyl-1-naphthoic acid (m.p. 172–173°)[18] and, from its origin, must be assigned the structure 4-phenyl-2-naphthoic acid (XV) by exclusion. An acid of this melting point, but of undefined structure, had been reported previously by Wagner-Jauregg[19] in addition to a carboxyphenylnaphthalene of m.p. 172–173° in a series of degradation products from the adduct of two moles maleic anhydride and 1,1-diphenylethylene. The reported analysis for the Wagner-Jauregg acid, 261.5–263.5°, suggests that it is a monocarboxyphenylnaphthalene, and from its mode of genesis it is very likely identical with our acid XV.

Successful addition to styrylcyclohexene having been accomplished with citraconic anhydride and quinone, it was desired to effect appendage of an additional ring-bearing angular methylation. Toward this end, 5-methoxytoluquinone (X) was attempted in the diene addition, but, in spite of previous successes with this dienophile,[20a] no crystalline product could be isolated. Nevertheless, the efficiency of employing a toluquinone in the Diels–Alder reaction rather than commencing with the citraconic adduct and constructing the next ring therefrom by laborious means compelled a search for other appropriate quinone dienophiles. Such was found in 5-*p*-tolylthiotoluquinone (XXI), which is readily prepared from *p*-toluquinone and *p*-thiocresol, and which bears a gross electronic similarity to the methoxytoluquinone, known to undergo diene addition on the methylated side.[20a] Addition of styrylcyclohexene to the thio-substituted toluquinone XXI proceeded after long reflux in benzene, or preferably toluene, and the adduct is formulated on the basis of the discussion on stereochemistry (*vide supra*) as *cis–anti*-1,4-dioxo-4a-methyl-9-phenyl-2-*p*-tolylthio-1,4,4a,4b,5,6,7,8,10,10a-decahydrophenanthrene (XXII). The thio ether function having served the purpose of directing addition toward angular methylation[20b] (for a discussion on the position of the methyl *vide infra*), it was next desired to desulfurize, reduce the dioxoethylenic bond while preserving the styryl double bond, and isomerize the *cis* ring juncture to *trans*. The usual method of desulfurization by means of Raney nickel did not prove particularly adaptable. The results were erratic and over-reduction of the carbonyl and styryl functions could not be cleanly avoided. A method which was devised to overcome this difficulty, and which served uniquely to accomplish the three desired purposes just specified, consisted of refluxing for 8 hr. with zinc in acetic acid. Thus, *trans–anti*-1,4-dioxo-4a-methyl-9-phenyl-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydrophenanthrene (XXIII) was produced from XXII by this means, which has been applied in other series of our investigations, and which will be reported in greater detail in subsequent

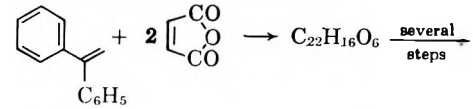
(15) J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 58 (1938).

(16) I. N. Nazarov, V. F. Kucherov, and V. M. Andreyev, *Dokl. Akad. Nauk SSSR*, **102**, 751 (1955).

(17)(a) F. Winternitz and C. Balmossiere, *Tetrahedron*, **2**, 100 (1958); I. N. Nazarov, V. F. Kucherov, and V. M. Andreyev, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **67**, 77 (1955); *Chem. Abstr.*, **50**, 1713 (1956). (b) J. Heer and K. Meischer, *Helv. Chim. Acta*, **31**, 219 (1948); **32**, 1572 (1949).

(18) J. v. Braun and E. Anton, *Ber.*, **67B**, 1051 (1934).

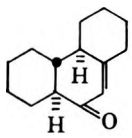
(19) T. Wagner-Jauregg, *Ann.*, **491**, 1 (1931).



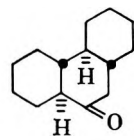
acid (171.5–173.5°) + acid (261.5–263.5°)

(20)(a) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. MacLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952); M. Orchin and L. W. Butz, *J. Org. Chem.*, **8**, 509 (1943). (b) This course of the Diels–Alder reactions with alkylthio-substituted quinones has been firmly established in several other cases and, for a disclosure of these results, see V. Georgian and L. L. Skaletzky, *ibid.*, **29**, 51 (1964).

publications. The *trans* ring juncture is postulated on the basis of findings by Robins and Walker[21] and our own investigations on zinc–acetic acid reductions of Diels–Alder products from quinone and 3,20-diacetoxypregna-5,16,20-triene.[22] Short treatment of a few minutes' duration without heat of a *cis*-1,4-dioxo-Δ^2-octalin with zinc–acetic acid usually permits the reduction of the ethylenic bond with survival of the *cis* ring juncture. Prolonged treatment supplemented by heating results in reduction concomitant with isomerization to a *trans* ring fusion. Moreover, whereas *cis*-α decalone isomerizes only extremely slowly to *trans*-α-decalone at room temperature,[23] *cis*-1,4-dioxodecalins have been found to be considerably less stable with respect to their *trans* isomerides.[24] The conditions employed in the reduction of XXII to XXIII, *i.e.*, 8-hr. refluxing, ensure that the stereochemistry of XXIII is almost certainly *trans–anti*. This assignment is further corroborated by the proof in the case of a similar desulfurization of the adduct of butadiene and 5-*p*-tolylthiotoluquinone. The angularly methylated *trans* ring fusion is clearly evident by the single strong infrared absorption at 1450 cm.$^{-1}$ [25] of the resulting 8a-methyl-Δ^2-octalin. Such a result is in consonance with the greatest stability of the *trans–anti–trans* form of perhydrophenanthrenes (*cf.* W. S. Johnson[26]). A *trans–anti* configuration has been elucidated experimentally in a closely related case for the condensation product XXIV of sodiocyclohexanone and 1-acetylcyclohexene.[27]

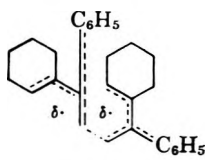


XXIV

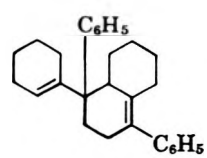


XXV

The Diels–Alder reaction between styrylcyclohexene and mesaconic acid yielded only a heavy acidic oil from which no identifiable product could be obtained. When the reaction was attempted with fumaric acid, the product isolated, m.p. 198–200°, was found on elemental analysis to contain no oxygen and appeared to be simply a Diels–Alder dimer of the diene to which structure XXVII is provisionally assigned. This structure is based on a consideration of the principles governing the orientational course of the diene reaction between unsymmetrical addends presented and discussed in detail in our first paper of this series,[1b] in which the phenyl–methyl relationship in III was elucidated. Application of those principles in the addition of citraconic anhydride and 5-*p*-tolylthiotoluquinone to styrylcyclohexene leads to the suggested structures XVI and XXII for these adducts. By way of brief recapitulation it may be stated that *the gross structural character of the adduct will be determined by an association of the addends in the transition state (of possibly a spin-paired nature)*[28a] *generating greatest electron delocalization.*

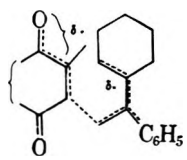


XXVI



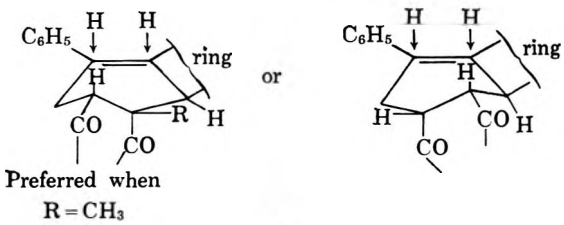
XXVII

We may envision as illustrative of this principle the transition state XXVI, as the precursor to XXVII, resulting in electron delocalization involving both aromatic rings, tertiary benzyl and secondary ring carbon atoms. Alternate association of the components to that depicted in XXVI would lead to higher energy transition states. Analogous transition states may be constructed as intermediates in the formation of XVI and XXII, such states (XVIa and XXIIa synoptic forms) being of lower energy than those leading to the adducts inverse to XVI and XXII.[28b]



XVIa and XXIIa

Finally, an account may be in order on the configurational assignments at the ring junctures established on hydrogenation to the products XIV, XVII, and XX. The complete configurations have been assigned as *cis–anti–trans–cis* by analogy to the hydrogenation of XXIV to *trans–anti–trans* 9-oxoperhydrophenanthrene (XXV).[27,29] This assignment of configuration may be reinforced by a conformational analysis in which the most favorable half-chair conformations are selected bearing the smallest number of axial substituents (other than hydrogen) with catalyst approach invoked from the least hindered side.[30] Such a picture, illustrated in C, compels the stereochemical arrangement indicated in the previous formulas:



C

(21) P. A. Robins and J. Walker, *J. Chem. Soc.*, 642, 1612 (1952); 3960 (1954).

(22) V. Georgian and Lupe T. Georgian, *J. Org. Chem.*, **29**, 58 (1964).

(23) W. Hückel, *Ann.*, **441**, 1 (1925).

(24) R. M. Lukes, G. I. Poos, and L. H. Sarett, *J. Am. Chem. Soc.*, **74**, 1401 (1952).

(25) Paper III in this series; *cf.* also, R. H. Baker, L. S. Minckler, and A. S. Hussey, *J. Am. Chem. Soc.*, **81**, 2379 (1959).

(26) W. S. Johnson, *Experientia*, **8**, 315(1951).

(27) R. P. Linstead, S. B. Davis, and R. R. Whetstone, *J. Am. Chem. Soc.*, **64**, 2009 (1942).

(28)(a) Recent evidence has accumulated which indicates that, while the Diels–Alder reaction may involve transient intermediates in which one bond has been formed [ref. 12 of C. Walling and J. Peisach, *ibid.*, **80**, 5819 (1958); R. P. Lutz and J. D. Roberts, *ibid.*, **83**, 2198 (1961)], the intermediacy of a triplet biradical has been ruled out [N. J. Turro and G. S. Hammond, *ibid.*, **84**, 2841 (1962)]. (b) See also F. Winternitz and C. Balmossiere, *Tetrahedron*, **2**, 100 (1958); L. D. Bergelson (reporting on I. N. Nazarov's work), *ibid.*, **6**, 161 (1959); M. F. Ansell and G. T. Brook, *J. Chem. Soc.*, 4518 (1956), for additional experimental evidence corroborating the orientational course of Diels–Alder reactions involving addends of the general type discussed in this publication.

(29) See also P. A. Robins and J. Walker, *ibid.*, 642 (1952).

(30) R. P. Linstead W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *J. Am. Chem. Soc.*, **64**, 1985 (1942).

Experimental[31]

α-Bromostyrene.—To a solution of 528 g. of styrene dibromide in 1200 ml. of ethanol there was added with stirring 112 g. of potassium hydroxide in the minimum amount of ethanol. The addition was made in a thin stream, and the reaction was maintained at room temperature with occasional cooling. Immediate precipitation of potassium bromide followed and, after addition was complete, stirring was continued until neutrality was reached. Water was added and the product was taken up in ether. The ether solution was washed with water, dried over magnesium sulfate, and distilled to yield α-bromostyrene, 236 g. (64%), b.p. 80–85° (10 mm.), lit.[32] b.p. 77° (9 mm.).

Dihydroresorcinol methyl ether (V) was prepared by methylating dihydroresorcinol[33] (111 g.) in 1 l. of acetone with 111 g. of anhydrous potassium carbonate, and 93 ml. of dimethyl sulfate. The reaction mixture was stirred at ordinary temperature for 12 hr. The solids were filtered, the acetone was distilled, and the product, 75 g., was distilled at 105–111° (11 mm.).

3-(α-Styryl)-Δ²-cyclohexenone (VII) and *cis–anti*-8-oxo-4-phenyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylic Acid (VIII).—A solution of α-styrylmagnesium bromide (IV)[7] was prepared by the addition of 104 g. of α-bromostyrene in 500 ml. of anhydrous ether to 13 g. of magnesium turnings (under nitrogen) in the usual manner for the preparation of a Grignard reagent. After the addition of the halide was complete, the reaction was stirred for 0.5 hr. longer and then refluxed 10 min.

Then, with ice cooling, there was added in a thin stream a solution of 72 g. of dihydroresorcinol methyl ether in 100 ml. of dry ether, and stirring was maintained 5 hr., after which a solution of 350 ml. of water and 35 g. of sulfuric acid was added and agitation was continued 2 hr. longer. The ether layer was separated and, combined with additional ether extracts of the aqueous layer, was washed with water, sodium carbonate solution, water, and saturated sodium chloride solution, and was dried over magnesium sulfate. Evaporation of the ether *in vacuo* with very gentle heat left a residue of 100–110 g. of a dark yellow oil, VII, which could not be distilled without extensive polymerization. In one experiment there was obtained from this size run 15 g. of distillate, VII, b.p. 150–170° (1.0 mm.), whose infrared spectrum indicated the presence of conjugated carbonyl. This material could not be characterized further at this point because of its extreme instability, and it was used forthwith in the diene addition with maleic anhydride.

A solution of 13 g. of the aforementioned product, freshly distilled, and 6.4 g. of maleic anhydride in 100 ml. of toluene was refluxed for 20 hr. The volatiles were then removed *in vacuo* on the steam bath and the residual oil was taken up in 10% sodium hydroxide solution. This alkaline solution was extracted several times with ether, treated with Norit, and acidified. The precipitated gum was taken up in ether, and this solution was washed with water and dried over magnesium sulfate. After the ether solution was evaporated the residual thick oil was allowed to stand for about 1 month when it was noticed that some crystallization had taken place. A little chloroform was added as a thinner, and the crystals were filtered and were recrystallized from acetone and then from ethyl acetate, m.p. 208–210°. Infrared absorption revealed no conjugated carbonyl and thus expression VIII best fits the composition of this substance.

Anal. Calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.73. Found: C, 68.85; H, 5.71.

The **dinitrophenylhydrazone of VIII** prepared in the usual fashion was yellow and had m.p. 245–247° (from ethanol).

Anal. Calcd. for $C_{24}H_{22}N_4O_8$: C, 58.29; H, 4.45. Found: 57.85; H, 4.61.

Reported recrystallization resulted in orange and reddish products which indicated gradual transformation to the dinitrophenylhydrazone of the conjugated carbonyl tautomer IX.

Attempted Diels–Alder Addition of VII with Citraconic Anhydride (II) and 5-Methoxytoluquinone (X).—These additions were attempted by refluxing equimolar quantities of the reactants in anhydrous benzene for 35–38 hr. The experiments with citraconic anhydride, worked up as in the previous case with maleic anhydride, yielded only polymeric tars. In those cases with 5-methoxytoluquinone, the latter was recovered unchanged in 80–90% yield by direct crystallization from the reaction solution after partial evaporation of solvent.

1-(α-Styryl)cyclohexanol (XI).—To a solution of α-styrylmagnesium bromide prepared from 126 g. of α-bromostyrene and 17 g. of magnesium turnings in 700 ml. of anhydrous ether there was added with ice-bath moderation of the reaction a solution of 68 g. of cyclohexanone in 500 ml. of anhydrous ether. A yellowish complex gradually precipitated and stirring was continued for 2 hr. with cooling after the addition was complete. Ice (300 g.) and a solution of 50 g. of ammonium chloride in 250 ml. of water were added, and the ether layer was separated and combined with several additional ether extracts of the aqueous phase. The ether solution was washed with water several times and dried over sodium sulfate. The product, 1-(α-styryl)cyclohexanol (XI), was distilled *in vacuo*, yielding 100 g. (72%), b.p. 100–105° (0.1 mm.), $n^{25}D$ 1.5500. A small forerun was rejected. Infrared absorption indicated an hydroxyl band at 2.8–2.9 μ.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.10; H, 8.96. Found: C, 83.32; H, 8.79.

1-(α-Styryl)cyclohexene (XII).—A mixture of 35 g. of 1-(α-styryl)cyclohexanol (XI) and 45 g. of fused powdered potassium bisulfate (Mallinckrodt) was heated at 150–155° under the passage of a slow stream of nitrogen for 1 hr. The cooled reaction was taken up in ether and water, and the ether solution was washed with water, bicarbonate solution, water to neutral reaction, and finally with saturated sodium chloride solution. It was dried over sodium sulfate and the product was distilled *in vacuo*, yielding 23 g. (73%) of 1-(α-styryl)cyclohexene (XII), b.p. 100–103° (1.0 mm.), $n^{25}D$ 1.5710. Infrared analysis indicated absence of hydroxyl. This diene could be stored in the cold a short time, but within 2 weeks considerable polymerization was encountered.

Anal. Calcd. for $C_{14}H_{16}$: C, 91.30; H, 8.74. Found: C, 90.93; H, 8.89.

Diels–Alder Adduct of Styrylcyclohexene XII and Maleic Anhydride, *cis–anti*-4-Phenyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylic Acid (XIIIa) and Anhydride XIII.—Maleic anhydride (3 g.) and 1-(α-styryl)cyclohexene (XII) (5.4 g.) were heated on the steam bath for 9 hr. A bright yellow color was noted on admixture of the two components. The cooled reaction melt was then taken into benzene and washed with water several times. After being dried over sodium sulfate, the solvent was evaporated leaving 5.5 g. of a crystalline compound, m.p. 112–115°. Recrystallization from benzene–cyclohexane or ethyl acetate–cyclohexane raised the melting point to 119.5–120.3°. This substance, insoluble in bicarbonate solution, possessed infrared absorption at 5.60 μ, diagnostic for the five-membered anhydride carbonyl of adduct XIII.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.60; H, 6.41. Found: C, 77.08; H, 6.58.

The anhydride XIII was taken up in dilute alkali and the **diacid XIIIa** was precipitated on acidification. It could be recrystallized from ethanol, m.p. 215–216° dec.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 72.00; H, 6.66. Found: C, 71.52; H, 6.82.

***cis–anti–trans–cis*-4-Phenyldecahydronaphthalene-1,2-dicarboxylic Acid Anhydride (XIV).**—The anhydride XIII (1.0 g.) was hydrogenated at ordinary temperature and pressure in 40 ml. of ethanol over 100 mg. of 5% palladium–charcoal. One molar equivalent of hydrogen was absorbed. The catalyst was filtered and washed with acetone. The combined organic solutions were evaporated, and the crude crystalline residue was filtered and washed with cyclohexane, yielding 900 mg., m.p. 150–155°. Recrystallization from acetone–cyclohexane afforded pure XIV, m.p. 156–157°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.12. Found: C, 75.91; H, 7.13.

4-Phenyl-2-naphthoic Acid (XV).—The anhydride XIII (2.0 g.) was converted to the diacid XIIIa as described previously, and the crude ether extract of the latter was methylated with an ethereal solution of diazomethane prepared from 4.0 g. of N-nitroso-N-methylurea. The oily diester resulting from evaporation of the ether was mixed with 500 mg. of 10% palladium–charcoal and heated at 300° for about 1.5 hr., at the end of which all gas evolution had practically ceased. The cooled reaction mixture was extracted with ethanol (Norit) and the residual oil, remaining after evaporation of the ethanol, was treated with 20

(31) All melting points are uncorrected. Analyses were performed by Miss Hildegarde Beck, Microanalytical Laboratory, Northwestern University. Infrared spectra were determined in chloroform solution on a Baird double beam instrument, Model AB-2.

(32) M. H. Jones, *Can. J. Chem.*, **34**, 108 (1956).

(33) R. E. Thompson, *Org. Syn.*, **27**, 21 (1900).

ml. of 5% alkali and 5 ml. of ethanol on the steam bath for 1 hr. The cooled alkaline solution was filtered (Norit) and extracted with ether a few times and then acidified. The precipitated material was taken up in ether and dried, and evaporation of the ether afforded 4-phenyl-2-naphthoic acid (XV), which was recrystallized from dilute ethanol, m.p. 261–263°.

Anal. Calcd. for $C_{17}H_{12}O_2$: C, 82.40; H, 4.88. Found: C, 82.18; H, 4.89.

Diels–Alder Adduct of 1-(α-Styryl)cyclohexene (XII) and Citraconic Anhydride, *cis-anti*-1-Methyl-4-phenyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylic Acid (XVI).—A mixture of 12 g. 1-(α-styryl)cyclohexene (XII) and 7.4 g. of citraconic anhydride (II) was heated on the steam bath 1 hr. and then refluxed in 40 ml. of dry benzene for 48 hr. The volatiles were removed *in vacuo* to eliminate also any unchanged citraconic anhydride, and the residue was treated with 10% alkali. The alkaline solution, after being extracted several times with ether, was acidified, and the precipitated material was extracted with ether. The dried (sodium sulfate) ether solution on evaporation deposited 5.4 g. of XVI, m.p. 224–227° dec. Recrystallization from ethanol raised the melting point to 232–233° dec.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.61; H, 7.00. Found: C, 73.02; H, 7.13.

***cis-anti-trans-cis*-1-Methyl-4-phenyldecahydronaphthalene-1,2-dicarboxylic Acid (XVII).**—The hydrogenation of 1.0 g. XVI in 50 ml. ethanol over 100 mg. 5% palladium–charcoal was conducted at ordinary temperature and pressure. One equivalent of hydrogen was absorbed in 6 hr., and the reaction was worked up in the usual way to yield 900 mg. of XVII, m.p. 254–256°, from ethanol. Additional recrystallization from ethanol raised the melting point to 258–259°.

Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.13; H, 7.64. Found: C, 72.34; H, 7.58.

Diels–Alder Addition of Diene XII with Quinone, *cis-anti*-1,4-Dioxo-9-phenyl-1,4,4a,4b,5,6,7,8,10,10a-decahydrophenanthrene (XVIII).—A solution of 15.0 g. of 1-(α-styryl)cyclohexene (XII) and 26 g. of quinone (large excess) in 100 ml. of dry benzene was refluxed for 7 hr., and the solvent was then evaporated. The residue was maintained *in vacuo* on the steam bath to eliminate any unchanged quinone and was then treated with a minimum quantity of ethanol which induced crystallization of XVIII, 3.0 g. (13%), m.p. 116–118°. The analytical sample was light yellow in color, m.p. 117–118°.

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.10; H, 6.89. Found: C, 82.60; H, 6.95.

Hydrogenation of XVIII, *cis-anti*-1,4-Dioxo-9-phenyl-1,2,-3,4,4a,4b,5,6,7,8,10,10a-dodecahydrophenanthrene (XIX) and *cis-anti-trans-cis*-1,4-Dioxo-9-phenyltetradecahydrophenanthrene (XX).—The hydrogenation of adduct XVIII (1.0 g.) was conducted in ethanol (50 ml.) over 100 mg. of 5% palladium–charcoal at ordinary temperature and pressure. One mole equivalent of hydrogen was absorbed fairly quickly (30 min.), and after the usual work-up a white substance of m.p. 145.5–146.5° was obtained by crystallization from acetone–cyclohexane. Infrared examination revealed no conjugated carbonyl and, accordingly, expression XIX fits the composition of this substance. The analytical sample melted at 146–147° (acetone–cyclohexane).

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.59; H, 7.54. Found: C, 81.56; H, 7.73.

When an analogous hydrogenation of XVIII was conducted so as to ensure the absorption of two molar equivalents of hydrogen (3–4 hr.), there was isolated by crystallization from acetone a substance of m.p. 202–204°, whose composition corresponds to XX. The analytical sample melted at 203–204° (acetone).

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.15. Found: C, 80.91; H, 8.08.

5(or 6?)-*p*-Tolylthiotoluquinone (XXI).—To a suspension of 122 g. of toluquinone in 200 ml. of absolute ethanol was added 62 g. of *p*-thiocresol. An exothermic reaction ensued, and a clear dark red solution soon resulted, whereupon the reaction was cooled to and maintained at room temperature overnight. The product, 5(6?)-*p*-tolylthiotoluquinone (XXI), was filtered, washed with ligroin (b.p. 86–100°), and recrystallized from benzene–ligroin twice, to give bright orange crystals, 40 g., m.p. 151–153°. The analytical sample had m.p. 154.5–155.5°.

Anal. Calcd. for $C_{14}H_{12}O_2S$: C, 68.90; H, 5.00; S, 13.13. Found: C, 69.40; H, 5.00; S, 13.16.

Diels–Alder Addition of Diene XII with 5-*p*-Tolylthiotoluquinone (XXI), *cis-anti*-1,4-Dioxo-4a-methyl-9-phenyl-2-(*p*-tolylthio)-1,4,4a,4b,5,6,7,8,10,10a-decahydrophenanthrene (XXII).—A solution of 5 g. of 1-(α-styryl)cyclohexene (XII) and 6.6 g. of 5-*p*-tolylthiotoluquinone (XXI) in 50 ml. of toluene containing a trace of hydroquinone was refluxed for 48 hr. The crystalline residue remaining after vacuum removal of solvent was triturated with a few milliliters of ethanol to dissolve some unchanged quinone. The filtered insoluble portion was recrystallized twice from benzene–hexane to yield 3.0 g. of XXII, pale yellowish in color, m.p. 205–208°. The analytical sample was recrystallized once again from ethanol, m.p. 207–209°. The infrared spectrum showed a strong characteristic band at 6.40 μ (thio-substituted enedione) in addition to the usual conjugated carbonyl bands.

Anal. Calcd. for $C_{28}H_{28}O_2S$: C, 78.50; H, 6.58. Found: C, 78.88; H, 6.38.

***trans-anti*-1,4-Dioxo-4a-methyl-9-phenyl-1,2,3,4,4a,4b,5,6,7,-8,10,10a-dodecahydrophenanthrene (XXIII).**—To a solution of 1.0 g. of adduct XXII in 50 ml. of acetic acid heated on the steam bath was added 10 g. of zinc dust in small portions with swirling during 15 min. The initial yellow color of the solution disappeared, and the reaction mixture was refluxed 8 hr. The zinc was filtered, most of the acetic acid was removed on the steam bath *in vacuo*, and the residue was taken up in sodium carbonate solution and ether. The ether solution was washed with water until the washings were neutral, dried over sodium sulfate, and evaporated. The residue was crystallized from benzene–hexane to yield XXIII, 525 mg., m.p. 145–147°. Infrared absorption revealed only nonconjugated carbonyl function.

Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.77; H, 7.84. Found: C, 82.03; H, 7.82.

Attempted Diels–Alder Additions of 1-(α-Styryl)cyclohexene (XII) with Fumaric Acid, Mesaconic Acid, and 5-Methoxytoluquinone (X), to Give 1-(α-Styryl)cyclohexene Dimer (XXVII).—No successful addition resulted from refluxing diene XII with 5-methoxytoluquinone in toluene or xylene solution for 36–48 hr.; heavy intractable oils resulted. The attempted addition with mesaconic acid (36-hr. reflux in propionic acid solution) resulted in recovery of most of the mesaconic acid.

A solution of 8.5 g. of diene XII and 8.0 g. of fumaric acid in 35 ml. of propionic acid was refluxed 60 hr. After the reaction cooled, a large amount of unchanged fumaric acid was filtered off, and the mother liquors were allowed to stand. A few weeks later it was noted that a small quantity of crystals had deposited, 400 mg., m.p. 195–200°. This substance was crystallized from dilute ethanol, whereupon it melted at 198–200°. Infrared analysis revealed no carbonyl bands, and elemental analysis, while not in excellent agreement with the dimer of XII, suggests strongly that it is indeed the nature of this material for which structure XXVII is advanced.

Anal. Calcd. for $(C_{14}H_{16})_2$: C, 91.2; H, 8.74. Found: C, 90.50; H, 8.77.

Acknowledgment.—This work was supported by a grant from the Research Corporation, New York, for which the authors are most grateful.

Alicyclic Syntheses. III. The Diels–Alder Reaction with Alkylmercaptotoluquinones. A Synthesis of *trans*-9-Methyl-Δ^6-octalin-1,4-dione[1]

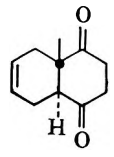
V. GEORGIAN[2a] AND L. L. SKALETZKY[2b]

Department of Chemistry, Tufts University, Medford, Massachusetts, and The Department of Chemistry, Northwestern University, Evanston, Illinois

Received October 29, 1962

The structures of the mercaptotoluquinols arising from toluquinone by the action of sodium thiosulfate have been established as the 5-mercapto and (principally) the 6-mercapto isomer, contrary to previous reports that this reaction was unidirectional and that the latter substance (m.p. 111–112°) was the 3-mercapto isomer. A corresponding change has been made in the methylmercaptotoluquinone structures and the latter have been utilized in the Diels–Alder reaction with butadiene to synthesize *trans*-9-methyl-Δ^6-octalin-1,4-dione, an intermediate of potential utility in steroid total synthesis. The course of the desulfuration–reduction of the alkylmercaptoquinone–diene adducts by means of zinc–acetic acid has been elucidated and found to proceed *via* the reduction initially of the dioxoethylenic function to a dihydro stage XV.

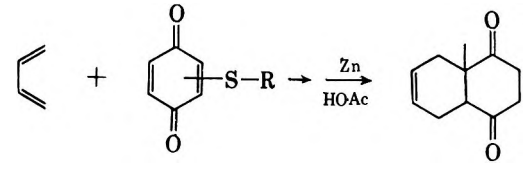
The potential utility of *trans*-9-methyl-Δ^6-octalin-1,4-dione (I) as the A/B ring moiety in projected total synthesis of steroids may be demonstrated. Apart



I

from the obvious gross relationship of this structure to that of the lower portion of the steroid molecule, this fragment bears the following features: (1) carbonyls at C-1 and C-4 which may be differentially masked or altered to permit attachment of rings C/D or C/D-homo by adaptation of methods already recorded in the now substantial lore of alicyclic synthesis[3]; (2) the C-4 carbonyl which, having served the function of controlling the stereochemistry of the ring fusion, also affords a means of introducing unsaturation at some appropriate juncture in a synthesis in the lower portion of the steroid molecule (either at 5,6 or 4,5, steroid numbering system), a matter of some concern in A/B-*trans* steroidal systems,[4] or alternatively of introducing alkyl or other groups at position 6 in the steroid molecule, a substitution which has yielded currently some of the most active progestational and antiphlogistic compounds[5]; (3) the Δ^6 olefinic function, which by virtue of its transformability into isomeric halohydrins either by hypohalous acids or chromyl chloride[6] or epoxidation, etc., is tantamount to having a C-2 or C-3 oxygen function in the steroid molecule. Thus, a facile route to I was desired.

Our previous experience with diene additions to *p*-tolylthiotoluquinone followed by zinc–acetic acid desulfuration, yielding what appeared to be most likely angularly methylated polycarbocyclic systems,[7] suggested as the most efficient way of obtaining I the Diels–Alder reaction of butadiene with a 5- or 6-alkylmercaptotoluquinone.



Whereas in the previous work[7] a *p*-thiocresyl moiety had been affixed to the quinone in a convenient one-step operation and without regard for its exact position thereon either at C-5 or C-6, it was felt a more deliberate synthesis of the simpler 5- or 6-methylmercaptotoluquinone would better serve the problem at hand and secure more firmly the structures postulated formerly for the diene adducts with thio-substituted quinones. Moreover, although the course of Diels–Alder reaction with this class of dienophiles leading to the angularly methylated structures[7] had been inferred from the parallel reactions with the electronically closely related alkoxytoluquinone system,[8] more corroborative evidence on this point was deemed necessary. To this end a synthesis of 5- and/or 6-methylmercaptotoluquinone was sought, and the butadiene addition to this system and the subsequent zinc–acetic acid desulfuration–reduction were studied.

Of the three possible methylmercaptotoluquinones only two isomers had been described. Alcalay[9] had reported the preparation of 5-methylmercaptotoluquinone (IV) from the corresponding mercaptan III

(1)(a) Contribution No. 296, Department of Chemistry, Tufts University; (b) this paper is abstracted in part from the Doctoral dissertation of L. L. Skaletzky, submitted to the Graduate School of Northwestern University in partial fulfillment of the requirements for the Degree of Doctor of Philosophy, August, 1959.

(2)(a) Department of Chemistry, Tufts University, Medford 55, Mass.; (b) U. S. Rubber Fellow, 1956–1957. Union Carbide Fellow, 1957–1958.

(3) In particular, see L. D. Bergelson, *Tetrahedron* **6**, 161 (1959), on the elaboration by I. N. Nazarov and co-workers of some interesting synthetic substances which resemble steroids.

(4) See R. N. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, A. G. Long, J. F. Oughton, L. Stephenson, T. Walker, and B. M. Wilson, *J. Chem. Soc.*, 4356 (1956), for a discussion of the problem and for references to earlier work in this area principally by Djerassi and co-workers.

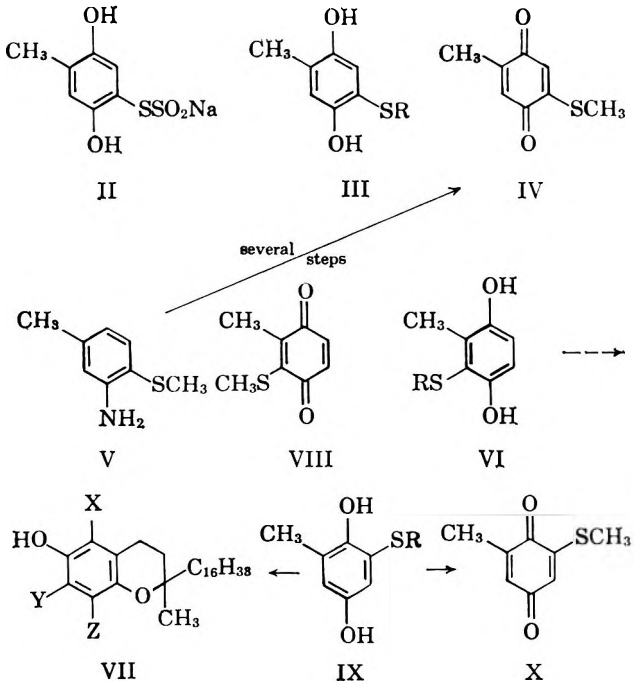
(5) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek, and J. A. Hogg, *J. Am. Chem. Soc.*, **78**, 6213 (1956); J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes, and W. E. Dulin, *ibid.*, **80**, 2904 (1958); H. J. Ringold, E. Batres, and G. Rosenkrantz, *J. Org. Chem.*, **22**, 99 (1957); J. A. Hogg, C. B. Spero, J. L. Thompson, B. J. Magerlein, W. B. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson, and J. A. Campbell, *Chem. Ind.* (London), 1002 (1958); A. Bowers, and H. J. Ringold, *J. Am. Chem. Soc.*, **80**, 4423 (1958); J. A. Edwards, A. Zaffaroni, H. J. Ringold, and C. Djerassi, *Proc. Chem. Soc.*, 87 (1959).

(6) S. L. Cristol and K. R. Eilar, *J. Am. Chem. Soc.*, **72**, 4353 (1950) H. L. Slates and N. L. Wendler, *ibid.*, **78**, 3749 (1956). See also L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., N. Y., 1959, Chap. 7, for a general treatment of steroid ring A olefins and oxidation products derived therefrom.

(7) V. Georgian and J. Lepe M., papers I and II in this series, *J. Org. Chem.*, **29**, 40, 45 (1964).

(8) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952); M. Orchin and L. W. Butz, *J. Org. Chem.*, **8**, 509 (1943).

(9) W. Alcalay, *Helv. Chim. Acta*, **30**, 578 (1947).

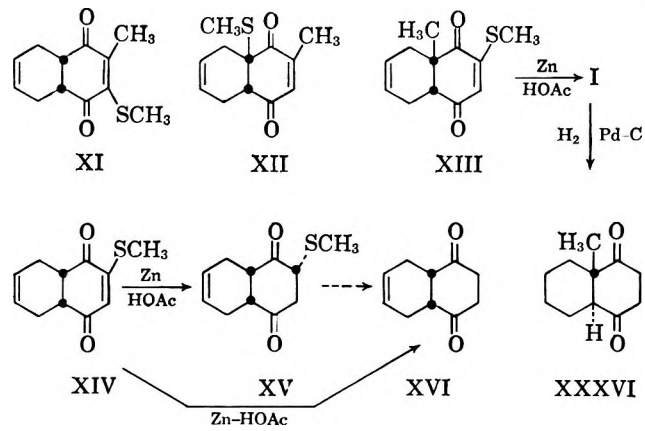


(R = H) by S-alkylation and oxidation with ferric chloride. Mercaptan III (R = H) was claimed to have been prepared in quantitative yield by the reaction of *p*-toluquinone with sodium thiosulfate and subsequent reduction of the resulting sodium aryl thiosulfate II with zinc and hydrochloric acid. Alcalay reported melting points for III (R = H) and IV, as 136° and 113°, respectively, but supplied no details as to a proof for the constitution of these substances.

Repetition of this work, however, paralleled the experiences of Karrer and Dutta[10] who, like us, found that this reaction led to more than a single product. Karrer and Dutta obtained by the Alcalay procedure a mixture of two mercaptans, separable into a minor fraction, m.p., 176–179°, and a major one, m.p., 111–112°. The minor product was converted into a methylmercaptotoluquinone, m.p. 139–140°, established unequivocally as the 5-isomer IV by means of an independent synthesis from methylmercapto-*m*-toluidine (V). The mercaptan of m.p. 176–179° is thus authentic III (R = H).

The corresponding methylmercaptotoluquinone from the preponderant lower melting mercaptan (111–112°) melted at 140–142°, depressed the melting point of the 5-isomer IV, and was assigned the structure of 3-methylmercaptotoluquinone (VIII). This assignment was based primarily on observation that the corresponding methylmercaptotoluquinol of m.p. 83–84° yielded on reaction with phytol (in a typical acid-catalyzed coumaran synthesis) a methylmercaptomethyltocol, which generated, after desulfuration, a substance which was taken to be 8-methyltocol (VII, X = Y = H, Z = CH_3; in the precursor, X = H, Y = SCH_3, Z = CH_3). The identification of the methyltocol was made solely on the basis of mixture melting point comparison of a derivative of the synthetic product with the corresponding one from δ-tocopherol, despite a small difference in their melting points. Structure VI (R = CH_3) was thereby deduced for the methylmercaptotoluquinol of m.p. 83–84°. Because of the possibility of isomorphism of these derivatives and the lack of additional more compelling structure proofs[11] for the intermediates involved in these transformations, this assignment of structure for the isomeric methylmercaptotoluquinone of m.p. 140–142° appeared rather tenuous. Thus, it was desired to approach the problem more directly, since its solution would in turn comprise an essential step in the structural elucidation of the Diels–Alder adducts from this class of quinones.

The position of the methylmercapto group in the quinone (m.p. 140–142°) was established by a study of the ultraviolet absorption spectrum of the Diels–Alder adduct of the quinone with butadiene. Under the conditions used in the diene addition of 5-methoxy-*p*-toluquinone with butadiene[8] (*ca.* 4 days at 100°), the quinone (m.p. 140–142°) gave an 80% yield of a light yellow adduct, which absorbed in the infrared at 5.89 and 6.00 mμ indicative of conjugated carbonyl function and gave an elemental analysis which was in agreement with the possible isomeric structures XI, XII, and XIII.



The ultraviolet spectrum of this adduct possessed a λ_{max}^{EtOH} 322 mμ (log ε 3.95). Structure XII may thus be dismissed as a possibility for this substance, since the chromophoric system of XII is known to absorb maximally at 237 mμ.[12] The bathochromic shifts upon substitution in the chromophoric system X–C=C–C=O have been recorded[13a] for the following auxochromic groups X: CH_3 (10), OCH_3 (50), SR (85 mμ), the shifts referring to systems where X = H. In the dioxoethylenic parent chromophore at hand, —COCX=CHCO—, the corresponding bathochromic shifts were found to be 15 and 47 mμ for X = CH_3 and OCH_3, respectively.[12] The butadiene–methylmercaptotoluquinone adduct shows a bathochromic shift of 100 mμ which is indicative of the presence of the SR auxochrome[13b] but does not distinguish between the two possible structures XI and XIII. As a comparison substance with a corresponding chromophoric system the adduct XIV from butadiene and methylmercapto-*p*-benzoquinone was prepared and found to possess maximum absorption at 332 mμ (log ε 3.83), coincident with that of the adduct in question. Therefore, the latter must be the angularly methylated structure XIII, and the toluquinone of m.p. 140–142° necessarily pos-

(10) P. Karrer and P. C. Dutta, *Helv. Chim. Acta.*, **31**, 2080 (1948).

(11) One further piece of information taken[10] in favor of structure VIII was that it could be converted to a bismethylmercapto derivative (assumed to be the 3,5 isomer) on direct reaction with methyl mercaptan, whereas the 5-mercaptoquinone IV did not yield a recognizable product; see also ref. 15.

(12) H. Bastron, R. Davis, and L. W. Butz, *J. Org. Chem.*, **8**, 515 (1943).

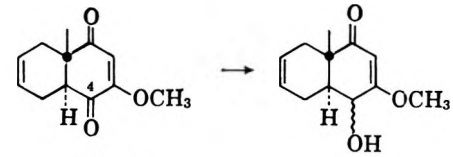
(13)(a) K. Bowden, E. Braude, and E. R. H. Jones, *J. Chem. Soc.*, 948 (1946); (b) see also H. P. Koch, *ibid.*, 387 (1949), on absorption spectra of unsaturated sulfides.

sesses the 6-methylmercapto structure X. The corresponding hydroquinone of 83–84° accordingly must be IX (R = CH_3) which forces the conclusion that Karrer and Dutta's methyltocol derived from IX possesses the structure of a 5- or 7-methyltocol. Subsequent to the termination of this phase of our work, these conclusions were confirmed by unequivocal syntheses[14] of 5-, 7- and 8-methyltocols (VII, X = CH_3, Y,Z = H; VII, Y = CH_3, X, Z = H; VII, Z = CH_3, X,Y = H, respectively) which served to settle the ambiguities with respect to these structures discussed previously. Karrer and Dutta's methyltocol was proved in fact to have been 7-methyltocol corroborating our conclusions concerning 6-methylmercaptotoluquinone (X).[15]

The proof of the course of the Diels–Alder reaction of dienes with 6-alkylmercaptotoluquinones resulting in addition to the methylated side of the quinone justifies with complete assurance the angularly methylated structures adduced previously in the analogous reactions with 5(or 6)-*p*-tolylthiotoluquinone.[7]

Since the Alcalay procedure did not avail a very convenient method of obtaining one particular mercaptotoluhydroquinone which would serve as a precursor to a conveniently blocked toluquinone useful in producing angularly methylated decalin or polycarbocyclic systems in general, the direct interaction of methyl mercaptan with toluquinone was investigated.[10,16] This reaction was carried out in the presence of excess methyl mercaptan and was followed by subsequent oxidation with ferric chloride. A good total yield (84%) of isomeric methylmercaptotoluquinones was obtained which could be separated only after chromatography on silica gel. There were isolated here also both the 5- (IV) and 6- (X) methylmercaptotoluquinones in 17% and 57% yields, respectively. Crystallization of the crude reaction mixture afforded only the 6 isomer (X) and a sharply melting (104°) mixture of isomers. This direct one-step method is accordingly preferred to that of Alcalay for the production of the 6 isomer (X).

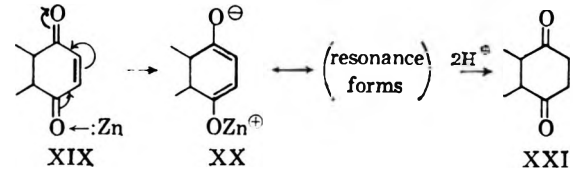
Attention was next directed to a study of the mechanism of the zinc–acetic acid desulfuration reaction discovered earlier in similar systems.[7] The simpler adduct XIV from methylmercaptobenzoquinone was studied first. When a solution of XIV, light yellow in color, in aqueous acetic acid was treated with zinc dust for 5 min. at 50°, a white solid was obtained which was found to contain sulfur, possessed infrared absorption characteristic of nonconjugated carbonyl groups, and gave an elemental analysis in accord with the dihydro derivative XV. The facile reduction of the conjugated ethylenic bond in simple diene–quinone adducts with zinc–acetic acid is well known and widely used,[17] but this result contrasts with the finding of Speziale, Stephens, and Thompson,[18] who showed that the analogous reaction of the *trans* isomeride of the 5-methoxytoluquinone–butadiene adduct (XVII) resulted in reduction of the C-4 carbonyl to an excellent yield of XVIII.



XVII XVIII

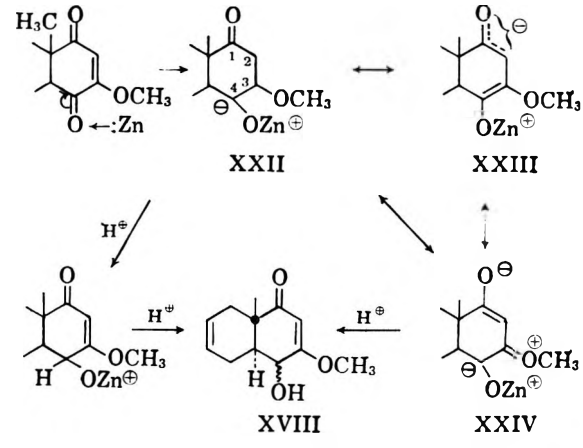
This difference is not without intrinsic interest and may well be accounted for on the basis of the changes symbolized in the following mechanistic schemes, A, B, and C. Zinc, as a source of electrons, may supply these electrons to the parent unsubstituted system XIX through one of the termini of the conjugation as depicted in XIX (arrows), Scheme A, to yield the enolate

Scheme A



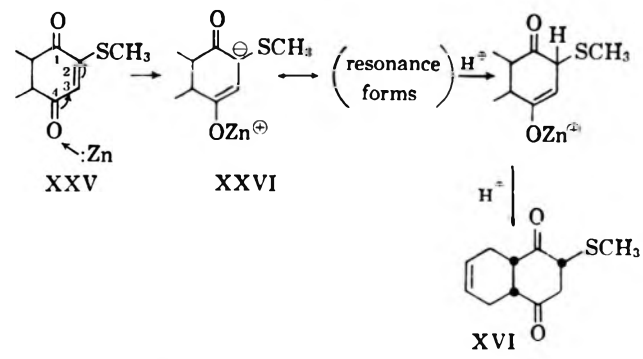
XIX XX XXI

Scheme B



XXII XXIII XVIII XXIV

Scheme C



XXV XXVI XVI

of lowest energy XX (plus usual resonance structures). Protonation of XX on oxygen will, of course, be reversible, ultimately leading to protonation on carbon with

(14) D. McHale, P. Mamalis, J. Green, and S. Marcinkiewicz, *J. Chem. Soc.*, 1600 (1958); D. McHale, P. Mamalis, S. Marcinkiewicz, and J. Green, *ibid.*, 3358 (1959); J. Green, D. McHale, P. Mamalis, and S. Marcinkiewicz, *ibid.*, 3374 (1959).

(15) The bismethylmercapto derivatives of toluquinone and of toluhydroquinone derived from X are thus very probably the 3,6-bis substitution products, since these substances were not derivable from IV.[10]

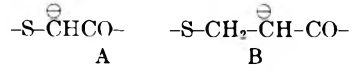
(16) A. Schöberl and A. Wagner "Methoden der Organischen Chemie," Vol. 9, Houben-Weyl, Ed., 4th Ed. Georg Thieme Verlag, Stuttgart, 1955, p. 130. See also A. Blackhall and R. H. Thomson, *J. Chem. Soc.*, 1138 (1953), for a related reaction of toluquinone and thioglycolic acid, as well as J. M. Snell and A. Weissberger, *J. Am. Chem. Soc.*, **61**, 450 (1939).

(17) K. Alder and G. Stein, *Ann.*, **501**, 247 (1933); C. Chuang and C. Han, *Ber.*, **68**, 876 (1935); P. A. Robins and J. Walker, *J. Chem. Soc.*, 3960 (1954); 177 (1957); 409 (1958).

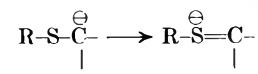
(18) A. J. Speziale, J. A. Stephens, and Q. E. Thompson, *J. Am. Chem. Soc.*, **76**, 5011 (1954).

production of the usually encountered dihydro product XXI. The methoxyl- and methylthio-substituted cases may now be expected to differ from or resemble this main reductive scheme by the course most likely to be taken in the protonation steps of the enolates in the respective cases. The most electronically attractive route for the approach of zinc to the methoxytoluquinone adduct is that *via* the C-4 carbonyl indicated in XXII, Scheme B, because of lower electron density on this oxygen than on the alternate one, which was supplied electrons by resonance with the conjugated methoxyl (vinylogous ester system). Although the resulting enolate XXII will have contributing structures involving the distribution of the negative charge on the C-1 oxygen and C-2, (XXIII), it may be expected reasonably that higher electron density will be located obtain on C-4 than on C-2. The electron delocalization demanded by the C-1 carbonyl will be satisfied by a flow from C-4 as well as from the methoxy group, XXIV. Thus, while protonation at the site of highest electron density (C-1 oxygen) will be reversible, C-4 protonation will compete favorably with C-2 protonation, because of the relatively higher electron density on the former, and lead to the observed product XVIII.

The methylmercapto-substituted case, Scheme C, is analogous to the basic Scheme A with the added qualification that, notwithstanding an apparently "wrong" initial approach by the zinc to the carbonyl oxygen conjugated with the methylthio group XXV, the resulting enolate XXVI will have considerable weight in the delocalization of the electron pair among the various contributing forms and may very reasonably be expected to influence protonation in the direction indicated to yield the observed product XV. In point of fact, the approach of zinc with its electrons to the oxygen atom indicated in XXV, Scheme C, is not at all "wrong" as it would have been in the corresponding methoxyl case (Scheme B), since the electron pair donor-type conjugative effect of a divalent sulfur function is much less than that of an oxide as demonstrated by Bordwell.[19] Moreover, the lack of shortening of the C–S bond in thioacetic acid[20] indicates a lower resonance effect of covalent sulfide than of covalent oxide, a point quite germane to the vinylogous thiol ester moiety present in XXV. Hence, no extraordinary electron density may be anticipated on the C-4 oxygen in XXV to ward off approach by zinc. Of especial significance to this scheme is the fact that there is generated thereby an enolate of lower energy than attack on the C-1 carbonyl would have produced, since in XXVI a sulfur atom is juxtaposed with the carbanionic center. Such carbanions as A were recognized by Woodward[21] as being of particular importance in determining the rate-controlled course of a Dieckmann reaction in competition with carbanions of the type B, and subsequent investigations[22] on similar systems have shown that sulfur has a decided acidifying influence on α hydrogens,

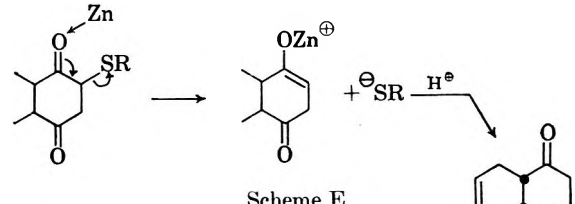


possibly due more to valence shell expansion of sulfur than to simple inductive stabilization of the resulting carbanion by the relatively low electronegativity of sulfur. Bordwell[19b] concluded on this point that the "presence of a powerful electron donor such as a carbanion is necessary to evoke a clearly recognizable electron pair acceptor-type conjugation in divalent sulfur groups," *i.e.*, precisely the situation obtaining in XXVI.

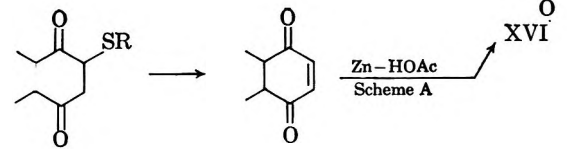


When a solution of XIV in aqueous acetic acid was treated with zinc dust at room temperature for longer periods (*ca.* 2 hr.) methyl mercaptan was evolved and the product *cis*-Δ^6-octalin-1,4-dione (XVI) was isolated in 61% yield. The structure of XVI was established by comparison (infrared and mixture melting point) with an authentic sample of XVI.[17] The exact sequence of events in this desulfuration reaction cannot be definitely particularized beyond the stage of a 2,3-dihydro intermediate XV. At this point an option is available of either direct reduction of the β-oxo sulfide structure, Scheme D, or acid-catalyzed β-elimination in the γ-oxo sulfide grouping, Scheme E, followed by reduction of the resulting ene-dione. Precedent exists for both views. Wahl[23] observed the liberation of benzyl mercaptan in the zinc-acetic acid treatment of

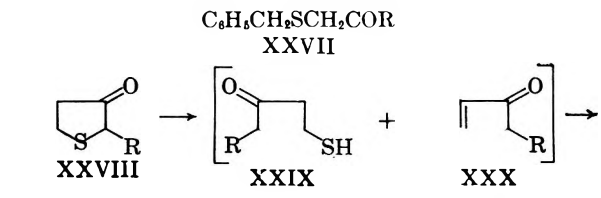
Scheme D

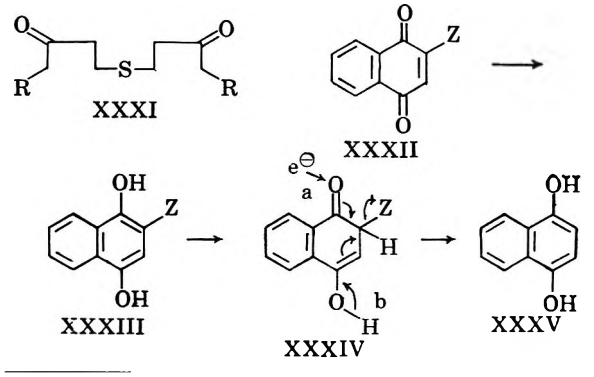


Scheme E



Scheme F





(19)(a) F. G. Bordwell and G. D. Cooper, *J. Am. Chem. Soc.*, **74**, 1058 (1952); (b) F. G. Bordwell and P. J. Boutan, *ibid.*, **78**, 854 (1956).

(20) W. Gordy, *J. Chem. Phys.*, **14**, 560 (1946), finds an interaction between —S— and C=O in thioacetic acid no greater than *ca.* 6%.

(21) R. B. Woodward and R. H. Eastman, *J. Am. Chem. Soc.*, **68**, 2229 (1946).

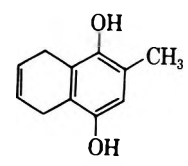
(22) W. J. Brehm and T. Levenson, *ibid.*, **76**, 5839 (1954); See also earlier work by E. Rothstein, *J. Chem. Soc.*, 155 (1940), and former papers.

(23) C. Wahl, *Ber.*, **55**, 1449 (1922).

β-oxo sulfides XXVII, and Schmid and Schnetzler[24] reported that 3-oxothiophanes of the type XXVIII under Clemmensen reduction yield bimolecularly produced sulfides, type XXXI. To explain their generation it is necessary to invoke the intercession of intermediates XXIX and XXX arising both by reduction of the sulfide bond α to the carbonyl (Scheme D) and acid-catalyzed β-elimination of a mercaptide (XXX would correspond to an intermediate in Scheme E). Additional analogies in this area may be found in the reductive elimination of certain electronegative groups, including alkylmercapto and arylmercapto, from 2-substituted naphthoquinones XXXII by means of stannous chloride yielding naphthohydroquinone XXXV.[25a] The course of this reduction may be viewed as proceeding through the hydroquinone form XXXIII which may then suffer further reduction through the intermediacy of a tautomer either directly (Scheme F), XXXIV (arrow a), or by acid-catalyzed β-elimination, XXXIV (arrow b), succeeded by reduction of the resulting quinone (not shown). Evidence suggesting the former direct reduction scheme was found[25a] in the reductive cleavage by stannous chloride of 1-*p*-tolylthio-2-naphthol to toluene-*p*-thiol and β-naphthol, in which case clearly only an intermediate of the type XXXIV (arrows a, functional group positions reversed, 4-OH lacking) can be envisaged. Thus, perhaps the balance of evidence weighs more in favor of Scheme D as the one applicable to our situation. This probability is further heightened by our observation (*vide infra*) that the over-all desulfuration–reduction reaction proceeded at a qualitatively slower rate in the case of the adduct XIII, which would necessitate approach by zinc to a more hindered carbonyl function, in this case, at the time of reductive cleavage of the mercapto moiety in a dihydro intermediate corresponding to XV[25b] with an angular methyl group.

The desulfuration–reduction of the 6-methylmercaptotoluquinone–butadiene adduct (XIII) required more strenuous conditions than those needed for the unmethylated model XIV. Slow evolution of methyl mercaptan (trapped as the yellow lead salt) was noted upon refluxing with zinc in aqueous acetic acid for a few hours. Isomerization of the *cis* ring junction was undoubtedly caused by this more vigorous treatment, and the product of m.p. 87°,[26a] 9-methyl-Δ⁶-octalin-1,4-dione (I), is thus assigned the *trans* configuration. The *trans* ring juncture is postulated on the basis of findings by Robins and Walker[26b] and our own investigations on zinc–acetic acid reductions of Diels–Alder products from quinone and 3,20-diacetoxypregna-5,16,20-triene.[26c] Short treatment of a few minutes' duration without heat of a *cis*-1,4-dioxo-Δ²-octalin with zinc–acetic acid usually permits the reduction of the ethylenic bond with survival of the *cis* ring juncture. Prolonged treatment supplemented by heating results in reduction concomitant with isomerization to a *trans* ring fusion. Moreover, whereas *cis*-α-decalone isomerizes only extremely slowly to *trans*-α-decalone at room temperature,[27a] *cis*-1,4-dioxodecalins have been found to be considerably less stable with respect to their *trans* isomerides.[27b] The *trans* ring assignment in structure I appeared to be confirmed by the infrared absorption of this compound showing a single strong band in the 1450–1475-cm.$^{-1}$ region characteristic of a *trans* angularly methylated decalin system.[27c] An identity was established also between this material and that of the same melting point obtained previously[27d] from an analogous set of reactions commencing with 5(or 6)-*p*-tolylthiotoluquinone and butadiene followed by zinc–acetic acid. Substance I could be hydrogenated over palladium–charcoal with the uptake of one mole of hydrogen to yield what is undoubtedly *trans*-9-methyldecalin-1,4-dione (XXXVI).

It was hoped to simplify the preparation of I by omitting the mercapto–quinone isomer separation, employing the total crude reaction mixture of predominantly 5- and 6-methylmercaptotoluquinones, and resorting to subsequent isomer elimination in the desulfuration–reduction step. A direct Diels–Alder reaction with butadiene on such a mixture of quinones, obtained from methyl mercaptan and toluquinone followed by oxidation with ferric chloride and crystallization to m.p. 104–135° (thus eliminating any unchanged toluquinone), resulted in a good yield of a distilled adduct whose ultraviolet absorption indicated *ca.* 60% of the angularly methylated material. However, zinc–acetic acid reduction of this mixture did not afford any overall better yield of I than had been obtained before. There was isolated in addition, in small yield, however, a substance melting at 166–168°, identified as 2-methyl-5,8-dihydro-1,4-naphthohydroquinone (XXXVII) by comparing it with an authentic sample of this



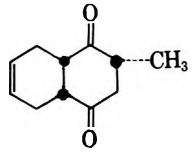
XXXVII

compound. The generation of this hydroquinone XXXVII may be due to the presence of the unknown 3-methylmercaptotoluquinone (VIII) in the original crude mercaptotoluquinone mixture employed in this Diels–Alder reaction. The precursor to compound XXXVII would then have been the adduct XI. This is indirect proof that all three available positions of tolu-

(24) H. Schmid and E. Schnetzler, *Helv. Chim. Acta*, **34**, 894 (1951).

(25)(a) D. B. Bruce and R. H. Thomson, *J. Chem. Soc.*, 1428 (1954). (b) The zinc–acetic acid desulfuration–reduction is particularly advantageous in securing dehydrodecalin systems such as I since Raney nickel has been found to over-reduce systems constructed similarly to those treated herein (ref. 7); see also R. K. Hill and J. G. Martin, *Proc. Chem. Soc.*, 391 (1959), and G. Stork, E. E. van Tamelen, L. J. Friedman, and A. B. Burgstahler, *J. Am. Chem. Soc.*, **75**, 384 (1953), for instances of over-reduction of ethylenic systems in attempted Raney nickel desulfurations.

(26)(a) Our product melted very close to the melting point, 85–86°, reported by Chuang and Han[17] for the substance obtained by mild zinc–acetic acid reduction of the following butadiene–tolquinone adduct.



A depression in melting point resulted on admixture, and the infrared spectra of the two substances differed. (b) P. A. Robins and J. Walker, *J. Chem. Soc.*, 642, 1612 (1952); 3960 (1954); 177 (1957). (c) V. Georgian and Lupe T. Georgian, paper IV in this series, *J. Org. Chem.*, **29**, 58 (1964).

(27)(a) W. Hückel, *Ann.*, **441**, 1 (1925); (b) R. M. Lukes, G. I. Poos, and L. H. Sarett, *J. Am. Chem. Soc.*, **74**, 1401 (1952); (c) R. H. Baker, L. S. Minckler, and A. S. Hussey, *ibid.*, **81**, 2379 (1959); (d) V. Georgian, J. Lepe M., and L. L. Skaletzky, unpublished results, manuscript in preparation.

quinone are attacked by methyl mercaptan in the order C-6 > C-5 ≫ C-3.

Recently there appeared what is undoubtedly the method of choice in preparing a monothiolated toluhydroquinone. It was found[28] that 5-bromotoluhydroquinone on being refluxed a short while with alcoholic sodium sulfide gave an excellent yield of 5-mercaptotoluhydroquinone (III, R = H). Methylation on sulfur may be readily effected, and oxidation by the usual means to 5-methylmercaptotoluquinone (IV) would make the latter most plentifully available for employment in the general synthetic scheme developed in this paper.

Experimental[29a]

Benzoquinone.— Benzoquinone was prepared according to a literature method.[29b] The yellow quinone, which was dried in a desiccator over calcium chloride, melted at 110–112° and was used without further purification.

Potassium S-(1,4-dihydroxy-2-phenyl)thiosulfate (II).—The thiosulfate was prepared according to a literature procedure.[29c] To a solution of 99 g. (0.62 mole) of anhydrous sodium thiosulfate in 200 ml. of water, cooled in an ice–salt bath, was added with stirring a warm (40–50°) solution of 43.2 g. (0.4 mole) of quinone in 150 ml. of glacial acetic acid. The addition time was 0.75 hr., and the reaction mixture was maintained at 0–10°. The red reaction mixture, after a few minutes additional stirring, became almost colorless and was saturated with potassium chloride. After 2 hr. in the cold room, the white precipitate was filtered and washed with cold saturated potassium chloride solution. The white solid was dried in air and used directly in the reduction with zinc and hydrochloric acid.

2-Mercaptohydroquinone.—To the crude potassium S-(1,4-dihydroxy-2-phenyl)thiosulfate dissolved in 8 *N* hydrochloric acid was added slowly zinc dust (2 g. of zinc dust for 1 g. of potassium salt in 30 ml. of 8 *N* hydrochloric acid.) Hydrogen and hydrogen sulfide were immediately evolved and the solution was maintained at 40–50° by cooling in a cold water bath when necessary. After being cooled, the acid solution was extracted several times with ether. The ether extracts were dried (sodium sulfate) and evaporated to dryness in a desiccator in the presence of potassium hydroxide. Several recrystallizations from benzene gave 2-mercaptohydroquinone, 15 g. (27% based on quinone), as colorless needles, m.p. 118° (lit.[9] m.p. 118°).

2-Methylmercaptoquinone.—To a cold solution of 15 g. (0.105 mole) of 2-mercaptohydroquinone in 270 ml. of 2% sodium hydroxide solution containing a little sodium hydrosulfite was added with stirring 14.5 ml. (0.105 mole) of methyl sulfate in three portions. After each addition the solution was stirred for 15 min. and finally until the complete disappearance of the methyl sulfate. The solution was acidified and the hydroquinone was oxidized at 20° with 105 ml. of 2 *N* ferric chloride. The orange solid was filtered, washed well with water, and dried in a vacuum desiccator over potassium hydroxide. The orange quinone was purified by crystallization from methanol. The yield was 9.1 g. (56%) of 2-methylmercaptoquinone, m.p. 146–146.5° (lit.[9] m.p. 148°).

***cis*-2-Methylmercapto-5,8,9,10-tetrahydro-1,4-naphthoquinone (XIV).**—A mixture of 10 ml. of 1,3-butadiene, 5.7 g. of 2-methylmercaptoquinone, and 10 ml. of anhydrous benzene containing a trace of hydroquinone was heated in a sealed Carius tube at 110 ± 5° for 4 hr. The tube was cooled in acetone–Dry Ice and opened. Evaporation of the benzene gave 5.3 g. (69%) of yellow Diels–Alder adduct, m.p. 81–84°. The product on recrystallization from ether–hexane gave XIV as yellow needles, m.p. 85–86°. The ultraviolet spectrum showed an absorption maximum, λ_{max}^{EtOH} 332 mμ (log ε 3.83). Infrared spectrum showed carbonyl bands at 5.89 and 6.0, and double bond band at 6.4 μ (C=C–S–R).

Anal. Calcd. for $C_{11}H_{12}O_2S$: C, 63.43; H, 5.81. Found: C, 63.62; H, 5.73.

Zinc–Acetic Acid Reduction of *cis*-2-Methylmercapto-5,8,9,10-tetrahydro-1,4-naphthoquinone. A. Five-Minute Reduction *cis*-2-Methylmercapto-2,3,5,8,9,10-hexahydro-1,4-naphthoquinone (XV) (*cis*-2-Methylmercapto-Δ^6-octalin-1,4-dione).— To 1 g. of zinc dust suspension in 3 ml. of water at 50° was added dropwise with vigorous stirring glacial acetic acid (3 ml.) containing 0.5 g. of 2-methylmercapto-5,8,9,10-tetrahydro-1,4-naphthoquinone (XIV). After the addition was complete (5 min.), the yellowish solution was decanted from the zinc, diluted with water, and extracted with ether. The ether extract was washed with water, sodium bicarbonate solution, and then with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the ether and addition of alcohol precipitated some white solid, which was filtered and recrystallized several times from aqueous alcohol to give XV as needles, m.p. 111–112°. The solid gave a positive sulfur test.

Anal. Calcd. for $C_{11}H_{14}O_2S$: C, 62.84; H, 6.71. Found: C, 63.21; H, 6.44.

B. Two-Hour Reduction. *cis*-2,3,5,8,9,10-Hexahydro-1,4-naphthoquinone (XVI) (*cis*-Δ^6-Octalin-1,4-dione).—To a stirred solution of 0.5 g. of *cis*-methylmercapto-5,8,9,10-tetrahydro-1,4-naphthoquinone (XIV) in 95% acetic acid there was added 5 g. of zinc dust in five portions over 1 hr. The suspension was stirred for an additional hour during which time traces of methyl mercaptan were detected by lead acetate paper. The solution was decanted from the zinc which was washed thoroughly with acetone. The acetic acid–acetone solution was concentrated *in vacuo* and the residue extracted with benzene. The benzene solution was washed with water, sodium bicarbonate solution, and again with water. The dried (sodium sulfate) benzene was concentrated to 0.24 g. (51%) white solid, m.p. 101–103°. Crystallization from ether–hexane gave the *cis*-2,3,5,8,9,10-hexahydro-1,4-naphthoquinone (XVI) as colorless needles, m.p. 103–104°. No sulfur could be detected on sodium fusion. Alder and Stein reported the melting point of *cis*-2,3,5,8,9,10-hexahydro-1,4-naphthoquinone as 108°.[30] However, preparation of the diketone according to their directions gave colorless needles, m.p. 103–104°. A mixture melting point of the desulfuration product and authentic *cis*-2,3,5,8,9,10-hexahydro-1,4-naphthoquinone of Alder and Stein did not depress. The infrared spectra of these two materials were superimposable.

Addition of Methyl Mercaptan to Toluquinone. 5-Methylmercaptotoluquinone (IV) and 6-Methylmercaptotoluquinone (X).—To a solution of methyl mercaptan (15–25 g.) in 250 ml. of methanol, cooled in an ice–salt bath at 0–5°, was added with vigorous stirring a solution of 30 g. (0.25 mole) of toluquinone in 150 ml. of methanol. During the half hour addition period, each drop of the quinone solution gave a fleeting red coloration. After the addition was complete, the yellow solution was concentrated *in vacuo* to 250 ml. The mixture of methylmercaptotoluquinones was oxidized with 250 ml. of 2 *N* ferric chloride solution at 20°. The orange precipitate was filtered, washed well with water, and dried in a vacuum desiccator over potassium hydroxide. The crude methylmercaptotoluquinone mixture, 35.1 g. (84%), melted at 104–135°. A 15-g. sample of the methylmercaptotoluquinone mixture was crystallized several times from methanol to give 5 g. of 6-methylmercaptotoluquinone (X), m.p. 140–142°. From the mother liquors, was isolated material of sharp m.p. 104° which could be purified by sublimation, but which was not encountered later after chromatography over silica gel, and must have been a sharply melting mixture of isomers.

A separation of the crude methylmercaptotoluquinone mixture could be obtained by chromatography over silica gel using ether–hexane as the eluting agent. The orange 6-methylmercaptotoluquinone (X) (57%), m.p. 140–142°, and 5-methylmercaptotoluquinone (IV) (17%), m.p. 136–137°, were isolated. These two quinones were shown to be different, since a mixture melting point showed a depression (m.p. 105–125°) and their infrared spectra were quite different in the fingerprint region. The infrared spectra showed bands at 6.03, 6.07, 6.15, and 6.4 μ. The

(28) J. Green, D. McHale, P. Mamalis, and S. Marcinkiewicz, *J. Chem. Soc.*, 3374 (1959).

(29)(a) All melting points and boiling points are uncorrected. Microanalyses were performed by Miss H. Beck Microanalytical Laboratory, Northwestern University. Infrared spectra were measured on a Baird Model AB-2 double-beam spectrophotometer or on a Perkin-Elmer Infracord. Ultraviolet spectra were measured in 95% ethanol on a Beckman Model DU spectrophotometer. (b) H. W. Underwood, Jr. and W. L. Walsh, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 553. (c) German Patent 175,070 (1905); *Frdl.*, **8**, 140 (1905).

(30) K. Alder and G. Stein, *Ann.*, **501**, 277 (1933). P. Robins and J. Walker, *J. Chem. Soc.*, 409 (1958), reported m.p. 103–105° for this compound in agreement with our value.

substance, m.p. 104°, was probably a mixture of the two monomethylmercaptotoluquinones described previously, since its infrared spectrum had only those bands which appeared in the spectra of the 140–142° and 136–137° isomers. The monomethyl mercaptotoluquinone of Alcalay,[9] m.p. 113°, was not encountered. Analytical samples of each were prepared by recrystallization from methanol.

Anal. Calcd. for $C_8H_8O_2S$: C, 57.14; H, 4.79. Found for IV, m.p. 136–137°: C, 57.22; H, 4.72. Found for X, m.p. 140–142°: C, 57.42; H, 4.79. Found for isomer mixture, 104°: C, 57.23; H, 4.61.

Samples of IV and X prepared by the combined Alcalay[9]–Karrer[10] procedure were found to be identical with those prepared previously by infrared and melting point comparisons.

Diels–Alder Reaction of 1,3-Butadiene and 6-Methylmercaptotoluquinone (X, 140–142° Monomethylmercaptotoluquinone Isomer). 2-Methylmercapto-9-methyl-5,8,9,10-tetrahydro-1,4-naphthoquinone (XIII).—Butadiene (15–20 ml.), 3 g. of 6-methylmercaptotoluquinone (isomer, m.p. 140–142°), and 30 ml. of anhydrous benzene containing a trace of hydroquinone were heated in a sealed Carius tube at 100° for 4 days (96 hr.). The color of the reaction mixture changed during this period from red to light yellow.

The Carius tube was opened, and the benzene solution was filtered to remove some traces of butadiene polymer. The reaction tube was washed out with several portions of benzene. The combined benzene solution was concentrated to 5.1 g. of yellow oil. The oil was taken up in ether and was washed several times with sodium hydroxide–sodium hydrosulfite solution in order to remove traces of quinone still present. (These washings resulted in a loss of product since it was later shown that the diketone was somewhat soluble in dilute base.) The ether solution was washed with water and dried over sodium sulfate. Evaporation of the ether gave 4.6 g. of yellow oil which solidified on standing several days at room temperature. Crystallization from ether–ligroin (35–60°) gave 3.1 g. (80%) of Diels–Alder adduct as yellow needles, m.p. 79–80°. The 2-methylmercapto-9-methyl-5,8,9,10-tetrahydro-1,4-naphthoquinone shows a band λ_{max}^{EtOH} 332 mμ (log ε 3.95), and the infrared spectrum shows carbonyl bands at 5.89 and 6.0 μ.

Anal. Calcd. for $C_{12}H_{14}O_2S$: C, 64.85; H, 6.35. Found: C, 64.83; H, 6.10.

Zinc–Acetic Acid Reduction of 6-Methylmercaptotoluquinone–Butadiene Adduct XIII. *trans*-9-Methyl-Δ⁶-octalin-1,4-dione (I).—The adduct XIII (0.68 g.) dissolved in 100 ml. of 95% acetic acid was refluxed with 3 g. of zinc dust for 2.5 hr. During this period a stream of nitrogen swept the methyl mercaptan evolved into a lead acetate trap, where it precipitated a yellow lead salt. Then 3 g. more of zinc was added and the reaction mixture was refluxed an additional 2.5 hr.

The acetic acid solution was decanted from the zinc–zinc acetate solids which were washed thoroughly with glacial acetic acid. The acetic acid was concentrated *in vacuo* and the residue was extracted with ether. The ether layer was washed with water, sodium bicarbonate solution, and water and was dried over sodium sulfate. Evaporation of the ether gave 0.44 g. (81%) white solid, m.p. 60–65° which gave a negative sulfur test. Recrystallization of this material from hexane afforded *trans*-9-methyl-Δ⁶-octalin-1,4-dione (I), m.p. 86.5–87.0°. Infrared showed nonconjugated carbonyl absorption at 5.80 μ. A mixture melting point with *cis*-2-methyl-2,3,5,7,9,10-hexahydro-1,4-naphthoquinone (m.p. 85–86°[17]) showed a large depression, and the infrared spectra of the two compounds differed.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.12; H, 8.02.

***trans*-9-Methyldecalin-1,4-dione (XXXVI). Hydrogenation of I.**—The diketone I, of m.p. 87°, was hydrogenated in a microvolumetric hydrogenation apparatus in 10 ml. of ethanol over 5% palladium–charcoal at room temperature and at near atmospheric pressure. Hydrogen, 23.5 ml. (93%), was absorbed in *ca.* 0.5 hr. The catalyst was filtered, and the alcohol was stripped to yield *trans*-9-methyldecalin-1,4-dione (XXXVI), m.p. 95.5–97°. Recrystallization from hexane afforded the analytical sample, m.p. 97.0–97.4°.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.34; H, 8.65.

Diels–Alder Reaction of the Crude Methylmercaptotoluquinone Mixture and Butadiene.—In a sealed Carius tube, 10 g. of methylmercaptotoluquinone mixture (m.p. 104–135°, containing essentially 5- and 6-methylmercaptotoluquinones), 30 ml. of butadiene, 40 ml. of anhydrous benzene, and 0.1 g. of hydroquinone were heated at 100° for 4 days. The contents were combined with a run using 6 g. of the crude quinone mixture and corresponding amounts of the other reagents.

The benzene solution was concentrated and the yellow oil distilled in vacuum to give 11.9 g. of yellow oil which showed a strong band in the ultraviolet at λ_{max}^{EtOH} 332–333 mμ (log ε 3.73). Since the crude quinone mixture shows no absorption at this wave length, from the relative intensities of absorption of this reaction mixture and of pure XIII it was estimated that there was approximately 55–60% of angular methylated adduct in the reaction mixture. This reaction product was submitted to zinc–acetic acid reduction–desulfuration as in the following experiment.

Zinc–Acetic Acid Reduction of the Isomeric Mixture of Methylmercaptotoluquinone–Butadiene Adducts. *trans*-9-Methyl-Δ⁶-octalin-1,4-dione (I) and 2-Methyl-5,8-dihydro-1,4-naphthohydroquinone (XXXVII).—To 4.0 g. of Diels–Alder adduct of the isomeric methylmercaptotoluquinones and butadiene obtained from the previous procedure, dissolved in 200 ml. of 95% acetic acid there was added 12 g. of zinc dust, and the reaction mixture was refluxed 2 hr. A nitrogen stream swept the methyl mercaptan produced into a lead acetate trap where it was precipitated as the yellow lead salt.

The reaction mixture was permitted to cool, the supernatant liquid was decanted, and the zinc sludge was washed thoroughly with acetone. The acetic acid–acetone solution was concentrated *in vacuo* and the residue extracted with ether. The ether extract was washed with water, sodium carbonate solution, and again with water. The dried ether solution (sodium sulfate) was evaporated to a small volume which was put on silica gel chromatographic column. Elution with ether–ligroin (35–60°) gave 0.4 g. of solid, m.p. 166–168°, and 0.7 g. of solid, m.p. 52–65°.

The substance, m.p. 166–168°, was shown to be identical with 2-methyl-5,8-dihydro-1,4-naphthohydroquinone (XXXVII), m.p. 166–168°, prepared according to the directions of Chuang.[17] These two materials did not depress on mixture melting point and had superimposable infrared spectra.

The low melting material after many recrystallizations from hexane gave 0.2 g. of a white solid, m.p. 85–86°, which gave a negative sulfur test. Further recrystallization from hexane gave the diketone I as colorless needles, m.p. 87°. A mixture melting point with *cis*-2-methyl-2,3,5,8,9,10-hexahydro-1,4-naphthoquinone (m.p. 85–86°[17]) showed a large depression, and the infrared spectra of the two compounds differed.

***cis*-2-Methyl-5,8,9,10-tetrahydro-1,4-naphthoquinone.**—A solution of 2.4 g. of toluquinone, 4.4 g. (7 ml.) of butadiene and 10 ml. of benzene was heated in a sealed tube at 105° for 5 hr. The yellow solution was concentrated *in vacuo* and the residue was crystallized from ether–ligroin (35–60°) to give 2.0 g. (58%) of colorless needles, m.p. 79.5–80.5° (lit.[17] m.p. 79–81°).

***cis–syn*-2-Methyl-2,3,5,8,9,10-hexahydro-1,4-naphthoquinone (*cis–syn*-2-Methyl-Δ⁶-octalin-1,4-dione).**—A solution of the preceding butadiene–toluquinone adduct (0.7 g.) in 3 ml. of glacial acetic acid was added dropwise to a well stirred suspension of 1 g. zinc dust in 3 ml. of water at 50°. After the addition was complete, the colorless solution was quickly decanted. The acetic acid solution was cooled and the reduction product was filtered and washed with cold water. One crystallization from ligroin (35–60°) gave the diketone, 0.5 g. (72%), m.p. 85.5–86° (lit.[17] m.p. 85–86°).

2-Methyl-5,8-dihydro-1,4-naphthohydroquincne (XXXVII).—2-Methyl-5,8,9,10-tetrahydro-1,4-naphthoquinone dissolved in glacial acetic acid was isomerized with a trace of hydrogen bromide in glacial acetic acid. The precipitated hydroquinone was filtered and washed with cold water. The product, after drying in air, melted at 165.5–168°.

Acknowledgment.—The authors wish to express their gratitude to Research Corporation for financial assistance during some phases of this work.

Alicyclic Syntheses. IV. Diels–Alder Additions to 3β,20-Diacetoxypregna-5,16,20-triene[1]

V. GEORGIAN AND LUPE T. GEORGIAN

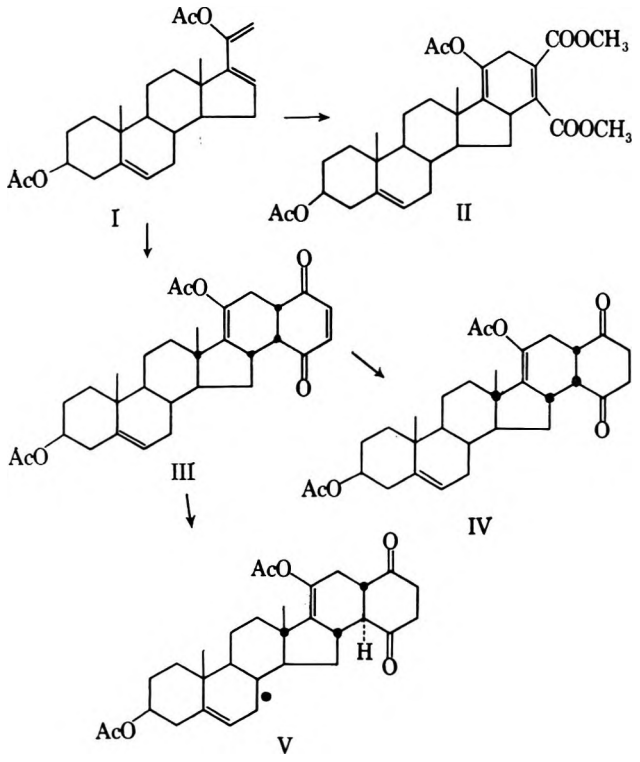
The Department of Chemistry, Tufts University, Medford, Massachusetts, and Department of Chemistry, Northwestern University, Evanston, Illinois

Received October 29, 1963

The Diels–Alder reaction of 3β,20-diacetoxypregna-5,16-20-triene (I) with quinone, dimethyl acetylenedicarboxylate, citraconic anhydride, and 5(or 6)-*p*-tolylthiotoluquinone is reported. The adducts with the latter quinone and with quinone itself have been reduced with zinc–acetic acid to yield hexacarbocyclic "extended-steroidal" ring systems. The stereochemical courses of the diene additions and of the reduction process is discussed.

As one phase of our general interest in the synthesis of polycarbocyclic ring systems approaching steroid proportions, we wished to investigate the application of the Diels–Alder reaction to acetoxydienes incorporated in ring systems of already substantial size. Such a system is to be found in 20-acetoxy-16,20-steroid dienes, which are readily obtainable from Δ^{16}-pregnan-20-ones with isopropenyl acetate.[2] While we were interested in the ultimate utility of this reaction scheme for the synthesis of angularly methylated "extended-steroidal" ring systems, the diene addition to the title compound was investigated first with simpler dienophiles.

An earlier patent disclosure indicated that 20-acetoxy-16,20-dienes could add maleic anhydride and *p*-benzoquinone.[3,4] This observation has been confirmed for both additions, and dimethyl acetylenedicarboxylate was found to add to the title compound I as well yielding the pentacarbocyclic adduct II. The addition product[3c] to *p*-benzoquinone is postulated to have the stereochemical configuration shown in III based on the general mode of attack to steroidal centers of unsaturation from the α (β approach hindered by 18 axial angular methyl) side.[5] This will result in a β configuration for the C-16 hydrogen. The *cis* β hydrogens of the newly created ring juncture result from biplanar orientation between the quinone and diene moieties in the transition state resulting in maximum overlap of the π-electron systems.[6] Reduction of adduct III with zinc and acetic acid at room temperature for just a few minutes resulted in the dihydro reduction product IV still represented as having a *cis* E/F ring fusion. When the reduction with zinc was conducted at reflux temperature for 4 hr., a much higher melting (m.p. 305°) isomeric reduction product V was obtained which is considered to possess the *anti–trans* D/E/F ring system. These deductions are based on the investigations of Robins and Walker[7] who ascertained that zinc–acetic acid reductions of dioxoethylenic functions of a few minutes duration and without heat permitted reduction of the ethylenic bond with survival of a *cis* ring juncture, whereas prolonged refluxing resulted in reduction concomitant with isomerization to a *trans* ring fusion. Moreover, while *cis*-α-decalone isomerizes only extremely slowly to *trans*-α-decalone at room temperature,[8] *cis*-1,4-dioxodecalins have been found to be much less stable with respect to their *trans* ring isomers.[9] The difference between isomers IV and V is reflected interestingly enough in their infrared (Nujol mull) spectra in the carbonyl region. While a precise assignment of bands is difficult, the observation was made that *cis* isomer IV has a very strong band at 5.72 (probably due to two acetate carbonyls) and two other strong (but a little weaker than the one at 5.72) bands at 5.81 and 5.90 μ, possibly each due to one of the two ring carbonyls. The *trans* isomer V has an identical band at 5.72 (two acetate carbonyls) and now only *one* other carbonyl (as strong as the 5.72 band) at 5.82 μ, possibly resulting from the two ring carbonyls. The latter coincidence of absorption



(1) Contribution No. 297 from the Department of Chemistry, Tufts University, Medford 55, Mass.

(2) R. B. Moffett and D. I. Weisblat, *J. Am. Chem. Soc.*, **74**, 2183 (1952).

(3) (a) R. H. Mazur and G. P. Mueller, U. S. Patent 2,753,343; *Chem. Abstr.*, **51**, 2070 (1957). (b) R. H. Mazur, U. S. Patent 2,753,359; *Chem. Abstr.*, **51**, 4436 (1957). (c) R. H. Mazur, U. S. Patent 2,812,335; *Chem. Abstr.*, **52**, 6418 (1958).

(4) For a closely related case of Diels–Alder reaction of 20-methyl-16,20-dienes with maleic anhydride, see F. Sondheimer and R. Mechoulam, *J. Org. Chem.*, **24**, 106 (1959).

(5) *Cf.* L. F. Fieser, *Experientia*, **6**, 312 (1950).

(6) Rule of maximum accumulation of unsaturation of K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937).

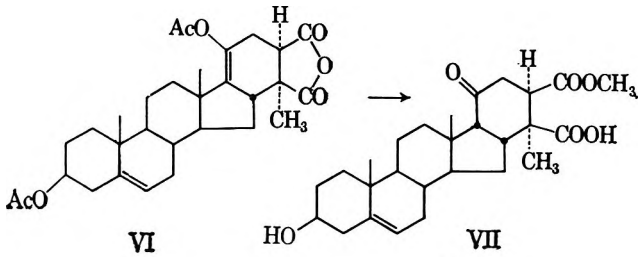
(7) P. A. Robins and J. Walker, *J. Chem. Soc.*, 642, 1612 (1952); 3960 (1954); 177 (1955).

(8) W. Hückel, *Ann.*, **441**, 1 (1925).

(9) R. M. Lukes, G. I. Poos, and L. H. Sarett, *J. Am. Chem. Soc.*, **74**, 1401 (1952).

for the ring carbonyls may reflect the circumstance that they are in a comparable environment which a flattened-out all *trans* ring system would afford, while the slightly different positions of absorption for the ring carbonyls in the *cis* isomer might be due to different molecular environment, into which *cis* E/F ring fusion would force them. Molecular models indicate such a difference, and the conclusions drawn above on the stereochemistry of IV and V, based on many previous analogies,[7] find some additional support in this spectral observation.

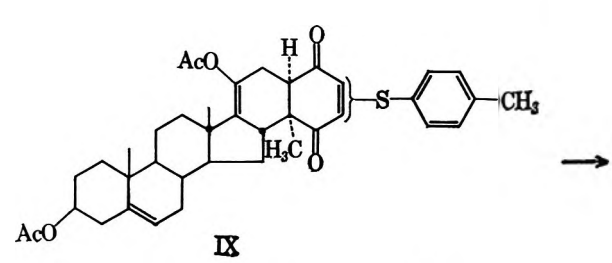
The ability of the acetoxydiene I to add to methylated dienophiles was investigated next with promising results. When treated with citraconic anhydride in refluxing toluene for 48 hr., an adduct was produced to which we assign the orientation and configuration symbolized in formula VI for reasons presented subsequently. The anhydride VI was hydrolyzed in



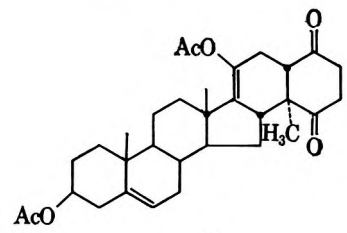
alkaline methanol to yield what turned out to be a monomethyl ester of the diacid. Although it is not known which way the anhydride was opened, it seems reasonable to indicate attack on the less hindered carbonyl leading to structure VII. A *cis* D/E ring junction is considered more likely to have been produced in the ketonization at C-20, since otherwise there would result two *trans* fused cyclohexane rings on ring D which appear very strained on models. The carbonyl functions on VII are apparently still *cis*, since the compound on being heated is readily changed to a very high-melting (over 300°) anhydride VIII.

To append an angularly methylated decalin ring system at position 16,17 on the steroid nucleus the Diels–Alder reaction of the diene I was conducted with 5(or 6)-*p*-tolylthiotoluquinone. The latter dienophile, as well as 5- and 6-methylmercaptotoluquinone, have been shown in allied investigations[10] to yield angularly methylated polycarbocyclic ring systems with dienes when the diene addition is succeeded by zinc–acetic acid reduction; and so, in the present case, an adduct resulted which is portrayed as IX. The orientational course of this Diels–Alder reaction and the *anti–cis* stereochemistry of the D/E/F ring system is discussed subsequently. The infrared spectrum of IX indicated,

(10) (a) V. Georgian and J. Lepe M., papers I and II of this series, *J. Org. Chem.*, **29**, 1, 40, 45 (1964); (b) V. Georgian and L. L. Skaletzky, paper III of this series, *J. Org. Chem.* **29**, 51 (1964).



IX



X

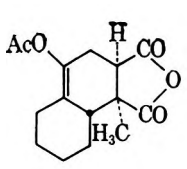
in addition to the acetate carbonyl absorption at 5.73, a set of carbonyl bands at 5.88, 5.96, and 6.40 μ characteristic of the thio-substituted enedione chromophore in IX.[11] Zinc–acetic acid reduction over an 18-hr. period afforded a reduction product, the hexacarbocyclic dione X (similar infrared carbonyl absorption with that of compound V). The *trans* E/F ring system is assigned on the same basis as that used previously in connection with the E/F configuration of structure V as well as on the experimental evidence available from a parallel investigation of the course of reduction of the butadiene-6-methylmercaptotoluquinone adduct resulting in *trans*-9-methyl-Δ^6-octalin-1,4-dione.[11,12] The prolonged hot acid exposure to X during the conversion of IX to X almost certainly ensures that X possesses the most stable *trans* E/F fusion.

Lastly, the orientation of the methyl group in and the stereochemical configuration of the angular methylated adducts VI and IX may be discussed. These assignments follow from (1) *a priori* consideration of the best transition state together with support by analogy to previously established results with similar Diels–Alder reactions, and (2) a departure from the *endo* addition precept of Alder–Stein[6] recognized as operative in those reactions requiring the forcing conditions[13] (higher reaction temperatures and prolonged reaction times), which were necessary to the generation of adducts VI and IX. With respect to this latter point (2), it may be said that *endo* addition has been encountered in Diels–Alder reactions with the more reactive and less encumbered dienophiles such as maleic anhydride[13] and quinone. In the case particularly germane to our discussion of VI and IX, of addition of citraconic anhydride[13c] and 2,6-xyloquinone[13a] to 1-(1-acetoxyvinyl)cyclohexene (both requiring long periods of heating) the products were

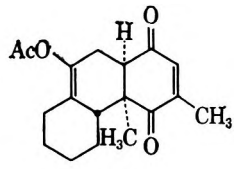
(11) L. L. Skaletzky, Ph.D. dissertation, Northwestern University, 1959. Similar absorption was shown by butadiene adduct of *p*-tolylthiotoluquine.

(12) Paper III of this series, ref. 10b.

(13) (a) M. F. Ansell and G. T. Brooks, *J. Chem. Soc.*, 4518 (1956); (b) J. Heer and K. Miescher, *Helv. Chim. Acta*, **31**, 219 (1948); **32**, 1572 (1949); (c) F. Winternitz and C. Balmossiere, *Tetrahedron*, **2**, 100 (1958); (d) I. N. Nazarov, V. F. Kucherov, and V. M. Andreyev, *Dokl. Akad. Nauk SSSR*, **102**, 751 (1955); (e) I. N. Nazarov, V. F. Kucherov, and V. M. Andreyev, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **67**, 77 (1955); *Chem. Abstr.*, **50**, 1713 (1956); (f) I. N. Nazarov, V. F. Kucherov, V. M. Andreyev, and G. M. Segal, *Dokl. Akad. Nauk SSSR*, **104**, 729 (1955); *Chem. Abstr.*, **50**, 11, 304 (1956).



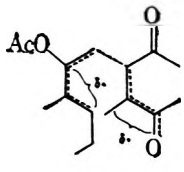
XI



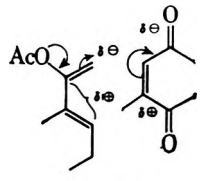
XII

those resulting from *exo* addition and bear the configurations shown in XI and XII, respectively.

Concerning the 1,4 relationship of the angular methyl to the acetoxyl group, point 1, the preceding examples of the synthesis of XI and XII indicate quite clearly the orientational course taken by Diels–Alder reactions of the type leading to VI and IX as well. An understanding of the reason for this directional control may be had in considering a picture for the transition state in these reactions, pictured synoptically as in XIII.[14,15] Association of the addends in this



XIII



XIV

manner will lead to a transition state involving the establishment of the initial bond[15] between the termini of the olefinic systems with electron delocalization at a secondary carbon and a tertiary carbon α to oxygen in the diene and at a tertiary carbon α to carbonyl in the dienophile. Combination of the components alternate to that shown in XIII would lead to higher energy transition states. Similar analysis may be made of the systems leading to the postulation of structures VI and IX. In suggesting acceptance of the validity of these conclusions, we wish to draw attention to the significant fact that the established closely related structures of XI and XII are contrary to those which would have been predicted purely on polar grounds,[16] *e.g.* XIV.

Experimental[17]

3β,20-Diacetoxypregna-5,16,20-triene (I).—This substance was prepared essentially according to the published procedure[2] from 16-dehydropregnenolone acetate.

Adduct of I and Maleic Anhydride.—A solution of 4.0 g. of diacetoxypregnatriene I and 1.0 g. of maleic anhydride in 100 ml. of dry benzene was refluxed 4 hr. Some of the benzene was boiled off until crystallization commenced, and after being cooled somewhat, white crystals, 3.4 g., m.p. 245–254°, were filtered and washed with 1:1 benzene–hexane. The product could be recrystallized from chloroform–cyclohexane or from benzene–cyclohexane, m.p. 254–256° (lit.[3a] m.p. 241–243°). Infrared spectra showed in addition to strong acetate carbonyl absorption at 5.73, the characteristic pattern of a five-membered anhydride with carbonyl bands at 5.40 (w), 5.60 μ (s).

Anal. Calcd. for $C_{29}H_{36}O_7$: C, 70.14; H, 7.31. Found: C, 70.06; H, 7.11.

Adduct II of I and Dimethyl Acetylenedicarboxylate.—A solution of 8.0 g. of 3β,20-diacetoxypregna-5,16,20-triene (I) and 3.0 g. of dimethyl acetylenedicarboxylate in 200 ml. of dry benzene was refluxed 8 hr. After the reaction was stripped of volatile matter on a rotary evaporator with steam bath heat, the white crystalline residue was recrystallized from ethyl acetate to yield 6.3 g. of adduct II, m.p. 113–114°. The infrared spectra showed three bands at 5.60, 5.68, and 5.75 and a weak double bond at 6.26 μ.

Anal. Calcd. for $C_{31}H_{40}O_8$: C, 68.87; H, 7.46. Found: C, 68.82; H, 7.22.

Adduct III of I with *p*-Benzoquinone.—A solution of 4.0 g. of 3β,20-diacetoxypregna-5,16,20-triene and 1.0 g. of *p*-benzoquinone in 100 ml. of dry benzene was refluxed 4 hr. The benzene solution was concentrated to the point of incipient crystallization, treated with Norit, and brought to a saturation point with hexane. On being cooled, substance III was produced, 3.6 g., m.p. 227–228°. Recrystallization raised the melting point to 228–229°. Infrared absorption showed ester carbonyls at 5.73 and ketone carbonyl at 5.93, and a double C–OAc stretch band at 8.06–8.16 μ.

Anal. Calcd. for $C_{31}H_{38}O_6$: C, 73.49; H, 7.56. Found: C, 73.82; H, 7.50.

Zinc–Acetic Acid Reduction of III for a Short Period (*cis* **Compound IV).**—A mixture of 1.0 g. of quinone adduct III in 50 ml. of glacial acetic acid plus 1.0 g. of zinc dust was stirred at room temperature for 15 min. Chloroform (60 ml.) was added; the mixture was filtered and treated with aqueous carbonate solution to neutralize the acetic acid. The chloroform solution was separated, dried (sodium sulfate), and evaporated. The crystalline residue was recrystallized from benzene–hexane or from ethanol to yield IV, m.p. 247–247.6°. Infrared spectra showed no OH bands, and carbonyl absorption at 5.72 (vs), 5.81 (s), 5.90 (s), broad C–OAc stretch band at 8.1–8.2 μ.

Anal. Calcd. for $C_{31}H_{40}O_6$: C, 73.20; H, 7.93. Found: C, 72.90; H, 7.64.

Vigorous Reduction of III with Zinc–Acetic Acid (*trans* **Compound V).**—A mixture of 0.5 g. of adduct III in 30 ml. of glacial acetic acid and 0.5 g. of zinc dust was refluxed for 4 hr. The hot reaction mixture was diluted with sufficient ethyl acetate to contain the product in solution (*ca.* 100–125 ml.). The filtered solution was evaporated somewhat to the point of crystallization and then allowed to cool. The filtered product V was recrystallized from chloroform–cyclohexane, m.p. 305–307°. Infrared spectra showed no OH bands, carbonyl bands at 5.73 (vs) and 5.82 (vs), C–OAc stretch bands at 8.05 and 8.24 μ.

Anal. Calcd. for $C_{31}H_{40}O_6$: C, 73.20; H, 7.93. Found: C, 73.22; H, 7.77.

Adduct of I with Citraconic Anhydride (Substance VI).—A solution of 4.0 g. of diene I and 1.12 g. of citraconic anhydride[18] in 80 ml. of pure toluene was refluxed for 48 hr. The solvent was removed *in vacuo* and the residue was recrystallized from chloroform and then from ethyl acetate to yield the adduct VI, 2.2 g., m.p. 283–283.4°. Infrared absorption was shown for strong acetate carbonyl at 5.73 and for the characteristic five-membered anhydride pattern at 5.40 (w) and 5.60 μ (s).

Anal. Calcd. for $C_{30}H_{38}O_7$: C, 70.56; H, 7.50. Found: C, 70.26; H, 7.37.

Methanolysis of VI to Half Methyl Ester VII.—A solution of 0.50 g. of citraconic anhydride adduct VI in 50 ml. of dry methanol was treated with two sodium hydroxide pellets and heated at reflux for 45 min. The methanol was stripped *in vacuo* and the solid residue was taken up in a little water and acidified with hydrochloric acid. The precipitated product was filtered and recrystallized from methanol to yield VII. The melting behavior of this substance was erratic as upon gradual heating it

(14) For additional and more detailed discussion of and references to this subject of Diels–Alder additions between unsymmetrical addends, see ref. 10a.

(15) Recent evidence has accumulated which indicates that, while Diels–Alder reactions may involve transient intermediates in which one bond has been formed [R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959); C. Walling and J. Peisach, *J. Am. Chem. Soc.*, **80**, 5819 (1958); and R. P. Lutz and J. D. Roberts, *ibid.*, **83**, 2198 (1961)], the intermediacy of a triplet biradical has been ruled out [N. J. Turro and G. S. Hammond, *ibid.*, **84**, 2841 (1962)] and is not to be read into formula XIII.

(16) Many previously recorded cases involving unsymmetrical addends conform to this same ostensible anomaly. Accordingly, it has proved fruitful, in accounting for products, to treat such cases, even those wherein polar factors appear to suffice, in terms of the single electron delocalization used in the previous. For an extensive study of Diels–Alder reactions between unsymmetrical addends consult the series of papers by Alder, *et al.*, *Ber.*, **86**, 1372 (1953), also paper I in this series, and references contained therein, (see ref. 10a).

(17) All melting points are uncorrected. Infrared spectra were taken as Nujol mulls on a Perkin-Elmer Model 21 spectrophotometer. Elemental analyses were performed by the microanalytical laboratory of the Smith, Kline and French Laboratories, Inc.

(18) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 140.

tended to go to the anhydride VIII. Gradual heating produced a m.p. 287–290° with a change indicated at *ca.* 235–240°. When placed in a preheated bath at 270°, there was an immediate melting with gas evolution, and when the sample was removed thereafter resolidification took place to a material which then did not melt below 300°. Infrared spectra of VII showed only ketone and acid (ester) carbonyl absorption at 5.75, 5.85, whereas an infrared spectra taken on a crude melt of VII indicated the five-membered anhydride carbonyl pattern with bands at 5.40 (w) and 5.60 μ (s).

Anal. Calcd. for $C_{27}H_{38}O_6 \cdot H_2O$: C, 68.20; H, 8.48. Found: C, 68.16, H, 8.44.

Adduct of I with 5(or 6)-*p*-Tolylthiotoluquinone (Product IX).—A solution of I (4 g.) and 2.5 g. 5(or 6)-*p*-tolylthiotoluquinone in 80 ml. of toluene, containing a pinch of hydroquinone was refluxed 48 hr. The toluene was then removed *in vacuo* and the residue was recrystallized from benzene–hexane to afford 2 g. of pale yellowish white crystals (IX), m.p. 300–302°. The infrared absorption of IX indicated ester carbonyls at 5.70–5.73 and ketone bands at 5.88 and 5.96 μ; in addition a band at 6.40 μ (ms) is characteristic of thio-substituted enedione.[11] Also evident were C–OAc stretching bands at 8.05 and 8.23 μ.

Anal. Calcd. for $C_{39}H_{46}O_6S$: C, 72.87; H, 7.21. Found: C, 72.73; H, 7.03.

Zinc–Acetic Acid Reduction of Compound IX (Product X).—A mixture of 1.0 g. of adduct of the acetoxytriene and 5(or 6)-*p*-tolylthiotoluquinone, 80 ml. of 95% acetic acid, and 6.0 g. of zinc dust was refluxed for 14 hr. The filtered solution together with acetic acid washings was evaporated on the steam bath with a rotary evaporator, and the residue was taken up in chloroform, washed with bicarbonate solution and saturated sodium chloride solution, and dried (sodium sulfate). The dark residue remaining after the chloroform removal was recrystallized from dilute ethanol and once again from ethanol to yield X as white needles, m.p. 241–242°.

Anal. Calcd. for $C_{32}H_{42}O_6$: C, 73.50; H, 8.10. Found: C, 73.64; H, 7.92.

Acknowledgment.—We wish to acknowledge with thanks supplies of steroidal starting material from the Julian Laboratories, Inc., and Smith Kline and French Laboratories.

Acridizinium Derivatives from Hydroquinone Dimethyl Ether

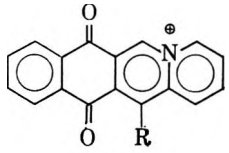
C. K. BRADSHER AND MARVIN W. BARKER[1]

Department of Chemistry, Duke University, Durham, North Carolina

Received August 8, 1963

The reaction of an excess of picolinaldoxime with 2,5-bis(bromomethyl)-1,4-dimethoxybenzene affords a salt which can be cyclized (and oxidized) to yield 4a,11a-diazoniapentacene-6,13-quinone dibromide. 2,5-Dimethoxybenzyl bromide, and a quaternary salt prepared therefrom, both undergo bromination in position 6.

Recently[2] it was shown that 2-bromomethyl-1,4-dimethoxynaphthalene could be converted to quinolizinium derivatives (I), the first examples of quinones in the quinolizinium series. The present communication

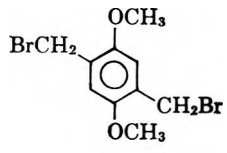


I

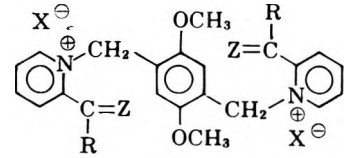
describes the results of our experiments with bromomethyl derivatives of hydroquinone dimethyl ether.

2,5-Bis(bromomethyl)-1,4-dimethoxybenzene (II), obtained by bromomethylation of the hydroquinone ether, was diquaternized by reaction with picolinaldoxime. The diquaternary salt (III, X = Br) was made to undergo a double cyclization and air oxidation by heating for 24 hr. at 100° in 48% hydrobromic acid. Similar results were obtained when the bisbromomethyl compound (II) was diquaternized with 2-(1,3-dioxolan-2-yl)pyridine[3] and the salt (IV) cyclized.

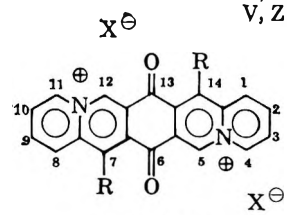
The yellow 4a,11a-diazoniapentacene-6,13-quinone (VI) dibromide is not only extremely insoluble in common solvents, but like the related 6a-azonianaphthacenequinone salts[2] is attacked by most polar solvents to yield a blue solution. The analytical sample was prepared by crystallization from a trifluoroacetic–acetic



II



III, Z = NOH; R = H
IV, Z = O(CH$_2$)$_2$O; R = H
V, Z = O; R = C$_6$H$_5$



VI, R = H
VII, R = C$_6$H$_5$

acid mixture. No method was found for the purification of the perchlorate or picrate.

In order to obtain further analytical evidence for the existence of the new quinone system, the diphenyl derivative (VII) was prepared. Quaternization of 2,5-bis(bromomethyl)-1,4-dimethoxybenzene (II) with 2-benzoylpyridine occurred in only 18% yield, but the cyclization–oxidation of the salt (V) occurred in greater than 50% yield.

The ultraviolet absorption spectra (Table I) of the new salts in both neutral and acidified solutions in methanol indicate that the attack of the solvent under neutral conditions upon the aromatic system of the quinone (VI and VII) must be more extensive than was observed with 6a-azonianaphthacenequinone salts.[2]

While 2-bromomethyl-1,4-dimethoxybenzene may be isolated from the reaction products obtained in the

(1) This research was supported by a research grant (NSF-G 19901) of the National Science Foundation. Taken in part from a thesis submitted in partial fulfillment of the requirements for the Ph.D. degree, Duke University.

(2) C. K. Bradsher and M. W. Barker, *J. Org. Chem.*, **28**, 1669 (1963).

(3) C. K. Bradsher and J. C. Parham, *ibid.*, **28**, 83 (1963).

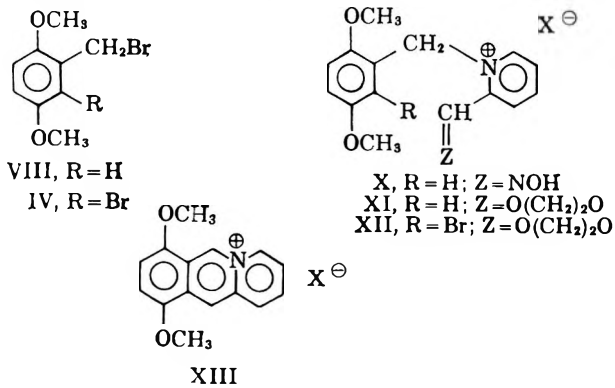
TABLE I

ULTRAVIOLET ABSORPTION MAXIMA (AND LOG EXTINCTION COEFFICIENTS) OF 4a,11a-DIAZONIAPENTACENE-6,13-QUINONE SALTS

Compound	Acidified,[a] λ_{max} mμ (log ε)	Neutral, λ_{max} mμ (log ε)
VI (dibromide)		227 (4.64)
	251 (4.70)	241[b] (4.57)
	378[b] (4.40)	359[b] (4.34)
	385 (4.41)	372 (4.38)
VII (diperchlorate)	235[b] (4.52)	238 (4.51)
	255 (4.56)	360 (4.02)
	382[b] (4.17)	375 (4.09)
	390 (4.20)	

[a] Approximately 10^{-3} *M* in hydrochloric acid. [b] Shoulder.

bromomethylation of hydroquinone dimethyl ether, the material used in our experiments was obtained by the method of Shulgin and Gal.[4] The bromomethyl compound (VIII) reacted with picolinaldoxime af-



fording a salt (X) which cyclized readily in hydrobromic acid yielding a red compound at first believed to be XIII.[5] The analysis of a recrystallized sample gave results which corresponded to formula XIII *plus one mole of hydroxylamine hydrobromide*. Observation of the red crystals under a microscope revealed only a single type and left the possibilities that the product might be a mixed salt, or the intermediate to be expected if cyclization had occurred, but hydroxylamine had not been eliminated. While the ultraviolet absorption spectrum clearly pointed to the mixed salt explanation, confirmatory experiments were carried out. Fortunately pure 7,10-dimethoxyacridizinium bromide (XIII, X = Br) could be prepared by ion exchange of the picrate obtained from the mixed salt. Crystallization of the bromide (XIII) with hydroxylamine hydrobromide gave a homogenous salt identical in every way with the red cyclization product.[6] Mixed salt formation is not general, for crystallization of the bromide (XIII) with ammonium bromide yielded no evidence of a mixed salt. An alternative synthesis of XIII perchlorate *via* the quaternary salt (XI) from 2-(1,3-dioxolan-2-yl)pyridine avoids the possibility of mixed salt formation.

Since it was found that 2-bromomethyl-1,4-dimethoxybenzene readily undergoes monobromination, it was thought that the bromination product would form a useful starting material in the synthesis of a bromo-7,10-dimethoxyacridizinium bromide. When the quaternary salt (XII) failed to cyclize it was suspected that bromination of the 2-bromomethyl-1,4-dimethoxybenzene had occurred *ortho* rather than *para* to the bromomethyl group, and the product was IX. This was confirmed by oxidation with 2-nitropropane and sodium methoxide to the known[7] 2,5-dimethoxy-6-bromobenzaldehyde. It is of interest that, when quaternary salt XI was brominated, the orientation was again *ortho* since the only product isolated was XII.

Experimental

All analyses were by Dr. Ing. A. Schoeller, Mikroanalytisches Laboratorium, Kronach, West Germany. Melting points were determined using a Laboratory Devices Mel-Temp block and are uncorrected. Infrared spectra were measured in potassium bromide pellets using the Perkin-Elmer Model 21 spectrophotometer. The ultraviolet absorption spectra were recorded using a Cary Model 14 recording spectrophotometer with methanol as the solvent. Wave lengths are recorded in millimicrons (mμ) and shoulders are indicated by an asterisk (*).

2,5-Bis(bromomethyl)-1,4-dimethoxybenzene (II).—A stirred suspension of 1,4-dimethoxybenzene (69 g.) and paraformaldehyde (33 g.) in glacial acetic acid (100 ml.) and carbon tetrachloride (600 ml.) was saturated with hydrogen bromide at room temperature. The solid was collected and recrystallized from chloroform as colorless needles; yield, 31.4 g. (19%); m.p. 196–198°. The analytical sample melted at 203–203.5°. Concentration of the acetic acid–chloroform mother liquor yielded impure 2-bromomethyl-1,4-dimethoxybenzene.

Anal. Calcd. for $C_{10}H_{12}Br_2O_2$: C, 37.06; H, 3.73; Br, 49.33. Found: C, 37.29; H, 3.45; Br, 49.78.

2,5-Bis(1-methylene-2-aldoximinomethylpyridinium bromide)-1,4-dimethoxybenzene (III, X = Br).—A solution of the bisbromomethyl compound (II, 13 g.) and picolinaldoxime (12.2 g.) in dimethylformamide (400 ml.) was allowed to stand for 30 days at room temperature. Ether was then added to assure complete precipitation, and the yellow powder, 11.6 g. (51%), was collected. This material gave evidence of decomposition starting at 220° and did not melt below 350°. The analytical sample which formed pale yellow needles from methanol showed similar behavior on heating.

Anal. Calcd. for $C_{22}H_{24}Br_2N_4O_4$: C, 46.49; H, 4.26; N, 9.86. Found: C, 46.67; H, 4.40; N, 9.73.

The **diperchlorate** (III, X = ClO_4) was recrystallized from methanol solution as colorless needles, m.p. 224–225°.

Anal. Calcd. for $C_{22}H_{24}Cl_2N_4O_{12}$: C, 43.50; H, 3.98; N, 9.23. Found: C, 43.68; H, 3.97; N, 9.22.

2,5-Bis[1-methylene-2-(1,3-dioxolan-2-yl)pyridinium bromide]-1,4-dimethoxybenzene (IV).—A solution of the bisbromomethyl compound (II, 10 g.) and 2-(1,3-dioxolan-2-yl)pyridine[3] (11.8 g.) in dimethylformamide (200 ml.) was allowed to stand at room temperature for 11 days. Ether was added to precipitate the salt, 13.3 g. (69%), m.p. 197–198°. Recrystallization from methanol–ethyl acetate gave colorless needles, m.p. 198.5–199°.

Anal. Calcd. for $C_{26}H_{30}Br_2N_2O_6$: C, 49.85; H, 4.83; N, 4.47. Found: C, 49.68; H, 5.05; N, 4.63.

The **diperchlorate** (IV, X = ClO_4) crystallized from methanol as colorless needles, m.p. >350°.

Anal. Calcd. for $C_{26}H_{30}Cl_2N_2O_{14}$: C, 46.93; H, 4.55; N, 4.21. Found: C, 47.34; H, 4.32; N, 4.55.

4a,11a-Diazoniapentacene-6,13-quinone Dibromide (VI, X = Br). A. From the Oximino Salt (III).—A mixture of the crude oximino diquaternary salt (III, 0.5 g.) and 48% hydrobromic acid (10 ml.) was heated for 17 hr. on the steam bath. Heating for shorter periods gave material which could not be purified. The solution was diluted with water and cooled giving 0.3 g. (71%) of a dark solid, m.p. >350°. The infrared spectrum exhibited a strong band at 5.94 μ in the carbonyl region. The compound was very sensitive to attack by polar solvents, and even distilled water afforded blue solutions. The solution became yellow on addition of acid. Recrystallization of the

(4) A. T. Shulgin and E. M. Gal, *J. Chem. Soc.*, 1316 (1953).

(5) The preliminary work on this problem was done by Dr. T. W. G. Solomons.

(6) For another example of mixed salt formation in the benzoquinolizinium series, see C. K. Bradsher and N. L. Yarrington, *J. Org. Chem.*, **28**, 78 (1963).

(7) L. Rubenstein, *J. Chem. Soc.*, 1998 (1925).

product from trifluoroacetic acid–acetic acid afforded a yellow powder, m.p. >350°.

B. From the Bisdioxolanylpyridinium Salt (IV).—Cyclization of the bisdioxolanylpyridinium salt (IV, X = Br, 0.5 g.) under the conditions used with III afforded 0.2 g. (52%) of the quinone (VI).

Anal. Calcd. for $C_{20}H_{12}Br_2N_2O_2$: C, 50.87; H, 2.56; N, 5.93. Found: C, 50.88; H, 2.92; N, 5.89.

The diperchlorate (VI, X = ClO_4), m.p. >350°, was practically insoluble in organic solvents (including trifluoroacetic acid and N-methylpyrrolidone) and was not obtained in pure form.

2,5-Bis(1-methylene-2-benzoylpyridinium bromide)-1,4-dimethoxybenzene (V).—A solution of the bisbromomethyl compound (II, 10 g.) and 2-benzoylpyridine (11.9 g.) in dimethylformamide (300 ml.) was allowed to stand at room temperature for 18 days. Addition of ether precipitated the product as a hygroscopic yellow powder, m.p. 200–201°; yield, 3.95 g. (18%). Recrystallization of the product from methanol–ethyl acetate afforded short yellow needles, m.p. 194–195°, which appeared on analysis to be hydrated.

Anal. Calcd. for $C_{34}H_{30}Br_2N_2O_4 \cdot {}^3/_2H_2O$: C, 56.91; H, 4.63; N, 3.90. Found: C, 57.10; H, 4.46; N, 4.25.

7,14-Diphenyl-4a,11a-diazoniapentacene-6,13-quinone Dibromide (VII).—The quaternary salt (V, 2 g.) was heated in 48% hydrobromic acid (20 ml.) on the steam bath for 24 hr. while air was passed through. The acid was removed under reduced pressure (aspirator) at 100° and the yellow residue crystallized from methanol to yield 1.02 g. (53%), m.p. >350°. The infrared spectrum exhibited a strong absorption at 5.95 μ. Like its congener (VI) the new salt was sensitive to attack by water and polar solvents. Recrystallization from an acidified water solution gave yellow needles, m.p. >350°.

Anal. Calcd. for $C_{32}H_{20}Br_2N_2O_2$: C, 61.56; H, 3.23; N, 4.49. Found: C, 61.32; H, 3.32; N, 4.60.

The perchlorate crystallized from water as yellow needles, m.p. >350°.

Anal. Calcd. for $C_{32}H_{20}Cl_2N_2O_{10} \cdot {}^1/_2H_2O$: C, 57.15; H, 3.15; N, 4.16. Found: C, 57.36; H, 3.41; N, 4.14.

1-(2,5-Dimethoxybenzyl)-2-aldoximinomethylpyridinium Bromide (X, X = Br).—A solution containing 14.4 g. of 2,5-dimethoxybenzylbromide[5] (VIII) and 12.2 g. of picolinaldoxime in 55 ml. of dimethylformamide was allowed to stand at room temperature for 7 days. After addition of ethyl acetate the yellow solid was collected; yield, 18.5 g. (48%); m.p. 185–187°. Recrystallization from methanol gave yellow prisms, m.p. 184.5–185°.

Anal. Calcd. for $C_{15}H_{17}BrN_2O_3$: C, 50.99; H, 4.82; N, 7.93. Found: C, 51.09; H, 4.76; N, 7.78.

Mixed Salt of 7,10-Dimethoxyacridizinium Bromide (XIII, X = Br) with Hydroxylamine Hydrobromide.—A solution of 1 g. of the oximino salt (X) and 7.5 ml. of 48% hydrobromic acid was heated and stirred for 10 min. on the steam bath. The acid was removed under reduced pressure (aspirator) and the residue crystallized from methanol–ethyl acetate as red needles; yield, 0.84 g. (65%); m.p. 227–229° dec.; λ_{max}, 251 mμ (log ε 4.36), and 396 (4.08); λ_{min} 331 (3.46).

Anal. Calcd. for $C_{15}H_{18}Br_2N_2O_3$: C, 41.49; H, 4.17; N: 6.45. Found: C, 41.62; H, 4.16; N, 6.62.

7,10-Dimethoxyacridizinium Picrate (XIII, X = $OC_6H_2(NO_2)_3$).—A small sample of the mixed salt was dissolved in ethanol and precipitated as the picrate by addition of a saturated solution of picric acid in ethanol. The picrate formed irregular orange crystals, m.p. 276–278°, and was free from hydroxylamine.

Anal. Calcd. for $C_{21}H_{16}N_4O_9$: C, 53.85; H, 3.44; N, 11.96. Found[8]: C, 53.90; H, 3.73; N, 11.96.

7,10-Dimethoxyacridizinium Bromide (XIII, X = Br).—A methanolic solution of the picrate was passed through an anion exchange column (Amberlite IRA-401) loaded with bromide ion. From the concentrated solution red-orange needles, m.p. 270° dec., were obtained by addition of ethyl acetate.

Anal. Calcd. for $C_{15}H_{14}BrNO_2$: C, 56.25; H, 4.41; N, 4.38. Found: C, 56.49; H, 4.57; N, 4.60.

Crystallization of 0.10 g. of the bromide (XIII, X = Br) from methanol–ethyl acetate containing an excess of hydroxylamine hydrobromide afforded 0.11 g. of orange needles, m.p. 227–227.5° dec. This material appeared uniform under the microscope. The material was identical with the mixed salt obtained by cyclization of the oxime (X, X = Br) as evidenced by infrared spectrum and mixture melting point determinations. No mixed salt was obtained when the bromide (XIII, X = Br) was crystallized in the presence of ammonium bromide.

Refluxing the bromide (XIII, X = Br) with 48% hydrobromic acid (ether-cleaving conditions) failed to yield a pure product. The crude ether-cleavage products gave no infrared spectral evidence of the formation of a carbonyl group when oxidation was attempted using air, ferric chloride, or potassium periodate.

1-(2,5-Dimethoxybenzyl)-2-(1,3-dioxolan-2-yl)pyridinium Bromide (XI, X = Br).—A solution of 2,5-dimethoxybenzyl bromide (VIII, 6.9 g.) and 2-(1,3-dioxolan-2-yl)pyridine (5 g.) in dimethylformamide (15 ml.) was allowed to stand for 7 days at room temperature. On addition of ethyl acetate, 11 g. (100%) of yellow solid was obtained, m.p. 161–163°. Recrystallization from methanol–ethyl acetate afforded yellow plates, m.p. 167.5–169°.

Anal. Calcd. for $C_{17}H_{20}BrNO_4$: C, 53.41; H, 5.27; N, 3.66. Found: C, 53.61; H, 5.17; N, 3.87.

The perchlorate crystallized from methanol–ethyl acetate as yellow plates with an unusual melting point behavior, m.p. 111°, resolidifying at 160° and finally decomposing at 210°.

Anal. Calcd. for $C_{17}H_{20}ClNO_8$: C, 50.81; H, 5.02; N, 3.49. Found: C, 50.90; H, 4.85; N, 3.59.

2,5-Dimethoxy-6-bromobenzyl Bromide (IX).—To a solution of 2,5-dimethoxybenzyl bromide (VIII, 11.55 g.) in 200 ml. of carbon tetrachloride cooled in an ice bath, a solution containing 8 g. of bromine in 30 ml. of carbon tetrachloride was added dropwise. After 24 hr. the carbon tetrachloride was washed with water until neutral, and then dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded an oil, which crystallized from ethyl acetate as colorless needles, m.p. 87.5–89°; yield, 9.7 g. (62%). Recrystallization afforded colorless needles, m.p. 102.5–103.5°.

Anal. Calcd. for $C_9H_{10}Br_2O_2$: C, 34.87; H, 3.25; Br, 51.56. Found[8]: C, 35.00; H, 3.07; Br, 51.66.

Oxidation of 2,5-Dimethoxy-6-bromobenzyl Bromide (IX).—A solution of the bromination product (IX, 0.92 g.) with 0.36 g. of 2-nitropropane in 20 ml. of methanol was added to a solution of 0.22 g. of sodium methoxide in 30 ml. of methanol. The mixture was allowed to stand at room temperature for 5 hr., and then concentrated on the steam bath. Water was added to the residue, and the mixture extracted with ether. The ethereal extract was washed with bicarbonate and dried. Evaporation of the ether afforded a yellow residue which crystallized from ethanol; yield, 0.15 g.; m.p. 130–131°; lit.[7] m.p. 125–126°. This was identical with an authentic sample, m.p. 129.5–130.5°, prepared by the method of Rubenstein[7] and gave no depression of mixture melting point.

1-(2,5-Dimethoxy-6-bromobenzyl)-2-(1,3-dioxolan-2-yl)pyridinium Bromide (XII, X = Br).—A solution of 2,5-dimethoxy-6-bromobenzyl bromide (IX, 3.8 g.) and 2-(1,3-dioxolan-2-yl)-pyridine (2 g.) in 35 ml. of dimethylformamide was allowed to stand for 7 days at room temperature. Ethyl acetate precipitated 2.9 g. (52%) of solid, m.p. 146–148°. Recrystallization from methanol–ethyl acetate gave colorless plates, m.p. 147–148.5°.

Anal. Calcd. for $C_{17}H_{19}Br_2NO_4$: C, 44.27; H, 4.15; N, 3.04. Found[8]: C, 44.18; H, 4.14; N, 3.24.

1-(2,5-Dimethoxy-6-bromomethyl)-2-(1,3-dioxolan-2-yl)pyridinium Perchlorate (XII, X = ClO_4). A. From the Bromide (XII, X = Br).—Addition of perchloric acid to an aqueous solution of the bromide followed by recrystallization of the product from methanol–ethyl acetate afforded colorless plates, m.p. 144.5–145°.

B. By Bromination of the Salt (XI).—To a solution of the quaternary salt (XI, X = Br, 1.4 g.) in 15 ml. of glacial acetic acid, 1.28 g. of bromine in 5 ml. of glacial acetic acid was added, and the precipitate which first formed (probably the tribromide) was dissolved by addition of 50 ml. of acetic acid. After the mixture had stood for 2 hr., the precipitate which had formed during this period was collected. The solid was dissolved in aqueous ethanol (100 ml.), silver chloride added, and the mixture stirred in the dark for 2 hr. to give the chloride anion. The silver salts were filtered off and the solution concentrated. Addition of perchloric acid to the solution afforded 0.22 g. of solid which crystallized from methanol–ethyl acetate as colorless needles, m.p. 144–144.5°. This was identical (mixture melting point) with the material obtained by procedure A.

Anal. Calcd. for $C_{17}H_{19}BrClNO_8$: C, 42.47. H, 3.98; N, 2.91. Found[8]: C, 42.45; H, 3.74; N, 3.11.

(8) Analysis were by A. Daessle, Montreal, Quebec, Canada.

The Synthesis of C-15 β-Substituted Estra-1,3,5(10)-trienes. I

E. W. CANTRALL, RUDDY LITTELL, AND SEYMOUR BERNSTEIN

Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York

Received July 1, 1963

The synthesis of C-15 β-substituted estra-1,3,5(10)-trienes by the frontal addition of nucleophiles to the Δ^{15}-17-one moiety of 3-methoxyestra-1,3,5(10),15-tetraen-17-one is described. Arguments are presented to support the assignment of the C-15 β-configuration to these compounds and also to rationalize their mode of formation on a kinetic basis.

Johnson and Johns[1] have described the preparation of 3-methoxyestra-1,3,5(10),15-tetraen-17-one (**1**) in five steps from estrone methyl ether (**4a**). They observed that tetraene **1** is readily isomerized by *p*-toluenesulfonic acid in refluxing benzene to give a mixture consisting of 3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one (**2**) and 3-methoxy-estra-1,3,5(10),14-tetraen-17-one (**3**). However, attempted isomerization with potassium hydroxide in methanol provided a 15-methoxyestrone of undetermined configurations at C-14 and C-15. This facile conjugate addition of methanol suggested to us the possibility of utilizing the Δ^{15}-17-one (**1**) as an intermediate for the synthesis of C-15 substituted estrogens.

Accordingly, we have prepared the 15-methoxy compound described by Johnson and Johns,[1] and directed our attention initially toward elucidating its configurational aspects. Treatment of the Δ^{15}-17-one (**1**) with aqueous potassium hydroxide in methanol afforded the 15-methoxy adduct product (**4b**) in practically quantitative yield.[2] The product was then submitted to optical rotational analysis utilizing a number of known 15α- and β-substituted steroids and their corresponding C-15 unsubstituted compounds. From Table I it can be seen that a 15β-substituent produces a large levorotatory shift, while a dextrorotatory shift of comparable magnitude is observed with a 15α-substituent.[3] On the basis of this analysis the methoxyl group of compound **4b** has been assigned the 15β-configuration. The assumption is made, however, that isomerization at the C-14 ring juncture did not occur prior to addition. This possible structural alteration was considered unlikely in view of the following observations.

It has been found that treatment of the C/D *cis* isomer, 3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one (**2**)[1] under the same conditions previously described for compound **1** resulted in a mixture consisting of 56% of starting material **2**, 28% of the Δ^{14}-17-one (**3**), and 10–15% of a substance of probable structure 3,15β-dimethoxy-14β-estra-1,3,5(10)-trien-17-one (**5**) in about 90% purity. The purity of **5** was determined by thin layer chromatographic analysis. Many attempts to purify **5**, which was contaminated with starting material **2**, by partition chromatography failed. Regardless, the assigned structure was based on spectral analysis. Its infrared absorption spectrum possessed a saturated carbonyl group at 1725 cm.$^{-1}$, while its n.m.r. spectrum displayed two methyl groups at 6.16 (C-3) and 6.63 τ (C-15). In addition the splitting constant for the C-15 hydrogen (triplet centered at 5.87 τ) is 8 c.p.s. for **5** as compared with 5 c.p.s. for **4b** which suggests that the hydrogen atoms at C-14 and C-15 in **5** are *trans* diaxial to each other.[4] Also the spectrum of

TABLE I

MOLECULAR ROTATION ANALYSIS

Compound	$[\alpha]_D$	$[M]_D$	$\Delta[M]_D$
3-Keto-5β-etianic acid methyl ester	+ 70°[a]	+233°	
15β-Hydroxy-3-keto-5β-etianic acid methyl ester	+ 37°[a]	+129°	−104°
15α-Hydroxy-3-keto-5β-etianic acid methyl ester	+ 95°[a]	+331°	+ 98°
Androst-4-ene-3,17-dione	+190° (EtOH)[b]	+544°	
15β-Hydroxyandrost-4-ene-3,17-dione	+148°[c]	+477°	− 97°
15α-Hydroxyandrost-4-ene-3,17-dione	+206° (MeOH)[c]	+622°	+ 78°
3-Methoxyestra-1,3,5(10)-trien-17-one	+171°[d]	+486°	
3,15β-Dimethoxyestra-1,3,5(10)-trien-17-one	+ 94°	+295°	−191°
15β-Benzyloxy-3-methoxyestra-1,3,5(10)-trien-17-one	+ 38°	+148°	−338°
15β-Hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one	+103°	+309°	−177°
15β-Cyano-3-methoxyestra-1,3,5(10)-trien-17-one	+ 30°	+ 93°	−393°
3-Methoxyestra-1,3,5(10)-trien-17β-ol	+ 77°[e]	+220°	
15β-Cyano-3-methoxyestra-1,3,5(10)-trien-17β-ol	− 28°	− 87°	−307°
15α-Carboxamido-3-methoxyestra-1,3,5(10)-trien-17β-ol	+109° (MeOH)	+359°	+139°
15α-Carboxy-3-methoxyestra-1,3,5(10)-trien-17β-ol	+130° (MeOH)	+430°	+210°

[a] A. Lardon, H. P. Sigg, and T. Reichstein, *Helv. Chim. Acta*, **42**, 1457 (1959). [b] L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, p. 519. [c] S. Bernstein, M. Heller, L. I. Feldman, W. S. Allen, R. H. Blank, and C. E. Linden, *J. Am. Chem. Soc.*, **82**, 3685 (1960). [d] G. F. Marrian and G. A. D. Haslewood, *Biochem. J.*, **26**, 25 (1932). [e] A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953).

(1) W. S. Johnson and W. F. Johns, *J. Am. Chem. Soc.*, **79**, 2005 (1957).

(2) The crude reaction product was analyzed by partition chromatography on Celite 545 and was found to be approximately 97% pure (see Experimental).

(3) See footnotes *a* and *c*, Table I, for previous rotational analyses of 15 substituted steroids.

(4) See, *e.g.*, H. Conroy, "Advances in Organic Chemistry," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1960, p. 309.

5 has a doublet centered at 7.63 τ (C-16 methylene) in contrast to that (7.45 τ) observed for **4b**. This appears to be consistent with anticipated increased shielding at C-16 in a structure represented by **5**.

Further chemical support for the retention of configuration at C-14 in the formation of **4b** from **1** was obtained as follows. 15β-Benzyloxy-3-methoxyestra-1,3,5(10)-trien-17-one (**4c**), prepared by the base-catalyzed addition of benzyl alcohol to 3-methoxyestra-1,3,5(10),15-tetraen-17-one (**1**), was reduced with sodium borohydride and acetylated to give 17β-acetoxy-15β-benzyloxy-3-methoxyestra-1,3,5(10)-triene (**6b**). Hydrogenolysis of the latter with a 10% palladium–charcoal catalyst in acetic acid gave the corresponding 15β-hydroxy derivative **6c**, which was in turn oxidized with chromic acid–pyridine to 17β-acetoxy-3-methoxyestra-1,3,5(10)-trien-15-one (**7**). The optical rotatory dispersion curve[5] of the latter in methanol solution displayed a strong positive Cotton effect (Fig. 1) characteristic of a C/D *trans*-15-keto steroid.[6,7] Potassium hydroxide in methanol (0.012 *N*) was added to the aforementioned solution and equilibration was allowed to proceed for 17 hr. The resultant dispersion curve indicated that **7** had to a large extent isomerized to the more stable C/D *cis* structure.[8] C/D-*trans*-15-Keto steroids have been shown on lithium aluminum hydride reduction to give the corresponding C/D-*trans*-15β-hydroxy derivative.[7] The reduction of the 17β-acetoxy-15-one (**7**) with lithium aluminum hydride gave 3-methoxy estra-1,3,5(10)-triene-15β,17β-diol (**6a**) identical with the product obtained by a similar reduction of 15β-hydroxy-3-methoxyestra-1,3,5-(10)-trien-17-one (**4d**). The latter was prepared by hydrogenolysis of the benzyl group of **4c** with a 10% palladium–charcoal catalyst in acetic acid. Thus it is concluded that the nucleophilic addition of methoxide and benzyloxide ions to the Δ^{15}-17-keto system of **1** proceeds without isomerization at C-14 to provide the corresponding 15β-substituted products, **4b** and **4c**, respectively.[9]

The question arises as to whether the formation of these 15β-substituted steroids is kinetically or thermodynamically controlled. For this purpose isomerization studies at C-15 were undertaken,[10] and 15β-cyano-3-methoxyestra-1,3,5(10)-trien-17β-ol (**6e**), Δ[M]D −393° was prepared from **1** in two stages

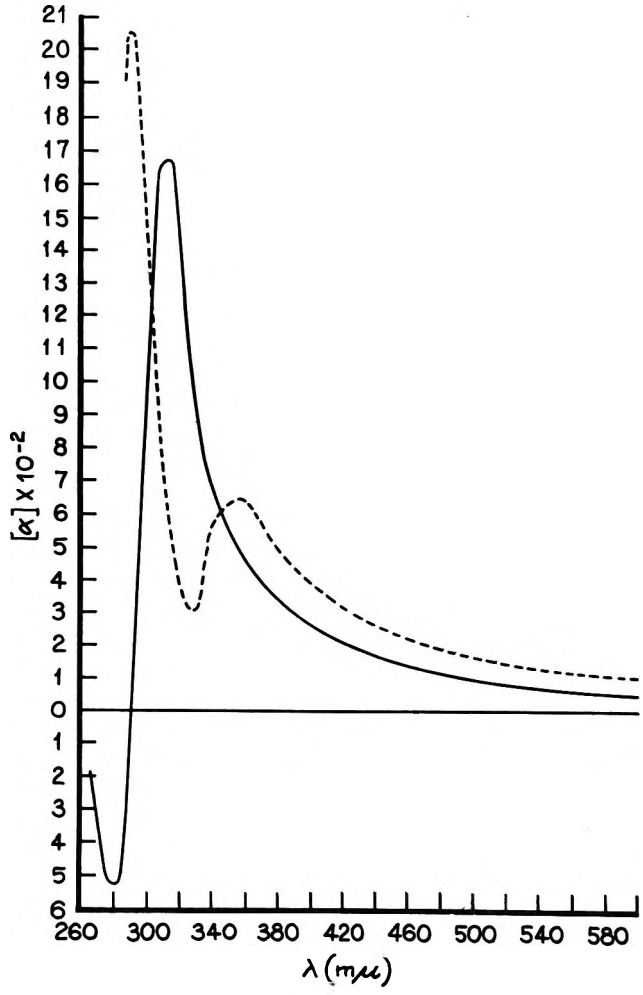


Fig. 1.—Optical rotatory dispersion curve of 17-β-acetoxy-3-methoxyestra-1,3,5(10)-trien-15-one. ———, *c* 0.034, 600–300; *c* 0.017, 320–290; *c* 0.0068, 300–265 mμ; - - - - -, *c* 0.0272, 600–290; *c* 0.01088, 310–284 mμ after addition of 1.00 ml. of 0.012 *N* KOH–CH_3OH.

(**1** → **4e** → **6e**). Treatment with potassium hydroxide in refluxing aqueous propanol gave the carboxamide **8a**. Its Δ[M]D +141 was indicative that the carboxamide group had epimerized to the thermodynamically more stable 15α-configuration. Similarly, hydrolysis of **6e** under more vigorous conditions (potassium hydroxide–aqueous ethylene glycol, 22-hr. reflux) afforded the carboxylic acid (**8b**) whose Δ[M]D +212° was also consistent with a 15α-configuration. Thus β-addition at C-15 represents kinetic control and appears to be irreversible.

If the addition of alkoxide to the *trans*-hydrindenone (**1**) were a readily reversible process, it would be anticipated that the corresponding 15α-alkoxy product or at least a mixture of it and the 15β-epimer would be formed. That the process is not reversible is demonstrated by the fact that **4b** is the exclusive product whether the reaction time is 15 min. or 24 hr.[11]

At this point the problem required an explanation or rationale for the formation of the C-15 β-substituted steroid by a frontal (β-face) approach of the nucleophile. One may have anticipated that the C-13 methyl

(5) We are indebted to Professor Kurt Mislow of New York University for the O.R.D. determinations.

(6) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 58.

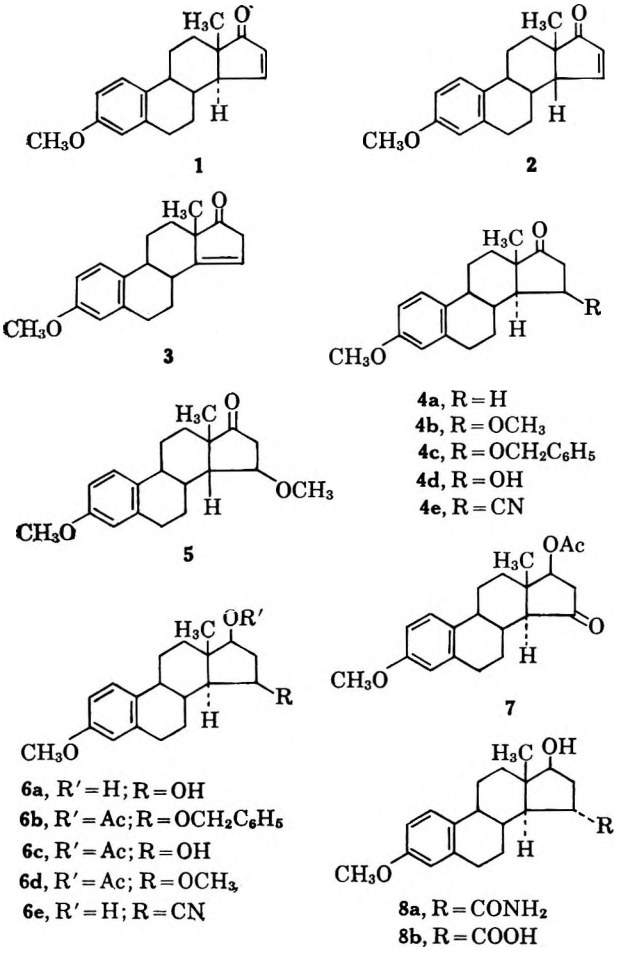
(7) Footnote *a*, Table 1.

(8) The relative stability of *cis*- and *trans*-hydrindanones has been studied by numerous investigators [*e.g.*, N. L. Allinger, R. B. Hermann, and C. Djerassi, *J. Org. Chem.*, **25**, 922 (1960), and references cited therein]. With 15-keto steroids the equilibrium between the C/D forms is apparently dependent on the size of the C-17-substituent. When the latter is small, or relatively so, the *cis* isomer is thermodynamically favored. Thus, Allinger, Hermann, and Djerassi have demonstrated that under equilibrium conditions the 14β *cis* isomer of 3β-acetoxy-15-ketoetianic acid methyl ester is preferably formed over the 14α *trans* isomer in the ratio of 87:13.

(9) J. Fajkos [*Chem. Listy*, **51**, 1894 (1957); *Collection Czech. Chem. Commun.*, **23**, 2154 (1958)] has reported a similar addition of methanol to 3β-acetoxyandrost-15-en-17-one without assigning a configuration to the methoxyl group. On the basis of rotational analysis (Δ[M]D −167°) and of its mode of preparation the compound most likely has a β-configuration at C-15.

(10) J. Fajkos and F. Sorm [*Chem. Listy*, **51**, 579 (1956); *Collection Czech. Chem. Commun.*, **22**, 1873 (1957)]; have shown that 16β-acetylandrost-4-en-3-one under equilibrating conditions isomerizes to the 16α-acetyl compound. Since 15β- and 16β-oriented groups are similarly related geometrically to the C-13 methyl group, it may then be expected that a 15β-substituent (quasi-axial) capable of isomerization would do so.

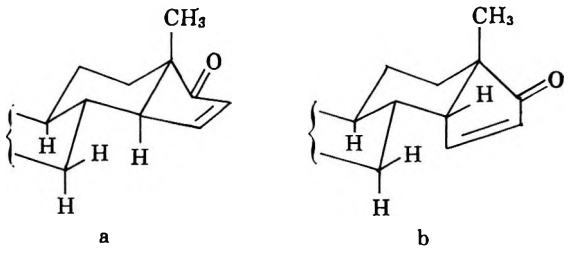
(11) In contrast to this, D. K. Fukushima and T. F. Gallagher [*J. Am. Chem. Soc.*, **73**, 196 (1951)] have shown that equilibration of 16α-methoxyprogesterone in methanolic potassium hydroxide at room temperature results in a mixture composed of 70% of starting material and 30% of 16-dehydroprogesterone.



group would have a similar steric influence upon the course of addition to a Δ^{15}-17-ketone as it does with a Δ^{16}-20-ketone where the entering group assumes the 16α-configuration.[11,12] There is, however, precedence for β-addition to C-15 as exemplified by the catalytic reduction and epoxidation of a Δ^{14}-17-ketone to the corresponding 14β-17-ketone,[13] and 14β,15β-epoxide,[14] respectively.

Brutcher and Bauer[15] have concluded from a study of three possible ring D conformations (two "envelope" and one "half-chair" conformations) that for 17β-substituted steroids one of the "envelope" conformations is preferred, that is the one in which C-13 lies above the plane defined by carbons 14, 15, 16, and 17. With 17-keto steroids, this conformation results in less 1,3-interactions; however, this advantage is outweighed by the resultant torsional strain inherent in it. Thus, these investigators[15] suggested that ring D of androstan-17-one assumes one of the other two possible conformations.

An examination of Dreiding models of the partial structures **a** and **b** corresponding to the 14α-Δ^{15}-17-one (**1**) and 14β-Δ^{15}-17-one (**2**), respectively, reveals that ring D of **1** can assume only the depicted "envelope"



conformation. In this conformation the plane defined by carbons 14, 15, 16, and 17 is slightly elevated from that of rings B and C, and the p-orbitals on the Δ^{15}-double bond have their upper lobe turned slightly toward the C-13 methyl group and the lower lobe at an oblique angle to rings B and C. If one draws an imaginary line through C-15 perpendicular to the carbons 14, 15, 16, and 17 plane and extending approximately 1.36 Å. (the C–O bond distance as measured from the models) one can *approximate* a depicting of a transition state. An examination of this working model reveals that geometrically frontal attack at C-15 would be favored over rear attack. We feel that the bar to rear attack may be ascribed principally to a marked eclipsed 1,2-interaction between a nucleophile entering on the α-face and the C-14 α-hydrogen in the transition state.

An examination of **b** in the same manner reveals that the α-face is shielded by the 7α- and 9α-hydrogens as to make addition in that manner less likely. Furthermore the low yield of the C-15 β-methoxy compound from **2** can be explained on the relative stability of the *cis*-hydrindenone over the *trans* isomer. The 14β-hydrogen of **2** should be removed more readily by base since the incipient anion would have its p-orbital β-oriented, thus retaining the C/D ring in the *cis* locking. This anion may then be re-protonated to give starting material or isomerized *via* the dienolate ion to give either starting material or nonconjugated ketone **3**. However in the case of the *trans*-hydrindenone (**1**), the strain inherent in that system can not be relieved by isomerization to **2** and/or **3** until the bond between C-14 and the 14α-hydrogen is ruptured. It is apparent, then, that the rate of nucleophilic addition to **1** is much greater than that for isomerization.

Experimental

Melting points are uncorrected. The optical rotations are for chloroform solution at 25° unless noted otherwise. The infrared absorption spectra were determined in potassium bromide disks, and the ultraviolet absorption spectra were determined in methanol. Petroleum ether refers to the fraction, b.p. 60–70°. The abbreviation HBV refers to holdback volume.

The authors are indebted to William Fulmor and associates for the infrared, ultraviolet, n.m.r., and optical rotation data. We wish also to thank Louis M. Brancone and associates for the analyses, and Charles Pidacks and associates for the partition chromatography.

3,15β-Dimethoxyestra-1,3,5(10)-trien-17-one (4b).—To a suspension of 3-methoxyestra-1,3,5(10),15-tetraen-17-one (**1**, 0.300 g., m.p. 175–177°, $[\alpha]_D$ −90°, lit.[1] m.p. 180–181°) in methanol (15 ml.) was added 5% aqueous sodium hydroxide (10 drops). The resulting solution was stirred at room temperature for 30 min. The product precipitated upon the addition of water and was collected, washed with water, and dried to give 0.314 g. of **4b**, m.p. 128–129°. Crystallization from ether gave 0.205 g., m.p. 130–131°, $[\alpha]_D$ +95°, lit.[1] m.p. 132–133°.

In another experiment with 0.300 g. of **1** conducted for the same period of time, the product(s) was precipitated with water

(12) (a) J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Am. Chem. Soc.*, **73**, 1528 (1951); (b) D. Gould, E. L. Shapiro, L. E. Finckenor, F. Gruen, and E. B. Hershberg, *ibid.*, **78**, 3158 (1956); (c) J. Romo, *Tetrahedron*, **3**, 37 (1958); (d) P. Bladon, *J. Chem. Soc.*, 3723 (1958); (e) R. H. Mazur and J. A. Cella, *Tetrahedron*, **7**, 130 (1959).

(13) A. F. St. Andre, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica, and C. R. Scholz, *J. Am. Chem. Soc.*, **74**, 5506 (1952).

(14) F. Sondheimer, S. Burstein, and R. Mechoulam, *ibid.*, **82**, 3209 (1960).

(15) F. V. Brutcher, Jr., and W. Bauer, Jr., *ibid.*, **84**, 2233, 2236 (1962).

and subjected to partition chromatography on Celite 545[16] using an *n*-heptane–Methyl Cellosolve solvent system. A HBV of 0.4–1.0 gave 5 mg. of an oil, presumed to be 3-methoxyestra-1,3,5(10),14-tetraen-17-one (**3**) based on its polarity. A HBV of 1.5–2.1 gave 0.292 g. (97%) of 3,15β-dimethoxyestra-1,3,5(10)-trien-17-one (**4b**), which was identical by comparison of its infrared spectrum and its mobility on thin layer chromatography (silica G, benzene–acetone–water, 2:1:2) with the specimen described previously.

15β-Benzyloxy-3-methoxyestra-1,3,5(10)-trien-17-one (4c).—To a solution of 3-methoxyestra-1,3,5(10),15-tetraen-17-one (**1**, 2.0 g.) in benzyl alcohol (60 ml.) was added powdered potassium hydroxide (1.5 g.). The resulting mixture was stirred under a nitrogen atmosphere at room temperature for 3.5 hr., during which time the base completely dissolved. The addition of ethyl acetate resulted in the precipitation of a salt which was filtered and the filtrate was steam distilled. The residue was extracted with ethyl acetate and evaporated to give an oil. The latter was chromatographed on 100 g. of Florisil.[17] The fractions eluted with ether–benzene (1:10) gave 2.19 g. of an oil, which crystallized from ether–petroleum ether to give 0.490 g., m.p. 87–89°. The mother liquors from the crystallization were evaporated and subjected to partition chromatography on Celite 545[16] using the *n*-heptane–Methyl Cellosolve solvent system. The eluate from the second HBV was evaporated to give 1.3 g. of an oil which crystallized from methanol, thus providing an additional 0.660 g. of **4c**, m.p. 90–92°. A sample for analysis was recrystallized from ether–petroleum ether and had m.p. 96–98°; λ_{max} 222, 278, and 288 mμ (ε 8800, 2000, and 2000); $[\alpha]_D$ +38°; ν_{max} 1760, 1625, and 736 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{30}O_3$ (390.50): C, 79.96; H, 7.74. Found: C, 79.84; H, 7.92.

17β-Acetoxy-15β-benzyloxy-3-methoxyestra-1,3,5(10)-triene (6b).—A solution containing 15β-benzyloxy-3-methoxyestra-1,3,5(10)-trien-17-one (**4c**, 0.660 g.), sodium borohydride (0.600 g.), and 10% aqueous sodium hydroxide (5 drops) was stirred at room temperature for 3 hr. The product precipitated as a gelatinous precipitate upon the addition of water and was collected and dissolved in ethyl acetate. The latter solution was washed with saturated saline, dried, and evaporated to give an intractable oil whose infrared spectrum (neat) showed no carbonyl maximum. The crude reduction product was acetylated for 1 hr. at 95° with pyridine (4 ml.) and acetic anhydride (1 ml.). The mixture was evaporated *in vacuo* and the residue was crystallized from methanol to give 0.474 g. of **6b**, m.p. 118–120°. Further recrystallization from methanol did not alter the melting point. A sample for analysis had λ_{max} 222, 278, and 288 mμ (ε 8700, 2200, and 2000); $[\alpha]_D$ −13°; ν_{max} 1750, 1620, 1258, and 738 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{34}O_4$ (434.55): C, 77.39; H, 7.89. Found: C, 77.58; H, 8.03.

17β-Acetoxy-3-methoxyestra-1,3,5(10)-trien-15β-ol (6c).—To a solution containing 15β-benzyloxy 17β-acetate **6b** (0.700 g.) in acetic acid (20 ml.) was added 10% palladium–charcoal catalyst (0.220 g.). The resulting mixture was stirred for 4.5 hr. in a hydrogen atmosphere at room temperature and atmospheric pressure. The catalyst was separated by filtration and washed with methanol. The combined filtrates were evaporated and the residue crystallized from acetone–petroleum ether to give 0.425 g., m.p. 126–128°. A sample for analysis was recrystallized from the same solvents and had m.p. 134–135°; λ_{max} 222, 278, and 288 mμ (ε 8800, 2030, and 1900); $[\alpha]_D$ +9°; ν_{max} 3500, 1720, 1612, and 1255 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.44): C, 73.22; H, 8.19. Found: C, 73.03; H, 8.40.

17β-Acetoxy-3-methoxyestra-1,3,5(10)-trien-15-one (7).—To a freshly prepared solution of chromium trioxide (0.345 g.) in pyridine (5 ml.) cooled to 0° was added **6c** (0.380 g.) in pyridine (10 ml.). The resulting mixture was stirred for 20 hr. at room temperature, diluted with chloroform, and filtered. The residue was washed twice with chloroform and the combined filtrates were evaporated to give an oil. The latter was triturated with water to give 0.200 g., m.p. 150–157°. Four crystallizations from acetone–petroleum ether gave the analytical sample, m.p. 156–158°; λ_{max} 222, 278, and 288 mμ (ε 10,300, 2500, and 2400); $[\alpha]_D$ +82°; ν_{max} 1740, 1612, and 1240 cm.$^{-1}$; O.R.D. in methanol (*c* 0.034, 600–300; *c* 0.017, 320–290; *c* 0.0068, 300–265 mμ), $[\alpha]_{600}$ +47°, $[\alpha]_{313}$ +1675°, $[\alpha]_{291}$ 0°, $[\alpha]_{281}$ −528°, $[\alpha]_{265}$ −176.5°.

Anal. Calcd. for $C_{21}H_{26}O_4$ (342.42): C, 73.66; H, 7.66. Found: C, 72.99, 73.10; H, 7.74, 7.75.

3-Methoxyestra-1,3,5(10)-triene-15β,17β-diol (6a). Method A. Reduction of 15β-Hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (4d).—To a solution of **4d** (0.195 g.) in tetrahydrofuran (50 ml.) was added a filtered solution of lithium aluminum hydride (0.300 g.) in tetrahydrofuran (20 ml.), and the resulting mixture was stirred at room temperature for 3 hr. The excess reagent was decomposed with water and the mixture was filtered. The filtrate was evaporated and the residue was crystallized from methanol to give 0.156 g., m.p. 184–186°. Recrystallization did not alter the melting point. The product showed λ_{max} 220, 278, and 288 mμ (ε 8800, 2300, and 2100); $[\alpha]_D$ +31°; ν_{max} 3440 and 1612 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{26}O_3$ (302.40): C, 75.46; H, 8.67. Found: C, 75.75; H, 8.80.

Method B. Reduction of 17β-Acetoxy-3-methoxyestra-1,3,5(10)-trien-15-one (7).—A solution containing **7** (0.100 g.) and lithium aluminum hydride (0.150 g.) in tetrahydrofuran (50 ml.) was allowed to stand at room temperature for 18 hr. The reaction mixture was worked up as described previously to give 0.080 g., m.p. 182–184°. The product was recrystallized from methanol and had m.p. 183–185°, $[\alpha]_D$ +34°. Its infrared spectrum was identical to that of the product described in method A and showed no depression in an admixture melting point determination.

15β-Hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (4d).—To a solution of 15β-benzyloxy-3-methoxy-estra-1,3,5(10)-trien-17-one (**4d**, 0.162 g.) in acetic acid (4 ml.) was added 10% palladium–charcoal catalyst (0.100 g.). The resulting mixture was hydrogenated at 28° and 729-mm. pressure for 4 hr. The catalyst was separated by filtration and was washed with methanol. The combined filtrates were evaporated, and the residue obtained was crystallized from acetone–ether to give 0.063 g. of **16**, m.p. 186–188°. A sample for analysis was recrystallized from acetone–petroleum ether and had m.p. 186–188°; λ_{max} 220, 278, and 288 mμ (ε 9000, 2180 and 2000); $[\alpha]_D$ +103°; ν_{max} 3500, 1730, and 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{24}O_3$ (300.38): C, 75.97; H, 8.05. Found: C, 75.06, 75.22; H, 8.25, 7.98.

15β-Cyano-3-methoxyestra-1,3,5(10)-trien-17-one (4e).—To a solution containing **1** (0.200 g.) and water (5 drops) in tetrahydrofuran (7 ml.) was added sodium cyanide (0.500 g.). The mixture was refluxed for 2.5 hr., poured into ice–water, and the resulting precipitate was collected, washed with water, and dried to give 0.200 g. of **4e**, m.p. 131–135°. A sample for analysis was recrystallized three times from ether and had m.p. 154–155°; λ_{max} 222, 278, and 288 mμ (ε 8500, 2000 and 1850); $[\alpha]_D$ +30°; ν_{max} 2240, 1744, and 1615 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{23}O_2N$ (309.39): C, 77.64; H, 7.49; N, 4.53. Found: C, 77.62; H, 7.62; N, 4.62.

17β-Acetoxy-3,15β-dimethoxyestra-1,3,5(10)-triene (6d).—To a solution of 3,15β-dimethoxy-estra-1,3,5(10)-trien-17-one (**4b**, 0.500 g.) in tetrahydrofuran (75 ml.) was added lithium aluminum hydride (0.5 g.) and the mixture was refluxed for 2 hr. The mixture was cooled and the excess reagent was decomposed by the dropwise addition of aqueous tetrahydrofuran. The salts were separated, washed with tetrahydrofuran, and the combined filtrates were evaporated to an oil which failed to crystallize. An infrared spectrum (neat) of the latter was devoid of any carbonyl absorption. Acetylation of the crude reduction product with acetic anhydride (1 ml.) and pyridine (1 ml.) for 1 hr. at 90° gave 0.43 g. of an oil which was shown to be homogeneous by thin layer chromatography. The oil was crystallized from ether–petroleum ether (b.p. 30–60°) and had m.p. 102–104°, $[\alpha]_D$ +10°.

Anal. Calcd. for $C_{22}H_{30}O_4$ (358.46): C, 73.71; H, 8.44. Found: C, 73.20, 73.21; H, 8.64, 8.38.

15β-Cyano-3-methoxyestra-1,3,5(10)-trien-17β-ol (6e).—A solution of 15β-cyano-3-methoxyestra-1,3,5(10)-trien-17-one (**4e**, 2.0 g.) and sodium borohydride (1.8 g.) in tetrahydrofuran–methanol (1:5, 180 ml.) was stirred for 3 hr. at room temperature. The solvents were evaporated, the residue was dissolved in benzene, and the extract washed with saturated saline, dried, and evaporated. One crystallization of the residue from benzene afforded 1.8 g. of **6e**, m.p. 193–195°, $[\alpha]_D$ −28°.

(16) Celite 545 is a trade-mark of the Johns-Manville Corp. for a grade of diatomaceous earth. That used for partition chromatography was washed with 6 *N* hydrochloric acid, water, and methanol, and was dried to constant weight.

(17) Florisil, a trade-mark of the Floridin Company for a synthetic magnesium silicate.

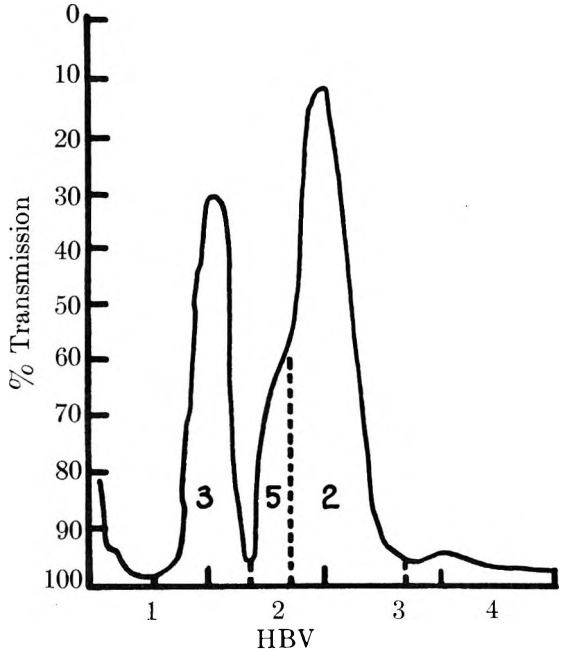


Figure 2

Anal. Calcd. for $C_{20}H_{25}O_2N$ (311.41): C, 77.13; H, 8.09; N, 4.50. Found: C, 76.78; H, 8.10; N, 4.44.

3-Methoxy-15α-carboxamido-estra-1,3,5(10)-trien-17β-ol (8a).—To a solution of benzene-solvated 15β-cyano-3-methoxyestra-1,3,5(10)-trien-17β-ol(6e, 0.800 g.) in ethanol (35 ml.) was added potassium hydroxide (2.5 g.) in water (7 ml.) and the solution was heated to reflux for 6 hr. A thin layer chromatographic analysis of the reaction mixture revealed that no hydrolysis had taken place. The ethanol was displaced with 1-propanol and the resulting solution was heated to reflux overnight. The reaction mixture was diluted with ethyl acetate, washed with dilute hydrochloric acid solution and with water, dried, and evaporated to 0.800 g. of a semicrystalline solid which was crystallized once from acetone–water and twice from acetone–petroleum ether to give 0.240 g., m.p. 208–210°, $[\alpha]_D$ +109° (methanol).

Anal. Calcd. for $C_{20}H_{27}O_3N$(329.42): C, 72.92; H, 8.26; N, 4.25. Found: C, 72.43, 72.40; H, 8.41, 8.18; N, 4.40.

A second crop, 0.170 g., m.p. 206–208°, was obtained from the mother liquors.

17β-Hydroxy-3-methoxyestra-1,3,5(10)-trien-15α-carboxylic acid (8b).—To a solution of 15β-cyano-3-methoxyestra-1,3,5(10)-trien-17β-ol(6e, 0.900 g.) in 40 ml. of ethylene glycol was added a solution of 3.0 g. of potassium hydroxide in 7 ml. of water. The resulting solution was refluxed for 22 hr., cooled, and acidified with dilute hydrochloric acid solution. The product was collected by filtration, washed with water, and dried to give 0.460 g., m.p. 181–184°. A sample for analysis was crystallized twice from methanol–water and twice from acetone and had m.p. 238–240°, $[\alpha]_D$ +130° (methanol).

Anal. Calcd. for $C_{20}H_{26}O_4$ (330.41): C, 72.70; H, 7.93. Found: C, 72.62; H, 8.15.

Attempted Addition of Methanol to 3-Methoxy-14β-estra-1,3,5(10),15-tetraen-17-one (2).[18]—To a solution of 2 (0.300 g.) in methanol (14 ml.) was added a 5% sodium hydroxide solution (0.7 ml.). The resulting solution was stirred 30 min. at room temperature, diluted with water, and the products were extracted with ethyl acetate. The extract was dried and evaporated to give 0.270 g. of an oil.

A pilot partition column on Celite 545[16] using an *n*-heptane–Methyl Cellosolve solvent system indicated the reaction mixture to contain 28.5% of **3**, 56.5% of **2**, and 15% of an unknown **5** occurring as a shoulder at HBV 1.5–1.8 on the peak corresponding to **2** (Fig. 2) A similar column run on a mixture obtained from a second run which was stirred for 24 hr. indicated the exact composition previously described. The remaining crude products of the two runs were combined (0.570 g.) and partitioned as described previously to give 0.100 g. of **3** and 0.235 g. of **2** (these compounds were identical by comparison of their thin layer chromatograms and their infrared spectra with the specimens described in ref. 18). In a larger run (0.900 g.) that peak corresponding to **5** was repartitioned twice using the same solvent system to give 0.060 g. of impure **5**. The latter was crystallized from methanol to give 0.028 g., m.p. 82–85°; the thin layer chromatogram indicated it to contain *ca.* 10% of **2**. The infrared spectrum of the crystallized sample showed only a 5-membered ring carbonyl maximum at 1725 cm.$^{-1}$ and its n.m.r. spectrum showed two O-methyl maxima at 6.16 (C-3) and 6.63 τ (C-15).

(18) 3-Methoxyestra-1,3,5(10),15-tetraen-17-one (**1**) was isomerized with *p*-toluenesulfonic acid for 15 min. in refluxing benzene according to the procedure of Johnson and Johns.[1] The resulting mixture was partitioned on Celite 545[16] using an *n*-heptane–Methyl Cellosolve solvent system. Holdback volumes 0.5–1.5 gave 3-methoxyestra-1,3,5(10),14-tetraen-17-one (**3**), m.p. 93–94°, $[\alpha]_D$ +293°. A HBV of 1.5–2.2 gave 3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one (**2**), m.p. 102–103°, $[\alpha]_D$ +477°.

Photodimerization of $\Delta^{4,6}$-Diene-3-keto Steroids

MORDECAI B. RUBIN, GEORGE E. HIPPS, AND DONALD GLOVER

Department of Chemistry, Carnegie Institute of Technology, Pittsburgh 13, Pennsylvania

Received August 8, 1963

Photoirradiation of heteroannular dienones such as $\Delta^{4,6}$-androstadien-3-on-17β-ol propionate and related steroids in homogeneous solution leads to formation of a single one of twenty possible dimeric products. This has been assigned the structure IIA or IID on the basis of physical properties and catalytic hydrogenation followed by thermal cleavage and identification of cleavage products. The dimerization can be reversed photochemically; the photostationary state has the composition 31% monomer and 69% dimer.

Although the photochemical reactions of conjugated and cross-conjugated dienones have been of considerable interest in recent years,[1] attention has been concentrated on homoannular systems where molecular rearrangement, valence-bond tautomerization, and ring cleavage are the predominant reaction paths. This paper describes the results obtained on reaction of a heteroannular dienone system where the more familiar photodimerization reaction of conjugated carbonyl compounds[2] is observed, albeit in an unexpected manner.[3]

Solutions of $\Delta^{4,6}$-androstadien-3-on-17β-ol propionate[4] (IA) in benzene–petroleum ether or benzene–

(1) For leading references see J. J. Hurst and G. H. Whitham, *J. Chem. Soc.*, 710 (1963); C. Ganter, E. C. Utzinger, K. Schaffner, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **45**, 2403 (1962); D. H. R. Barton, *ibid.*, **42**, 2604 (1959); P. de Mayo, "Advances in Organic Chemistry," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1960, pp. 367–425.

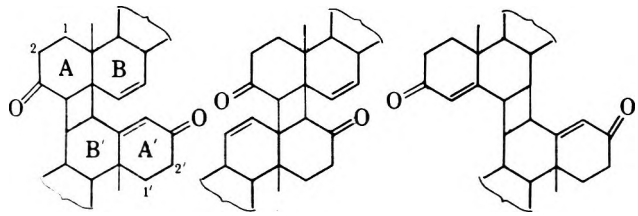
(2) A. Mustafa, *Chem. Rev.*, **51**, 1 (1952).

(3) After this work was completed, a report appeared [H. C. Throndsen, G. Cainelli, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **45**, 2342 (1962)] describing the determination of structure of the photodimer of $\Delta^{4,6}$-cholestadien-3-one. Our results confirm, by different methods, and extend the conclusions reached in this report.

(4) L. Ruzicka and W. Bosshard, *ibid.*, **20**, 328 (1937). The more convenient chloranil dehydrogenation procedure of E. J. Agnello and G. O. Laubach [*J. Am. Chem. Soc.*, **82**, 4293 (1960)] was used in this work.

dioxane remained homogeneous on exposure to light of wave length longer than 3000 Å. although occurrence of reaction was indicated by marked decrease in ultraviolet absorption. Chromatography of the reaction product on Florisil led to isolation of recovered starting material (64%) and a new crystalline compound (II), 34%, m.p. 168–169°, which regenerated IA quantitatively on heating for five minutes above its melting point. The dimeric nature of II was indicated by its molecular weight and the presence in its infrared spectrum of the original carbonyl bands of IA at 5.75 and 6.0 plus an additional band at 5.90 μ. In view of these facts and the well known tendency of conjugated carbonyl compounds to undergo photodimerization to derivatives of cyclobutane,[2] it seemed likely that II was a dimer of the cyclobutane type formed by interaction of one of the two double bonds of each monomer unit.

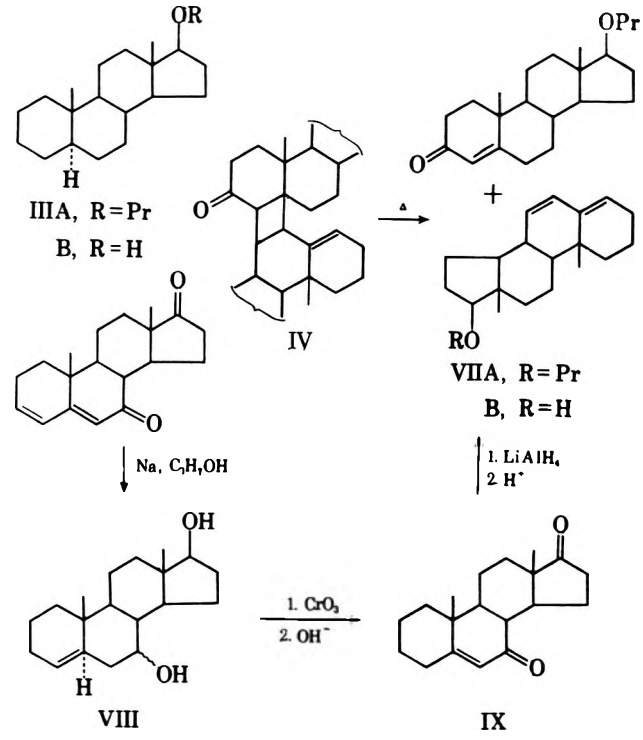
Neglecting finer details of stereochemistry at this point, the three structures IIA, B, C, and their head-to-head isomers need to be considered. Of these, only



IIA IIB IIC

IIA is in agreement with the infrared spectral data since it is the only one possessing both conjugated and unconjugated carbonyl[5] groups (as well as the side-chain ester group). The apparently anomalous ultraviolet absorption of II [254 mμ (ϵ 10,500)], representing a shift of 12 mμ from the usual position of the maximum in Δ^4-3-keto steroids, is explicable on the basis of the auxochromic effect of the cyclobutane ring[6] in IIA and also might be consistent with IIC but not with IIB. Further evidence in favor of IIA was provided by the n.m.r. spectrum of the dimer which showed three protons in the olefinic hydrogen region of the spectrum as singlets at 4.20 (1H) and 4.40 τ (2H),[7] consistent only with structure IIA or its head-to-head isomer.

Proof of the correctness of this structural assignment was provided by the results of catalytic hydrogenation of II and thermal cleavage of the reduction products. Barring the possibility of double bond isomerization during thermal cleavage, the positions of double bonds in the cleavage products should fix the points of attachment of the cyclobutane ring and allow an unequivocal choice between IIA, B, and C. Hydrogenation of II over pre-reduced platinum oxide in propionic acid[8] resulted in variable uptake of hydrogen which was explicable in terms of formation of varying proportions of a mixture of hexadecahydro (IIIA), hexahydro (IV), and tetrahydro (V) products, separable by chromatography on Florisil. In a typical run, 4.0 moles of hydrogen were absorbed per mole of IIA leading to 19% of IIIA, 61% of IV, and 10% of V.



The hexadecahydro product (IIIA) exhibited characteristic ester absorption at 5.79 and 8.39 μ and no absorption in the ultraviolet. It was identified as 5α-androstan-17β-ol propionate, the product of cyclobutane hydrogenolysis, by base-catalyzed hydrolysis to a solid, m.p. 138–152°, showing only hydroxyl absorption at 2.98 μ. Purification of this solid yielded 68% of 5α-androstan-17β-ol, m.p. 164–166° (IIIB), identical with an authentic sample.[9] None of the 5β isomer could be detected.

The hexahydro product (IV), m.p. 274–275°, contained only an unconjugated carbonyl group adjacent to a cyclobutane ring as shown by the maximum at 5.91 μ and the presence of only end absorption in the ultraviolet, 210 mμ (ϵ 8600). These observations plus the presence of a singlet at 4.37 τ (1H) in the n.m.r. suggested the structure shown. Confirmation was provided by the results of thermal cleavage of IV. Chromatography of the crude product obtained by heating IV for three hours at 270–280° in a sealed tube yielded, in addition to 33% of recovered starting material, 52% of testosterone propionate and 62% of a crystalline solid with ultraviolet absorption (230, 237, 246 mμ) characteristic of a heteroannular diene.[10] The spectrum did not allow a distinction between the two possible dienes, $\Delta^{3,5}$-androstadien-17β-ol propionate (VI) and $\Delta^{4,6}$-androstadien-17β-ol propionate (VIIA). However, the cleavage product was not identical with the 3,5-diene (VI) prepared by propionylation of the corresponding free alcohol[11] and was posi-

(5) The slight shift of the unconjugated carbonyl absorption to 5.90 μ has been observed in other cases where a cyclobutane ring is "conjugated" with a ketone; *cf.* A. Butenandt, L. Poschmann, G. Failer, U. Schiedt, and E. Biekert, *Ann.*, **575**, 123 (1951).

(6) J. J. Wren, *J. Chem. Soc.*, 2208 (1956); *cf.*, *inter alia*, G. Büchi and I. M. Goldman, *J. Am. Chem. Soc.*, **79**, 4741 (1957); P. D. Gardner, R. L. Brandon, and G. R. Haynes, *ibid.*, **79**, 6334 (1957).

(7) The poorly resolved triplet centered at 5.45 τ (due to the two C-17 protons) provided a convenient reference for determining the number of protons represented by each line in the spectrum in this and other cases.

(8) Milder reduction conditions afforded only small amounts of IIIA and recovered starting material.

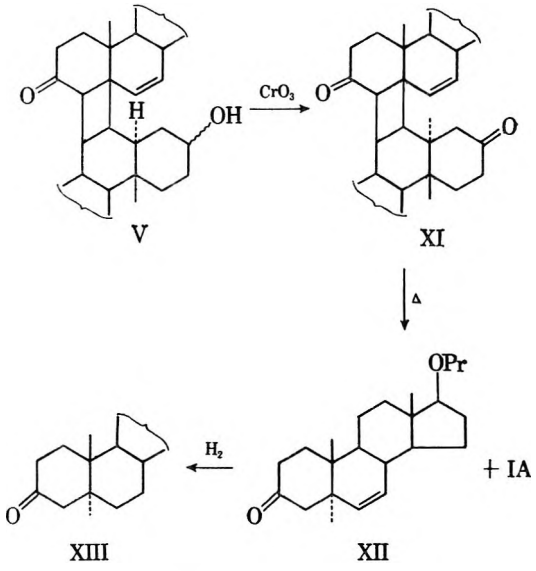
(9) C. W. Shoppee, D. G. Lewis, and J. Elks, *Chem. Ind.* (London), 454 (1950). The 5β isomer is reported to melt at 96°; F. Galinovsky, E. Kerschbaum, and H. Janisch, *Monatsh.*, **84**, 193 (1953).

(10) L. Dorfman, *Chem. Rev.*, **53**, 47 (1953).

(11) G. Rosenkranz, St. Kaufmann, and J. Romo, *J. Am. Chem. Soc.*, **71**, 3689 (1949).

tively identified as the 4,6-diene (VIIA) by comparison with a sample obtained by the following synthesis modeled on the procedure used by Eck and Hollingsworth[12] for the preparation of $\Delta^{4,6}$-cholestadiene. Reduction of $\Delta^{3,5}$-androstadiene-7,17-dione[13] with sodium in propanol afforded the homoallylic diol (VIII) as a mixture of epimers which was oxidized with chromium trioxide in acetone[14] and treated with base to give Δ^{5}-androstene-7,17-dione (IX, 5.75 and 6.01 μ). Reduction of IX with lithium aluminum hydride yielded the allylic alcohol (X) as a mixture of epimers. Acid-catalyzed dehydration of X proceeded readily to give 94% of $\Delta^{4,6}$-androstadien-17β-ol (VIIB) which was propionylated to VIIA with propionic anhydride in pyridine. Both VI and VIIA were shown to be stable under the conditions of the thermal cleavage reaction and subsequent chromatographic purification.

The tetrahydro product (V) obtained in the catalytic hydrogenation also contained no conjugation as evidenced by the presence of only end absorption in the ultraviolet, 210 mμ (ϵ 2400). In addition to an unconjugated carbonyl group adjacent to a cyclobutane ring (5.92 μ), the presence of a hydroxyl group (2.74 μ) and of two olefinic hydrogens (doublets at 3.99 and 4.45 τ, J_{AB} = 12 c.p.s.) was indicated. Thermal cleavage of V followed by chromatography did not lead to crystalline products. On the basis of spectral analysis of individual fractions, the presence of IA, a hetero-

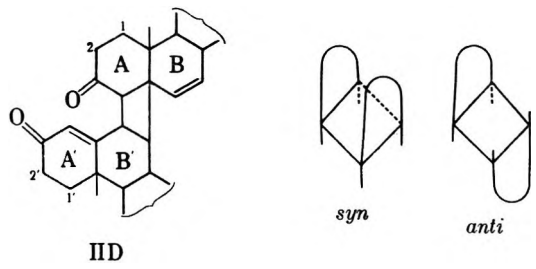


annular diene (or mlxture of dienes), and recovered V was suggested. Since the difficulties encountered might have been due to dehydration of the alcohol function at the high temperature of the thermal cleavage, V was oxidized (in nearly quanitative yield) to the diketone XI which again showed no evidence for conjugation, 5.9 μ, 210 mμ (ϵ 2700). The olefinic hydrogens in XI also appeared as a pair of doublets at 4.05 and 4.52 τ (J_{AB} = 11 c.p.s.).

Cleavage of XI by heating at 270–280° for three hours proceeded satisfactorily. Chromatography of the crude product afforded 39% of recovered XI, 53% of IA, and 47% of 5α-Δ^{6}-androsten-3-on-17β-ol propionate (XII). The latter compound was characterized by the absence of ultraviolet absorption, infrared maxima at 5.77 (propionate) and 5.84 μ, and presence of a partially resolved multiplet centered at 4.64 τ (2H) in the n.m.r. Catalytic hydrogenation to known 5α-androstan-3-on-17β-ol propionate[15] (XIII) confirmed the structure assignment.

The spectral properties of the hydrogenation products IV, V, and XI and the identification of their thermal cleavage products are consistent only with assignment of structure IIA to the photodimer. The formation of IV and V apparently represents a competition between reduction of the conjugated carbonyl group at C-3′ and of the double bond ($\Delta^{4'}$) adjacent to it.[16] When reduction of the carbonyl group occurs first, the resultant allylic alcohol can undergo hydrogenolysis ultimately leading to IV (the major product). The results suggest that the $\Delta^{4'}$-double bond is subject to considerably more steric hindrance than the adjacent carbonyl group. A similar observation has been made by Ushakov and Kosheleva[17] and confirmed by Jeger, *et al.*,[3] who noted that hydrogenation of the photodimer (XVI) of $\Delta^{4,6}$-cholestadien-3-one led to a tetrahydro product in which complete reduction of the C-4′ ketone to methylene occurred without hydrogenation of either of the two olefinic bonds present.

The exclusion of IIB and IIC leaves eight possible structures to be considered for the photodimer assuming that the cyclohexane-to-cyclobutane ring fusions are *cis*.[18,19] Both the head-to-tail (IIA) and head-to-head structures (IID) might possess either *cis*- or *trans*-



IID

A/B ring fusions and, in addition, the relationship of the two steroid halves might be either *syn* or *anti* (as illustrated) about the cyclobutane ring allowing a total of four head-to-tail and four head-to-head possibilities.

These eight possibilities can be reduced to four on the basis of the catalytic hydrogenation of IIA to V which must, on the basis of its thermal cleavage to 5α-andro-

(12) J. C. Eck and E. W. Hollingsworth, *J. Am. Chem. Soc.*, **63**, 107 (1941).

(13) J. R. Billeter and K. Miescher, *Helv. Chim. Acta*, **31**, 629 (1948).

(14) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(15) K. Miescher, H. Kagi, C. Scholz, A. Wettstein, and E. Tschopp, *Biochem. Z.*, **294**, 39 (1937).

(16) We have adopted the following notation for indicating position and stereochemistry in these dimers. The dimer, written with the upper half containing the ring A ketone "conjugated" with cyclobutane ring (this choice was made to conform with the structures presented by Jeger, *et al.*[3]), is considered to be composed of two independent steroid halves. For the upper half, positions and stereochemistry are designated in the usual manner; for the lower half, positions are designated as C-1′, C-2′, etc., and stereochemistry (α' or β') is related to the C-10′ methyl group of that half.

(17) M. I. Ushakov and N. F. Kosheleva, *J. Gen. Chem. USSR*, **14**, 1138 (1944); *Chem. Abstr.*, **40**, 4071 (1946).

(18) Preliminary reports have appeared describing the formation of the *trans*-bicyclo[4.2.0]octane system as minor product of the photoaddition of maleic anhydride to cyclohexene: P. de Mayo, R. W. Yip, and S. T. Reid, *Proc. Chem. Soc.*, 54 (1963); J. A. Barltrop and R. Robson, *Tetrahedron Letters*, 597 (1963).

(19) The photodimerization of dimethyl 3-keto-1,4-pentadiene-1,5-dicarboxylate has also been reported to lead to product in which *trans* fusion of cyclobutane and cyclohexane rings occurs: J. Corse, B. J. Finkle, and R. E. Lundin, *ibid.*, **No. 1**, 1 (1961).

stan-3-on-17β-ol propionate, possesses the 5′α′ configuration. From examination of models it seems extremely unlikely that hydrogenation from the α side of the lower steroid half of the dimer could occur if the cyclobutane ring were attached at the 6′α′,7′α′-positions since the upper half of the dimer would provide considerable hindrance to reaction at the 5′α′-position. The fact that 5α-androstan-17β-ol propionate (IIIA) also is formed in the catalytic hydrogenation to the exclusion of the 5β isomer is not necessarily significant since it is not clear at what stage in the reduction insertion of the 5α-hydrogen occurs.[20]

We have observed slow reversal of II to $\Delta^{4,6}$-androstadien-3-on-17β-ol (IC)[21] under mild acidic conditions as had been reported by Jeger, *et al.*,[3] for the dimer of $\Delta^{4,6}$-cholestadien-3-one. These authors suggested that this result supports the head-to-tail structure for the dimer. This interpretation appears to us to be based on the assumption of an initial protonation of either carbonyl group of the dimer followed by a stepwise fragmentation involving a series of carbonium ions. Such a mechanism applied to the head-to-head isomer would require a carbonium ion adjacent (or vinylogously adjacent) to a carbonyl group which would not be the case for the head-to-tail isomer where only isolated or allylic carbonium ions would be required. Unfortunately, the absence of detailed information on the mechanism of the acid-catalyzed cleavage and the lack of a standard (such as a second isomer) with which to compare the rate of cleavage make such an inference of limited value. Complete details of the structure of these photodimers await further investigation.

As has been noted, the nature of absorption in the olefinic hydrogen region of n.m.r. spectra has been of considerable value in elucidation of the structures of II and its degradation products. The usual broad envelope with occasional protruding sharp lines characteristic of the aliphatic hydrogen region of steroids[22] also was observed. All of the compounds which bore a 17-propionate exhibited a quartet centered at about 7.66 τ (J = 8 c.p.s.) due to the methylene protons adjacent to the ester carbonyl and a triplet centered at 8.86 τ (J = 8 c.p.s.) due to the propionate methyl group. In addition, the following lines due to angular methyl groups were observed: monomer (IA), 8.85 (C-19 protons) and 9.10 (C-18); dimer (II), 8.70, 9.15, 9.19, 9.25; hexahydro product (IV), 8.78, 9.20 (this line was approximately twice as intense as the lower field line); tetrahydro product (V), 8.93, 9.16 (broad), 9.31; XI, 8.74, 8.98, 9.15, 9.22, 9.32 τ. This apparently capricious pattern of absorption is presumably due to the operation of long-range shielding effects and might provide some clues to the detailed structure of the dimer.

Irradiation performed under conditions similar to those used with IA led to conversion of $\Delta^{4,6}$-androstadien-3-one (IB) to dimer XIV, $\Delta^{4,6}$-androstadien-3-on-17β-ol (IC) to XV, and $\Delta^{4,6}$-cholestadien-3-one (ID) to XVI (solutions remained homogeneous throughout irradiation). These dimers were all assigned partial structure IIA (or IID), differing only in substitution at C-17, on the basis of their spectral properties (see Experimental). In the case of XV the structure was confirmed by esterification with propionic anhydride and pyridine at room temperature to give material identical with the dimer of IA. The identical dimer (XVI) was obtained from ID by irradiation of petroleum ether solutions where the product crystallized during the course of the reaction or by irradiation of benzene–dioxane solutions which remained homogeneous through out the course of the reaction. In the latter case XVI was isolated by chromatography on Florisil. The physical properties of XVI were in good agreement with those reported by Jeger, *et al.*, for the dimer formed by irradiation of ethanol solutions of ID where the product crystallized during the course of the reaction.

Probably the most striking aspect of these dimerizations is the complete specificity observed. As noted previously, four isomers of IIA and four of IID are possible; consideration of the number of isomers which could result from dimerizations involving two α,β double bonds or two γ,δ double bonds leads to a total of twenty possible dimers from irradiation of IA. However, 98% of the original material was recovered either as unchanged starting material or as the single homogeneous product. Careful examination of individual fractions from column chromatography by infrared spectral comparison and thin layer chromatography did not indicate the presence of any other reaction product, nor did protracted irradiation result in any detectable by-products. In contrast, the dimerization of cyclopentenone in homogeneous solution[23] results in the formation of approximately equal amounts of *anti* head-to-head and *anti* head-to-tail dimers, two of the four possible products. The specificity of these steroid dimerizations is particularly remarkable since it was demonstrated that the dimerizations can be reversed photochemically. The composition of the photostationary state resulting from irradiation of IA or II in benzene–dioxane solution was 31% monomer and 69% dimer at 27–28°. Examination of molecular models provides no clue to preference for a single one of twenty possible products in a reversible reaction taking place in homogeneous solution. In fact, the products which involve the least steric hindrance are those formed by interaction of two α,β double bonds (IIB) and possessing the head-to-tail, *anti* configuration. Such isomers also might be predicted to accumulate upon irradiation, since they would have extremely weak light absorption at wave lengths above 3000 Å. Work in progress is concerned with the factors determining product structure in dimerizations of this type.

Experimental[24]

Photoirradiation of $\Delta^{4,6}$-Androstadien-3-on-17β-ol Propionate (IA). A. In Homogeneous Solution.—A solution of 7.25 g. of compound IA[4] [m.p. 135–136°, λ_{max} 284 mμ (ϵ 27,500)] in 35 ml. of 1:1 benzene–petroleum ether was irradiated for 7 hr.

(20) Treatment of II with reduced platinum oxide in propionic acid resulted in recovery of unchanged starting material.

(21) Hydrolysis of the ester group occurred under the conditions of the cleavage.

(22) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958); G. Slomp and B. R. McGarvey, *ibid.*, **81**, 2200 (1959); J. S. G. Cox, E. O. Bishop, and R. E. Richards, *J. Chem. Soc.*, 5118 (1960).

(23) P. E. Eaton, *J. Am. Chem. Soc.*, **84**, 2344, 2454 (1962).

(24) Photoirradiations were performed in nitrogen atmosphere in Pyrex vessels using a Pyrex-jacketed, water-cooled, 1000-w. General Electric high-pressure mercury lamp (AH-6). Melting points are corrected. The solvent for optical rotations was chloroform (1% solutions) and for ultraviolet measurements was 95% alcohol. Molecular weights were determined in benzene solution with a Mechrolab osmometer. N.m.r. spectra were determined at 60 Mc. with a Varian Associates HR-60 spectrometer using tetramethysilane as internal standard in deuteriochloroform solution.

and the clear solution then adsorbed on 350 g. of Florisil. Elution with five 1-l. portions of 7% ethyl acetate–benzene gave 4.65 g. (64%) of IA, m.p. 131–136° (infrared spectra of all fractions were identical with authentic IA; thin layer chromatograms[25] of all fractions showed the presence of only a single component, identical in R_f value with IA). The combined fractions after recrystallization from methylene chloride–petroleum ether gave 4.42 g. of white crystals, m.p. 135–136°.

Further elution with five 1-l. portions of 30% ethyl acetate–benzene and two of 50% ethyl acetate–benzene gave a total of 2.45 g. (34%) of photodimer II, m.p. 166–168° (infrared spectra of all fractions were identical; examination of thin layer chromatograms under ultraviolet light and by treatment with concentrated sulfuric acid revealed the presence of only a single component identical in R_f value with pure II). One crystallization of the combined fractions from methylene chloride–petroleum ether gave 1.52 g., m.p. 168–169°. A portion, recrystallized from the same solvent mixture, yielded the analytical sample, m.p.[26] 167–168°, 256 mμ (ε 10,800); λ_{max}^{KBr} 5.71, 5.86, 5.98, 6.21, 8.40 μ; $\lambda_{max}^{CHCl_3}$ 5.78, 5.90, 5.99, 6.24, 8.39 μ; $[\alpha]^{26}D$ +16 ± 2°.

Anal. Calcd. for $C_{44}H_{60}O_6$: C, 77.15; H, 8.83; mol. wt., 685. Found: C, 77.39; H, 8.78; mol. wt., 689.

B. In the Solid State.—A thin layer of 549 mg. of IA between two glass plates was irradiated on alternate sides for a total of 43 hr. The product after irradiation had λ_{max} 285 mμ (ε 26,200). Examination of the thin layer chromatogram indicated only a single component identical in R_f value with starting material.

Thermal Cleavage of Photodimer II.—Heating 18 mg. of II at 175° in a sealed, evacuated capillary for 5 min. produced a light yellow oil identical in infrared spectrum with IA, λ_{max} 283 mμ (ε 25,200).

Catalytic Hydrogenation of Photodimer II.—A solution of 3.145 g. (4.6 mmoles) of II in 50 ml. of anhydrous propionic acid was added to 315 mg. of pre-reduced platinum oxide in 50 ml. of anhydrous propionic acid at 32° (741 mm.). After 7 hr., 473 ml. (4.0 equiv.) of hydrogen had been absorbed. The catalyst was filtered, washed with ethyl acetate, and the combined solutions evaporated to dryness under reduced pressure on the steam bath. The resulting oil was chromatographed on 177 g. of Florisil.

Elution of 1 l. of benzene gave 595 mg. (19%) of oil which was crystallized from methanol to give 444 mg. of 5α-androstan-17β-ol propionate (IIIA), m.p. 54–56°; λ_{max} (CH_2Cl_2) 5.79, 8.39, no absorption 2.5–3.1 μ.

Elution with four 1-l. portions of 3% ethyl acetate–benzene gave 1.886 g. (61%) of the hexahydro product (IV). The analytical sample was obtained by crystallization from methanol, m.p. (sealed, evacuated capillary) 274–275°; end absorption, 210 mμ (ε 8700); λ_{max}^{KBr} 5.77, 5.91, 8.42 μ; $[\alpha]^{28}D$ +38 ± 2°.

Anal. Calcd. for $C_{44}H_{64}O_5$: C, 78.53; H, 9.59; mol. wt., 677. Found: C, 78.52; H, 9.62; mol. wt., 673.

Further elution with two 1-l. portions of 20% and three of 30% ethyl acetate–benzene yielded 331 mg. (10%) of tetrahydro product (V). The analytical sample was obtained by crystallization from methylene chloride–petroleum ether, m.p. (sealed, evacuated capillary) 276–278°; end absorption, 210 mμ (ε 2400); $\lambda_{max}^{CH_2Cl_2}$ 2.74, 5.78, 5.92, 8.39 μ; $[\alpha]^{27}D$ +62 ± 2°.

Anal. Calcd. for $C_{44}H_{64}O_6$: C, 76.70; H, 9.36; mol. wt., 689. Found: C, 76.44; H, 9.48; mol. wt., 704.

Hydrolysis of 5α-Androstan-17β-ol Propionate (IIIA).—A solution of 200 mg. of IIIA in 10 ml. of methanol containing 0.8 ml. of 10% aqueous potassium hydroxide was allowed to stand overnight at room temperature. After neutralization with acetic acid, the solution was concentrated on the steam bath under reduced pressure. The residue was taken up in ethyl acetate which was washed with water, dried over anhydrous sodium sulfate, and concentrated to give 167 mg. (100%) of white solid, m.p. 138–152°. Recrystallization from methanol gave 85 mg. (51%) of 5α-androstan-17β-ol (IIIB), m.p. 164–166°; lit.[9] m.p. 164°; λ_{max}^{KBr} 2.98, no absorption at 5.5–6.5 μ. The residue was a light yellow solid, m.p. 95–108° (lit.[9] m.p. 96° for 5β-androstan-17β-ol). An additional 28 mg. (17%) of IIIB was obtained by chromatography of the residue on Florisil.

Thermal Cleavage of Hexahydro Product IV.—Heating 380 mg. of IV at 270–280° in a sealed, evacuated tube for 3.5 hr. gave a light yellow oily product, λ_{max} 238 mμ (ε 12,000). This was dissolved in benzene and chromatographed on 19 g. of Florisil collecting 200-ml. fractions.

Elution with 50% benzene–petroleum ether gave 117 mg. (31%) of $\Delta^{4,6}$-androstadien-17β-ol propionate (VIIA), m.p. 99–102°, which was recrystallized from methanol to yield 96 mg., m.p. 103–104°, identical with the synthetic sample described subsequently.

Elution with 1, 2, 3, and 4% ethyl acetate–benzene gave a mixture which was rechromatographed on 12 g. of Florisil (100-ml. fractions). Six fractions of 0.5% ethyl acetate–benzene gave 127 mg. (33%) of solid, identical by infrared analysis with IV.

Further elution with two portions of 1% and four of 2% ethyl acetate–benzene gave a total of 101 mg. (26%) of solid identical by infrared with testosterone propionate. Crystallization from methanol afforded white crystals, m.p. 120–122°, undepressed on mixture with authentic material.

$\Delta^{3,5}$-Androstadien-17β-ol Propionate (VI).—$\Delta^{3,5}$-Androstadien-17β-ol was prepared by the procedure of Rosenkranz, *et al.*,[11] m.p. 155–157°; λ_{max} 228 mμ (ε 19,000), 234 (20,400), 243 (12,900). A solution of 600 mg. of this alcohol in 3 ml. of propionic anhydride and 6 ml. of pyridine was allowed to stand overnight in the dark at room temperature. The light yellow solution was taken to dryness on a rotary evaporator to give 526 mg. (73%) of solid, m.p. 134–140°. Several crystallizations from petroleum ether gave white crystals, m.p. 135–138°. When 282 mg. of the product was washed through 15 g. of Florisil with 50% petroleum ether–benzene, there was obtained 268 mg. of white solid, m.p. 136–138°. The infrared spectra in methylene chloride were identical before and after chromatography. One crystallization of the chromatographed material from petroleum ether gave the analytical sample, m.p. 138–139°; λ_{max} 228 mμ (ε 21,300), 234 (23,000), 243 (14,500); λ_{max}^{KBr} 5.78, 6.09, 8.40 μ; $[\alpha]^{27}D$ −177 ± 2°; n.m.r., 5.37 (triplet, J = 7 c.p.s.), 7.68 (quartet, J = 8 c.p.s.), 8.87 (triplet, J = 8 c.p.s.), 9.04, 9.17 τ; also lines at 364, 354, 343, 338, 326 (broad) c.p.s. downfield from tetramethylsilane.

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.17; H, 9.86.

A sample, heated for 3.5 hr. at 270–280° in a sealed, evacuated tube, was recovered unchanged as shown by infrared and ultraviolet analysis, m.p. 135–138°.

Δ^5-Androstene-7,17β-diols (VIII).—Eight and one-half grams of sodium was added in portions to a refluxing solution of 3.0 g. of $\Delta^{3,5}$-androstadiene-7,17-dione[13] in 200 ml. of 1-propanol. After all the sodium had reacted, the solution was cooled, poured into ice and water, and neutralized by addition of 22.2 ml. of glacial acetic acid. Methanol was removed by evaporation under reduced pressure on the steam bath and the residue extracted twice with ethyl acetate. The extracts were washed twice with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure on the steam bath to give 3.28 g. of tacky solid which showed only end absorption in the ultraviolet. One crystallization from aqueous methanol gave 2.41 g. (80%) of VIII, m.p. 155–170°. Further crystallization from aqueous methanol gave an analytical sample of mixed C-7 epimers, m.p. 175–183°; λ_{max}^{KBr} 2.93 μ; $[\alpha]^{30}D$ +61 ± 2° (*c* 0.5).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 79.23; H, 10.70.

Δ^5-Androstene-7,17-dione (IX).—A solution of 2.12 g. of diols VIII in 250 ml. of acetone maintained at 10–15° in an atmosphere of nitrogen was treated dropwise with stirring with 7 ml. of solution prepared from 2.137 g. of chromium trioxide and 1.84 ml. of concentrated sulfuric acid made up to 8 ml. with water.[14] After addition was complete, the solution was stirred for 15 min. and then poured into 1 l. of water. Acetone was removed under reduced pressure and the residual oily solution was extracted with ethyl acetate. The extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure on the steam bath.

The residue was dissolved in 200 ml. of warm methanol, 1 ml. of 10% aqueous potassium hydroxide solution added, and the solution refluxed for 5 min. After neutralization with acetic acid, the solution was concentrated under reduced pressure on the steam bath. The residue was dissolved in ethyl acetate, washed twice with water, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure on the steam bath

(25) V. Cerny, J. Joska, and L. Labler, *Collection Czech. Chem. Commun.*, **26**, 1658 (1961).

(26) The melting point varied with rate of heating due to thermal cleavage of II. The melting points reported here were obtained by placing the capillary in a bath at 160° and raising the temperature at the rate of 1°/per minute.

to give 2.08 g. of light yellow crystals, m.p. 96–164°; λ_{max} 238 mμ (ε 5400). One crystallization from methanol gave 530 mg. (25%) of IX, m.p. 164–173°. Further crystallization from methanol furnished the analytical sample, m.p. 180–181°; 238 mμ (ε 13,100); λ_{max}^{KBr} 5.75, 6.01, 6.16 μ; $[\alpha]^{27}D$ −116 ± 2°.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.84; H, 9.32.

Δ^5-Androstene-7,17β-diols (X).—Reduction of 520 mg. of IX with 653 mg. of lithium aluminum hydride in 75 ml. of ether afforded, after addition of water, filtration, and evaporation of solvent, 548 mg. of X, m.p. 107–170°; end absorption, 210 mμ (ε 9900); $\lambda_{max}^{CH_2Cl_2}$ 2.7 μ.

Reaction of 15 mg. of crude X with 150 mg. of activated manganese dioxide[27] in 3 ml. of chloroform at room temperature for 18 hr. afforded, after filtration and evaporation of solvent, 16 mg. of oil, 239 mμ (ε 6700); $\lambda_{max}^{CH_2Cl_2}$ 2.73, 6.02, 6.16 μ.

$\Delta^{4,6}$-Androstadien-17β-ol Propionate (VIIA).—A solution of 25 mg. of crude diol X in 5 ml. of 95% ethanol containing one drop of concentrated hydrochloric acid was refluxed for 2 hr. After cooling, the solution was neutralized with excess solid sodium carbonate, concentrated under reduced pressure, and the resulting white solid taken up in ethyl acetate and water. The layers were separated, the organic layer washed twice with water, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure on the steam bath. The crude alcohol, 24 mg. (94%), exhibited m.p. 137–157°; λ_{max} 230 mμ (ε 18,300), 238 (20,400), 246 (13,000); $\lambda_{max}^{CH_2Cl_2}$ 2.73 μ.

The crude product, 376 mg. from the reaction of 400 mg. of X as described, was esterified with 5 ml. of propionic anhydride and 10 ml. of pyridine overnight at room temperature. After removal of solvent on a rotary evaporator the residue was chromatographed on 18.5 g. of Florisil. Elution with one 200-ml. portion of petroleum ether and two of 10% benzene–petroleum ether gave a total of 360 mg. of VIIA, m.p. 91–103°. Crystallization from methanol and then petroleum ether gave the analytical sample, m.p. 103–104°; λ_{max} 230 mμ (ε 21,000), 238 (22,400), 246 (13,700); λ_{max}^{KBr} 5.74, 6.12, 8.40 μ; $[\alpha]^{28}D$ −3 ± 2°; n.m.r., 5.30 (multiplet), 7.64 (quartet, J = 8 c.p.s.), 8.86 (triplet, J = 8 c.p.s.), 9.04, 9.12 τ; also lines at 364, 355, 335, 329, 326 c.p.s. downfield from tetramethylsilane.

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.54; H, 9.84.

A sample, heated for 3 hr. at 270–280° in a sealed, evacuated tube, was recovered unchanged as shown by infrared and ultraviolet analysis, m.p. 98–104°.

Oxidation of Tetrahydro Product V to XI.—To a stirred solution of 352 mg. of V in 40 ml. of acetone maintained at 10–15° under nitrogen was added 0.145 ml. of a solution containing 2.137 g. of chromium trioxide and 1.84 ml. of concentrated sulfuric acid made up to 8 ml. with water.[14] After the dropwise addition was completed, the solution was stirred for 5 min. and then poured into water. The solution containing white solid was concentrated to remove acetone, the solid filtered and washed with water to give 348 mg. (99%) of XI, m.p. 268–271°, no absorption at 2.5–3.1 μ in methylene chloride solution. The sample for analysis was crystallized from methylene chloride–petroleum ether, m.p. 273–275° (sealed capillary); end absorption, 210 mμ (ε 2700); λ_{max}^{KBr} 5.76, 5.91, 8.44 μ; $[\alpha]^{28}D$ +60 ± 2°.

Anal. Calcd. for $C_{44}H_{64}O_6$: C, 76.70; H, 9.36. Found: C, 76.03; H, 9.48.

Thermal Cleavage of XI.—Heating 166 mg. of XI in a sealed, evacuated tube at 275° for 3 hr. gave an amber oil which failed to crystallize, λ_{max} 284 mμ (ε 7000). Fourteen milligrams of this was set aside and the remainder, dissolved in the minimum volume of benzene, was chromatographed on 8 g. of Florisil. Elution with 150 ml. of 2% ethyl acetate in benzene yielded 36 mg. (47%) of 5α-Δ^6-androsten-3-on-17β-ol propionate (XII), m.p. 125–136°; $\lambda_{max}^{CH_2Cl_2}$ 5.80–5.85, 8.4 μ; n.m.r., 4.64 (2H, broad), 5.33 (1H), 7.67 (quartet, J = 8 c.p.s.), 8.85 (triplet, J = 8 c.p.s.), 8.97, 9.09 τ. The material recovered from the n.m.r. determination was rechromatographed on Florisil and crystallized once to give the analytical sample of XII, m.p. 136–138°; λ_{max}^{KBr} 5.77, 5.84, 8.44 μ.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 75.78; H, 9.34.

Further elution with 240 ml. of 3% and 150 ml. of 5% ethyl acetate in benzene gave 40 mg. (53%) of material exhibiting an infrared spectrum identical with that of IA. Elution with 240 ml. of 10% and 150 ml. of 20% ethyl acetate in benzene afforded 60 mg. (39%) of recovered XI, identified by infrared analysis.

Androstan-3-on-17β-ol Propionate (XIII).—Hydrogenation of 17.2 mg. of XII in 5 ml. of ethyl acetate containing 3 mg. of 10% palladium on charcoal yielded, after filtration and concentration, 21.8 mg. of white solid, m.p. 110–119°, which was chromatographed on 1 g. of Florisil. Elution with 20 ml. of 5% ethyl acetate in benzene gave 11.8 mg. (69%) of XIII, m.p. 118–124°. One crystallization from hexane raised the melting point to 124–126°, lit.[15] m.p. 121–122°. This material exhibited an infrared spectrum identical with that of an authentic sample of XIII.[15]

Acid-Catalyzed Cleavage of Photodimer II.—A suspension of 100 mg. of II in 25 ml. of 5% *p*-toluenesulfonic acid in methanol was allowed to stand in the dark at room temperature. After 3.5 hr. the solid had completely dissolved; after an additional 17.5 hr. the solution was neutralized with 5% sodium hydroxide solution and methanol was removed under reduced pressure without heating. The residue was extracted with ethyl acetate, the extracts washed twice with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give 88 mg. of light yellow solid, m.p. 192–195°. The infrared spectrum was identical with that of an authentic sample of $\Delta^{4,6}$-androstadien-3-on-17β-ol.[28] One crystallization from ethyl acetate gave 41 mg., m.p. 199–202°, lit.[28] m.p. 204–205°.

Similar results were obtained by reaction with 5% hydrochloric acid in methanol for 33 hr. at room temperature in the dark.

$\Delta^{4,6}$-Androstadien-3-one (IB).—A suspension of 9.44 g. of Δ^4-androsten-3-one[5] and 18.87 g. of chloranil in 500 ml. of *t*-butyl alcohol[29] was refluxed for 3 hr. Excess chloranil was filtered after cooling, washed with *t*-butyl alcohol, and the combined solutions evaporated to dryness. The black residue was dissolved in ethyl acetate, washed with water and then with 5% sodium hydroxide solution until the washings were almost colorless, then with water and saturated salt solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure on the steam bath to give 15.75 g. of black tar. This was dissolved in benzene and washed through 200 g. of alkaline alumina with 1 l. of 1:1 benzene–petroleum ether and 1 l. of benzene to give, after concentration, 5.59 g. (59%) of light yellow solid, m.p. 146–147°. The analytical sample was obtained by crystallization from petroleum ether, m.p. 146–147° (transition from granules to cubes at 135–145° on the hot stage); λ_{max} 285 mμ (ε 25,500); λ_{max}^{KBr} 5.98, 6.15, 6.29 μ; $[\alpha]^{26}D$ +67 ± 3°.

Anal. Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.65. Found: C, 84.45; H, 9.47.

Photoirradiation of $\Delta^{4,6}$-Androstadien-3-one. Photodimer XIV.—A solution of 1.59 g. of IB in 20 ml. of 1:1 benzene–petroleum ether was irradiated for 24 hr. and the clear solution then adsorbed on 75 g. of Florisil. Elution with 3 l. of 1% ethyl acetate–benzene gave 767 mg. (48%) of IB, m.p. 140–147°. Further elution with 2 l. of 2% and two of 3% ethyl acetate–benzene gave 595 mg. (37%) of photodimer XIV, m.p. 152–155°. Three crystallizations from chloroform–petroleum ether and two from methanol gave the analytical sample, m.p. 155°; λ_{max} 256 mμ (ε 10,300); λ_{max}^{KBr} 5.90, 5.98, 6.22 μ; $[\alpha]^{27}D$ +12 ± 3°.

Anal. Calcd. for $C_{38}H_{52}O_2$: C, 84.39; H, 9.69; mol. wt., 540. Found: C, 84.50, 84.60; H, 9.59, 9.76; mol. wt., 500.

Heating 10 mg. of XIV in a sealed capillary at 165° for 5 min. afforded a yellow oil, λ_{max} 284 mμ (ε 21,200), which was identical with IB by infrared analysis.

Photoirradiation of $\Delta^{4,6}$-Androstadien-3-on-17β-ol (IC). Photodimer XV.—A solution of 580 mg. of IC[28] in 20 ml. of 1:1 benzene–dioxane was irradiated for 6 hr. After removal of solvent in an air stream without heating, a portion (123 mg.) of the crude product was crystallized from chloroform–ethyl acetate to give 60 mg. (49%) of XV, m.p. 199–201°. Three crystallizations from the same solvent mixture gave the analytical sample, m.p. 200–201.5°; λ_{max} 257 mμ (ε 10,000); λ_{max}^{KBr} 5.90, 6.05, 6.27 μ; $[\alpha]^{30}D$ +33°.

Anal. Calcd. for $C_{38}H_{52}O_4$: C, 79.68; H, 9.15. Found: C, 79.68; H, 8.72.

Esterification of 55 mg. of XV by reaction with 0.5 ml. of propionic anhydride in 1 ml. of pyridine at room temperature overnight gave a crude product which was chromatographed on 3

(27) Beacon Chemical Industries, Inc., Cambridge 40, Mass.

(28) C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).

(29) E. J. Agnello and G. O. Laubach, *ibid.*, **82**, 4293 (1960).

g. of Florisil. Elution with 100 ml. of 20% and 30 ml. of 50% ethyl acetate–benzene gave 49 mg. (74%) of II which, after one crystallization from methylene chloride–petroleum ether, gave 39 mg., m.p. 168.5–170°, identical by infrared spectrum and mixture melting point with II obtained by photoirradiation of IA.

Heating 13 mg. of XV in a sealed, evacuated capillary for 15 min. at 215° gave material exhibiting infrared and ultraviolet spectra identical with those of IC.

Photoirradiation of $\Delta^{4,6}$-Cholestadien-3-one (ID). Photodimer XVI. A. In Petroleum Ether.—A solution of 518 mg. of $\Delta^{4,6}$-cholestadien-3-one[30] (ID) in 15 ml. of petroleum ether was irradiated for 1.75 hr. at 3–4°. The solid which precipitated was filtered to give 247 mg. (48%) of dimer XVI, m.p. 175–177°. The yield could be raised to 79% by successive crop taking and reirradiation. The analytical sample was obtained by crystallization from ethyl acetate, m.p. 174.5–175°; $\lambda_{max}^{cyclohexane}$ 243 mμ (ε 10,600); λ_{max}^{KBr} 5.93, 5.98, 6.25 μ; $[\alpha]^{26}D$ +37°; lit.[3] λ_{max}^{alc} 258 mμ (ε 9100); $\lambda_{max}^{CHCl_3}$ 5.91, 6.02, 6.21 μ; $\lambda_{max}^{CCl_4}$ 5.89, 5.97, 6.23 μ; lit.[17] m.p. 173–174°, 179–180°; $[\alpha]D$ +37°.

Anal. Calcd. for $C_{54}H_{84}O_2$: C, 84.75; H, 11.07; mol. wt., 765. Found: C, 84.55; H, 10.93; mol. wt., 730.

Heating 16 mg. of XVI in a sealed capillary at 215° for 15 min. gave an oil, λ_{max} 284 mμ (ε 25,200), identical with ID by comparison of infrared spectra.

B. In Benzene–Dioxane Solution.—A solution of 206 mg. of ID in 5.4 ml. of 1:1 benzene–dioxane was irradiated for 5.5 hr. The solution remained clear. After removal of solvent under reduced pressure, the residue was chromatographed on 10 g. of Florisil. Elution with 800 ml. of 1% ethyl acetate–benzene yielded 87 mg. of starting material. Elution with 600 ml. of 3% ethyl acetate–benzene afforded 36 mg. (18%) of XVI. One crystallization from methylene chloride–ethyl acetate gave 18 mg., m.p. 172.5–173°; mixture melting point with product from the petroleum ether reaction, 172.5–173°. Infrared spectra were identical.

Reversibility of Photodimerization of IA.—A solution of 480 mg. of dimer II in 14 ml. of 1:1 benzene–dioxane was irradiated for 12.5 hr. The clear solution was concentrated under reduced pressure and the residue, λ_{max} 284 mμ (ε 11,800), chromatographed on 21 g. of Florisil as described for the photoirradiation of IA to give 46% of IA, m.p. 135–136°, and 38% of II, m.p. 167–169°. Identity was further established by comparisons of infrared spectra.

Photostationary States.—Solutions of IA (0.1 *M*) or II (0.05 *M*) in 1:1 benzene–dioxane were immersed in a water bath having a Pyrex window and irradiated until ultraviolet spectra of samples from each solution were identical. Compositions were calculated from the extinction coefficients of the monomer at 280 mμ (ε 26,900) correcting for the relatively weak absorption (ε 5200) of dimer at this wave length. At 3–4°, 15 hr. were required to attain equilibrium; the product of irradiation of IA contained 29% IA and 71% II, the product from II contained 28% IA and 72% II. At 27–28° equilibrium was attained in 3 hr.,[31] the compositions were 31% IA and 69% II in both cases.

Acknowledgment.—Financial support from the Squibb Institute for Medical Research is gratefully acknowledged. N.m.r. spectra were determined by Miss P. Zwitkowitz.

(30) A. L. Wilds and C. Djerassi, *J. Am. Chem. Soc.*, **68**, 1712 (1946). Use of the chloranil oxidation procedure as described for IB afforded ID in 65% yield.

(31) The considerable differences in duration of reaction may have been due to relative age of the lamp in the two sets of experiments.

Perhydroindanone Derivatives. IV. The 1,1a,4,4a-Tetrahydrofluoren-9-one System[1a]

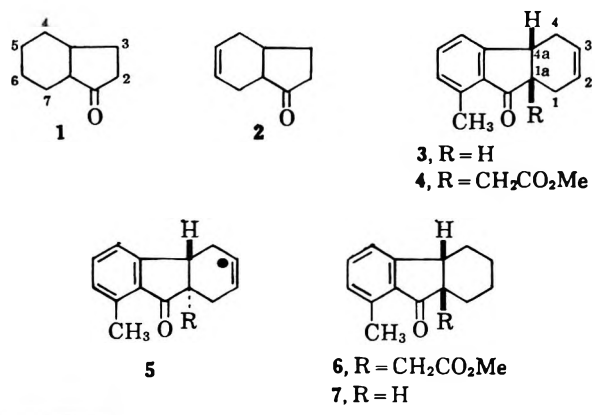
HERBERT O. HOUSE AND ROBERT G. CARLSON[1b]

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts

Received July 24, 1963

The *cis*-fused isomer (the more stable) of 8-methyl-1,1a,4,4a-tetrahydrofluoren-9-one (**3**) has been synthesized and found to give primarily the *cis*-fused product **4** on alkylation. Several possible routes to the 2-keto hexahydrofluorenone system **20** have been explored and a satisfactory preparative route is described.

Upon finding[2] that the relative stability of the *cis* isomer of perhydroindan-1-one (**1**, 75% *cis* at equilibrium) could be diminished by the introduction of a double bond at the 5–6-position (as in **2**, 53% *cis* at equilibrium), it became of interest to learn whether the alkylation of the tetrahydrofluorenone system **3** would lead to a mixture of the *cis* and *trans* ring-fused products **4** and **5** rather than only (or at least very largely) a *cis*-fused product such as **6** obtained from alkylation of the hexahydrofluorenone **7**.[3] The realization of such a nonstereoselective alkylation appeared to offer a possible route to intermediates useful for the synthesis of both allogibberic acid (*trans* B–C ring fusion) and epiallogibberic acid (*cis* B–C ring fusion) without requiring inversion of a center at some later stage.[4]



To examine this question the tetrahydrofluorenone **3** was prepared as indicated in Chart I following a sequence previously applied to 1-indanone.[5] Since a preliminary attempt to prepare the Diels–Alder adduct **10** led to a complex mixture (*cf.* ref. 5), we modified the procedure to generate the very reactive indenone **11** in the presence of excess butadiene. A single crystalline adduct **3** was isolated from this Diels–Alder reaction. This material was stable to refluxing methanolic sodium methoxide although these

(1) (a) Supported in part by Grant No. G-25214 from the National Science Foundation; (b) National Institutes of Health Predoctoral Fellow, 1960–1963.

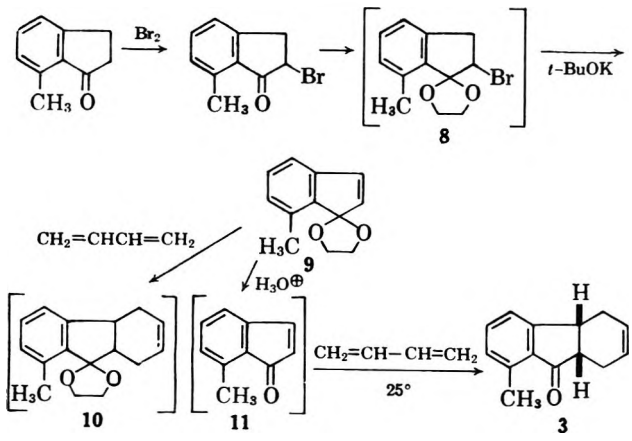
(2) H. O. House and G. Rasmusson, *J. Org. Chem.*, **28**, 31 (1963).

(3) H. O. House, V. Paragamian, and D. J. Wluka, *J. Am. Chem. Soc.*, **82**, 2561 (1960); **83**, 2714 (1961).

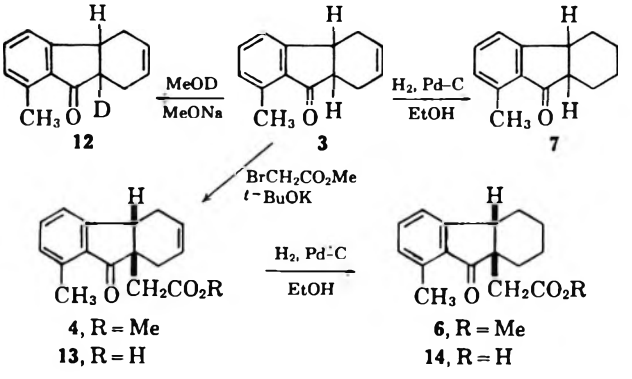
(4) For one method, albeit a circuitous one, of effecting this inversion in the system **4**, see H. O. House, R. G. Carlson, H. Müller, A. W. Noltes, and C. D. Slater, *ibid.*, **84**, 2614 (1962).

(5) H. O. House, V. Paragamian, R. S. Ro, and D. J. Wluka, *ibid.*, **82**, 1452, 1457 (1960).

CHART I



conditions were sufficiently vigorous to remove the proton α to the carbonyl function as demonstrated by conversion to the monodeuterated derivative **12**. Consequently, the product **3** is the more stable epimer in this series. The conclusion that the product **3** should possess the indicated *cis* stereochemistry by virtue of having been produced by a Diels–Alder reaction[6] is rendered equivocal because of the formation of the product in the presence of very dilute aqueous acid which could have epimerized an initially formed product. Several attempts to isolate the pure indenone **11** in order to remove this ambiguity led only to polymeric material. However, several additional facts indicate strongly that the *cis* stereochemical assignment is correct. Catalytic hydrogenation of **3** under conditions which permitted the reduction[2] of the tetrahydroindanone **2** to **1** without significant epimerization produced



the hexahydrofluorenone **7** previously assigned[3] the indicated *cis* configuration. Furthermore, examination of the n.m.r. spectra of **3** and **12** indicates that coupling between the proton at C-4a and each of the protons at C-4 as well as the proton at C-1a is 6–7 c.p.s. in each case. This observation suggests either that each of the three dihedral angles H–$C_{(1a)}$–$C_{(1a)}$–H and H–$C_{(4a)}$–$C_{(4)}$–H (for each C-4 proton) is approximately 30° or that one of the dihedral angles is approximately 30°, one is approximately 150°, and the third dihedral angle is either 30° or 150°.[7]

Examination of molecular models indicates that at least two conformations (a twisted boat or a chair cyclohexene ring) of the *cis*-tetrahydrofluorenone **3** are possible which would be consistent with such a combination of dihedral angles. However, it appears very difficult to reconcile the observed coupling constants with the dihedral angles (about 60°, 150°, and 180° as estimated from Dreiding models) present in the conformationally rigid 8-methyl-*trans*-1,1a,4,4a-tetrahydrofluoren-9-one. Our data are, therefore, in best agreement with the interpretation that the *cis* ring fusion in the tetrahydrofluorenone system **3** is more stable than the *trans* ring fusion as was previously found for the 1,1a,2,3,4,4a-hexahydrofluoren-9-one system.[5,8]

The alkylation of the tetrahydrofluorenone (**3**) produced primarily the ester **4** with a *cis* ring fusion as demonstrated by hydrogenation and subsequent hydrolysis to the previously known[3] *cis* acid **14**. In addition to the major alkylation product, the *cis* keto ester **4**, a minor product was formed in this reaction which had spectral properties similar to the *cis* ester **4** suggesting that it may be the corresponding keto ester having a *trans* ring fusion. However, we were unable to isolate a pure sample of this minor product to permit complete characterization. In any case, alkylation of the tetrahydrofluorenone system **3** does not offer a useful route to a *trans*-fused hexahydrofluorenone.

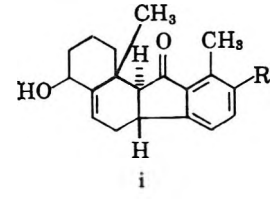
Several additional routes to a hexahydrofluorenone **6** having an oxygen substituent at C-2 (*cf.* ref. 4) have been examined. The results of these studies are summarized in Chart II. Of importance to our further synthetic work was the fact that, although cleavage of the diketone lactone **19** with zinc and acetic acid or calcium and liquid ammonia occurred very slowly, presumably because the acyloxy function occupied an equatorial position,[4,9] the reduction to form **20** was readily achieved with chromous chloride.[10]

With the *cis* keto ester **20** in hand, it was of interest to explore the possibility[11] that partial conversion of the *cis*-fused ester **20** to the *trans*-fused isomer **23** might be achieved by reaction of **20** with refluxing methanolic sodium methoxide to form the intermediate triketone

(6) J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).

(7) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 87.

(8) D. M. Bailey, D. P. G. Hamon, and, W. S. Johnson [*Tetrahedron Letters*, **No. 9**, 555 (1963)] have found the tetrahydrofluorenone system present in 11-ketoveratramine (**i**) to be more stable in the configuration having a *trans* fusion of the 5- and 6-membered rings. Since this system is analogous to the tetrahydrofluorenone (**3**) except for the presence of substituents at positions corresponding to C-1 and C-2 in **3**, we believe that the predominant factor stabilizing the *trans* isomer of 11-ketoveratramine is these substituents. The importance of a substituent in determining the position of the *cis–trans* equilibrium in a perhydroindanone system **1** is pointed up clearly in the effect of a 7-methyl substituent (ref. 2).



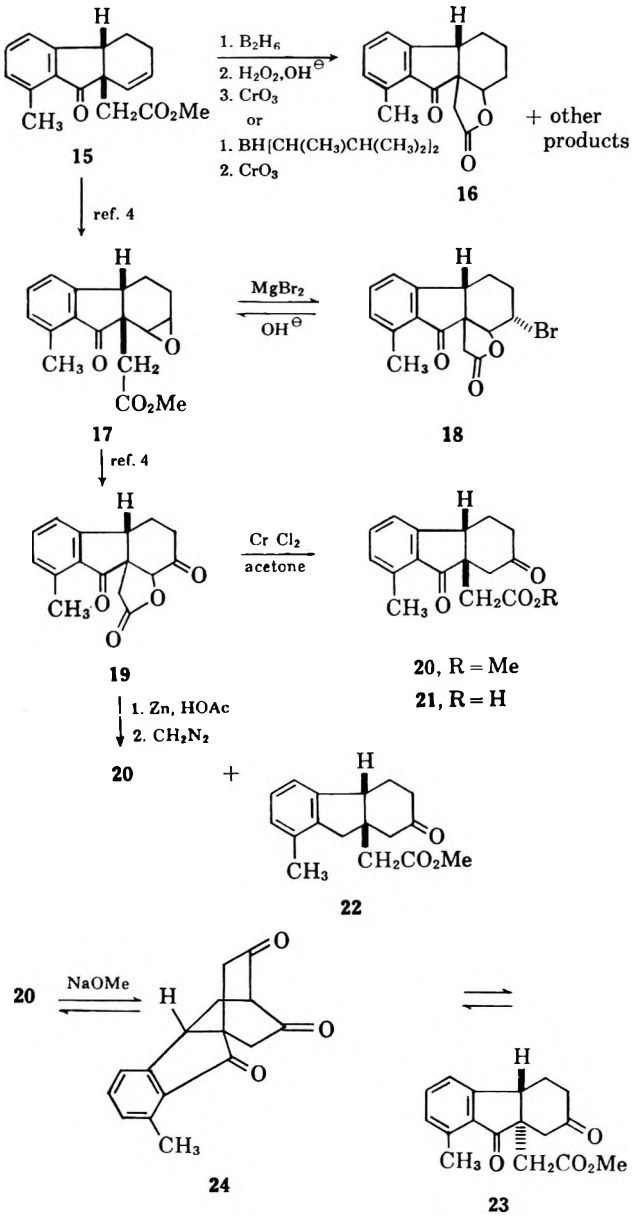
i

(9) The cleavage of an acyloxy group or a halogen atom α to a carbonyl function by a dissolving metal reduction has generally been found to occur more rapidly if the substituent being cleaved occupies (or can occupy) an axial position. For examples and discussion, see (a) F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez, and G. Rosenkrantz, *J. Am. Chem. Soc.*, **75**, 4712 (1953); (b) R. S. Rosenfeld and T. F. Gallagher, *ibid.*, **77**, 4367 (1955); (c) J. H. Chapman, J. Elks, G. H. Phillipps, and L. J. Wyman, *J. Chem. Soc.*, 4344 (1956).

(10) (a) G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4077 (1950); (b) W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954); (c) D. H. R. Barton and J. T. Pinhey, *Proc. Chem. Soc.*, 279 (1960); (d) D. H. R. Barton, T. Miki, and J. T. Pinhey, *ibid.*, 112 (1962); (e) G. Büchi and J. H. E. Loewenthal, *ibid.*, 280 (1962).

(11) (a) J. F. Grove and T. P. C. Mulholland, *J. Chem. Soc.*, 3007 (1960); (b) B. E. Cross, J. R. Hanson, L. H. Briggs, R. C. Cambie, and P. S. Rutledge, *Proc. Chem. Soc.*, 17 (1963).

CHART II



15 16 17 18 19 20, R = Me 21, R = H 20 22 24 23

24 followed by conversion to either 20 or 23. However, this procedure led only to recovery of the ester 20 and the corresponding acid 21 with no second component being isolated even after a 48-hr. reaction period. Therefore, it seems probable that the equilibrium position between the *cis* and *trans* keto esters (*i.e.*, 20 and 23) favors the *cis*-fused product 20 as was noted previously[11a] with similarly constituted degradation products of allogibberic acid and epiallogibberic acid.

Experimental[12]

2-Bromo-7-methylindanone.—To a cold (0°) solution of 14.36 g. (0.0982 mole) of 7-methylindanone[2] in 1.1 l. of ether was added, dropwise and with stirring over a 45-min. period, 15.70 g. (0.0983 mole) of bromine. The resulting solution was allowed to warm to room temperature and then washed with aqueous sodium bicarbonate, dried, and concentrated. Crystallization of the semisolid residue from an ether–petroleum ether (b.p. 30–60°) mixture afforded 15.14 g. (68.5%) of the bromo ketone as pale yellow needles, m.p. 45–48°. Recrystallization afforded the pure bromo ketone, m.p. 47.5–49°; with infrared absorption[13] at 1722 cm.$^{-1}$ (C=O); ultraviolet maxima[14] at 258 mμ (ε 13,400) and 303 (2320); and n.m.r. peaks[13] at 7.42 τ (3H singlet, Ar-CH_3), a multiplet in the region 6.0–7.0 (2H, $>CH_2$), a series of four peaks centered at 5.52 (1H, >CH–Br), and a complex multiplet in the region 2.4–3.1 (3H, aryl C–H).

Anal. Calcd. for $C_{10}H_9BrO$: C, 53.36; H, 4.03; Br, 35.51. Found: C, 53.13; H, 4.05; Br, 35.57.

The Ethylene Ketal (9) of 7-Methylindenone.—A solution of 12.00 g. (0.0534 mole) of the bromo ketone, 100 mg. of *p*-toluenesulfonic acid, and 5.00 g. (0.0798 mole) of ethylene glycol in 150 ml. of benzene was refluxed with continuous separation of water for 1 week, additional 5.00-g. portions of ethylene glycol being added after 42 and 114 hr. At this time the infrared spectrum of the reaction mixture exhibited only weak carbonyl absorption. The mixture was washed with aqueous sodium bicarbonate, dried, and concentrated to leave the crude bromo ketal 8 as a brown liquid. A solution of this crude ketal in 25 ml. of *t*-butyl alcohol was added, dropwise and with stirring over a 10-min. period, to a solution of potassium *t*-butoxide prepared from 3.12 g. (0.08 g.-atom) of potassium and 50 ml. of *t*-butyl alcohol. The resulting mixture was stirred at room temperature under a nitrogen atmosphere for 5 hr. and then poured into ice–water and extracted with ether. After the etheral extract had been washed with water, dried, and concentrated, distillation of the residue, first through a shortpath still (5.636 g., b.p. 97–105° at 0.1 mm.) and then through a Holtzmann column, separated 4.368 g. (43.4%) of the ketal, b.p. 86–88° (0.24 mm.). Upon redistillation of a portion of this material, the distillate crystallized as white prisms, m.p. 68–69°, which could be recrystallized from hexane. In a subsequent preparation from 20.0 g. (0.137 mole) of the indanone where the crude bromo ketone was used without purification, the yield of the indenone ketal 9, m.p. 67–68.5°, was 14.62 g. (55% based on the indanone). The product, which has no infrared absorption[13] in the 3- or 6-μ region attributable to hydroxyl or carbonyl functions, exhibits ultraviolet maxima[14] at 219 mμ (ε 29,000), 226 (25,000), 278 (2640), 287 (shoulder 2330), 300 (1840), and 311 (shoulder 1390); with n.m.r. peaks[13] at 7.68 τ (3H singlet, Ar-CH_3), a multiplet centered at 5.88 (4H, $-OCH_2-CH_2O-$), a pair of doublets (J = 5.5 c.p.s.) centered at 3.91 and 3.49 (2H, vinyl C–H), and a multiplet in the region 2.7–3.3 (3H, aryl C–H).

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43; mol. wt., 188. Found: C, 76.50; H, 6.55; mol. wt., 188 (mass spectrum).

8-Methyl-1,1a,4,4a-tetrahydrofluoren-9-one (3).—Into a cold (−5 to 0°) solution of 5.00 g. (0.0266 mole) of ketal 9 and 5 ml. of water in 25 ml. of tetrahydrofuran was distilled, through a tube containing molecular sieves, 14 g. (0.27 mole) of 1,3-butadiene. The resulting solution was cooled in a Dry Ice–acetone bath, 3 drops of concentrated hydrochloric acid was added, and then the flask was stoppered and stirred at room temperature for 8 days. The excess butadiene was allowed to evaporate from the resulting mixture, 50 ml. of saturated, aqueous sodium chloride solution was added, and the mixture was extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate, dried, and concentrated to leave 5.05 g. of yellow oil which solidified on standing. Distillation through a shortpath still separated 3.80 g. of the tetrahydrofluorenone 3, b.p. 118–128° (0.1 mm.), which was recrystallized from pentane to give 3.27 g. (62.5%) of the ketone as white prisms, m.p. 48.5–50.5°. An additional crystallization raised the melting point to 50–51°. The product has infrared absorption[13] at 1705 cm.$^{-1}$ (C=O); ultraviolet maxima[14] at 250 mμ (ε 12,050) and 298 (2510); and a series of n.m.r. peaks[15] in the region 2.4–3.0 τ (3H, aryl C–H), as well as a multiplet centered at 4.17 (2H, vinyl C–H), a singlet at 7.37 (3H, aryl CH_3), a complex series of peaks in the region 7.0–8.0 (5H), and a quadruplet of broad peaks (half-band widths 3–5 c.p.s., peak positions 204, 212, 218 and 225 c.p.s. from tetramethylsilane) centered at 6.42 (1H, benzylic C–H).

(12) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with either a Baird, Model B, or a Perkin-Elmer, Model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The n.m.r. spectra were determined at 60 Mc. with a Varian, Model A-60, n.m.r. spectrometer. The mass spectra were obtained with a CEC, Model 21-130, mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

(13) Determined in carbon tetrachloride solution.

(14) Determined in 95% ethanol solution.

(15) Determined as a solution in deuteriochloroform.

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12; mol. wt., 198. Found: C, 84.73; H, 7.17; mol. wt., 198 (mass spectrum).

A solution of 196 mg. (0.99 mmole) of the tetrahydrofluorenone **3** in the methanolic sodium methoxide prepared from 60 mg. (2.61 mg.-atoms) of sodium and 5 ml. of deuteriomethanol was refluxed for 3.5 hr. and then concentrated under reduced pressure. An additional 5-ml. portion of deuteriomethanol was added and the resulting solution was refluxed for 7.5 hr. and then poured into a mixture of pentane and deuterium oxide. After the pentane extract had been dried and concentrated, the residual oil (198 mg.) was crystallized from pentane to separate 116 mg. (59%) of the deuterated tetrahydrofluorenone **12** as pale yellow prisms, m.p. 49–51°. The material which did not depress the melting point of the starting ketone **3** and had the same R_f value on thin layer chromatography,[16] contained 17% d_0, 75% d_1, and 8% d_2 species. The deuterated ketone **12** has an n.m.r. spectrum[16] which differs from the spectrum of the undeuterated ketone **3** in lacking a complex multiplet attributable to one proton in the region 7.0–7.3 τ (C–H α to carbonyl) and in having a triplet (rather than a quartet) of broad peaks (half-band widths 3–4 c.p.s., peak positions 207, 213 and 219 c.p.s. from tetramethylsilane) centered at 6.43 (1H, benzylic C–H).

Hydrogenation of the Tetrahydrofluorenone 3.—A solution of 167 mg. (0.844 mmole) of the unsaturated ketone **3** in 8 ml. of ethanol was hydrogenated over 25 mg. of a 5% palladium-on-carbon catalyst at 27° and atmospheric pressure. After the hydrogen uptake (21.1 ml. or 1.01 equiv.) ceased (1 hr.), the mixture was filtered, and concentrated to leave 157 mg. (93%) of the hexahydrofluorenone **7** as a colorless oil which crystallized when cooled. Recrystallization from pentane separated 88 mg. (53%) of the pure ketone **7** as white prisms, m.p. 34–35°. The infrared spectra[13] of both the crude and recrystallized products are identical with the spectrum of a previously described[3] sample of *cis*-ketone **7**.

Alkylation of the Tetrahydrofluorenone 3.—A solution of 1.629 g. (8.21 mmoles) of the ketone **3** in the potassium *t*-butoxide solution obtained from 1.28 g. (32.8 mg.-atoms) of potassium and 35 ml. of *t*-butyl alcohol was refluxed for 10 min. and then cooled and treated, dropwise and with stirring over a 15-min. period, with 5.00 g. (32.7 mmoles) of methyl bromoacetate. The resulting mixture was refluxed for 5 min. and then concentrated, diluted with water, neutralized by the addition of a few drops of hydrochloric acid, and extracted with ether. After the ethereal extract had been dried and concentrated the residual brown oil (2.689 g.) was dissolved in a mixture of 1.0 g. (0.25 mole) of sodium hydroxide, 10 ml. of water, and 25 ml. of methanol. The resulting solution was refluxed for 11 hr., cooled, diluted with saturated aqueous sodium chloride solution, and extracted with ether. After acidification of the aqueous phase and extraction with ether, the ethereal solution was washed with water, dried, and concentrated. The crude acidic product (1.896 g.), which contained[16] one major component (acid **13**) and one minor component, was esterified with ethereal diazomethane to give 1.580 g. of crude ester **4**[16,17] (containing one major and one minor component) as a pale yellow oil. A combination of chromatography on silica gel and recrystallization from methanol separated 845 mg. (39%) of the major component,[17] ester **4** as pale yellow prisms, m.p. 69–71°. Recrystallization raised the melting point to 73–74°. The product has infrared absorption[13] at 1735 cm.$^{-1}$ (ester C=O) and 1705; ultraviolet maxima[14] at 250 mμ (ϵ 12,400) and 299 (2540); and a series of n.m.r. peaks[13] in the region 2.3–3.2 τ (3H, aryl CH), a multiplet centered at 4.28 (2H, vinyl C–H), a singlet at 6.45 (3H, OCH_3) superimposed on a multiplet (1H, benzylic CH), and a complex series of peaks in the region 7.2–7.9 (9H, aryl CH_3 and three CH_2 groups).

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 75.53; H, 6.71. Found: C, 75.54; H, 6.77.

The mother liquors remaining after this separation contained[17] approximately 90% of ester **4** (first eluted) and approximately 10% of a second component (second eluted) which may be the *trans* isomer corresponding to ester **4**. However, repeated efforts to separate a pure sample of the minor component served only to yield small quantities of an approximately equal mixture of ester **4** and the second product. The infrared spectrum of this mixture resembled closely the spectrum of the pure ester **4**.

(16) A thin layer chromatographic plate coated with silica gel was employed for this analysis.

(17) A gas chromatography column packed with General Electric Silicone No. SE30 suspended on ground firebrick was employed for this analysis.

Hydrogenation of the Unsaturated Ester 4.—A solution of 200 mg. (0.744 mmole) of ester **4** in 10 ml. of ethanol was hydrogenated over 30 mg. of a 5% palladium-on-carbon catalyst at 25° and atmospheric pressure. After the hydrogen uptake (18.3 ml. on 1.01 equiv.) had ceased (25 min.), the solution was filtered and concentrated to leave 202 mg. of colorless oil whose infrared spectrum[13] was identical with the spectrum of previously described[3] ester **6**. Crystallization from aqueous ethanol afforded 163 mg. (81%) of one crystalline form of ester **6**, m.p. 74–76°. Since this material tends to crystallize as a mixture of crystalline forms[3] which complicated comparison of samples, a solution of 100 mg. (0.364 mmole) of ester **6** and 310 mg. of 85% potassium hydroxide in a mixture of 4 ml. of methanol and 2 ml. of water was refluxed for 4.5 hr., then diluted with water, and extracted with ether. After the aqueous phase had been acidified and extracted with ether, this ethereal extract was dried and concentrated. Recrystallization of the residual solid (106 mg.) from an ethyl acetate–hexane mixture gave 61 mg. (65%) of the keto acid **14** as white prisms, m.p. 140.5–141.5°, which was identified by a mixture melting point determination and by comparison of infrared spectra[18] and thin layer chromatograms.[16]

Reaction of the Epoxy Keto Ester 17 with Magnesium Bromide.—To a solution of 500 mg. (1.74 mmoles) of epoxide **17**[4] in 25 ml. of benzene was added 1.7 ml. of an ethereal solution containing 5.22 mmoles of anhydrous magnesium bromide (from ethylene dibromide and magnesium). The resulting mixture was refluxed for 11 hr. and then diluted with benzene and washed with saturated aqueous ammonium sulfate. The benzene layer was dried and concentrated to leave 576 mg. of a pale yellow solid which gave a positive test for halogen and showed only one spot on thin layer chromatography.[16] Recrystallization from methanol gave 398 mg. (68.3%) of the bromo lactone **18** as white needles, m.p. 181.5–183.5°, which melted at 183–183.5° after recrystallization. The product has infrared absorption[19] at 1778 cm.$^{-1}$ (γ-lactone C=O) and 1704 (C=O) with ultraviolet maxima[14] at 252 mμ (ϵ 13,500) and 300 (2300).

Anal. Calcd. for $C_{16}H_{15}BrO_3$: C, 57.33; H, 4.51; Br, 23.84. Found: C, 57.11; H, 4.61; Br, 24.30.

A mixture of 200 mg. (0.597 mmole) of the bromo lactone **18**, 350 mg. (8.75 mmoles) of sodium hydroxide, 2 ml. of methanol, and 10 ml. of water was stirred at room temperature until solution was complete (30 hr.) and then successively extracted with ether, cooled, acidified to pH 3 with hydrochloric acid, and again extracted with ether. The final ethereal extracts were dried and concentrated and the residual solid (210 mg.) was esterified with ethereal diazomethane. After appropriate manipulations, crystallization of the resulting neutral product from methanol gave 114 mg. (66%) of the epoxy ester **17**, m.p. 101–103°, identified with an authentic sample by a mixture melting point determination and by comparison of infrared spectra and thin layer chromatograms.

Reaction of the Unsaturated Ester 15 with Diborane.—Subsequent preparations of the previously described[4] unsaturated ester **15** yielded a different crystalline form of the material as white prisms, m.p. 82.5–84° (lit.[4] m.p. 70.1–71°), which has infrared absorption[13] and thin layer chromatographic behavior identical with the material melting at 70.1–71°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.65; H, 6.72.

A cold (0°) solution containing 3.87 mmoles of diborane in 10 ml. of tetrahydrofuran was added to 2.00 g. (7.32 mmoles) of the unsaturated ester **15** and the resulting solution was stirred, under nitrogen, for 3 hr. at 0° and for an additional 2 hr. at room temperature. The reaction mixture was treated successively with 0.5 ml. of water, 10 ml. of 3 *N* aqueous sodium hydroxide and, after cooling to 0°, 10 ml. of 30% aqueous hydrogen peroxide. The mixture was then stirred at 0° for 3 hr. and at room temperature for 5 hr. An additional 5 ml. of 3 *N* aqueous sodium hydroxide was added and the reaction mixture was refluxed for 2 hr., then diluted with water, and extracted with ether. After the ethereal extract had been dried and concentrated, the residual oil (1.509 g.) was found to contain[16] at least four components. The infrared spectrum of the material indicated essentially complete reduction of the ester function. To a solution of 1.25 g. of this neutral material in 35 ml. of 90% aqueous acetic acid was added, dropwise and with stirring, 6 ml. of a 2.67 *M* solution of chromium trioxide in aqueous sulfuric acid. The reaction mixture was stirred

(18) Determined in chloroform solution.

(19) Determined as a suspension in a potassium bromide pellet.

for 3 hr. at room temperature and then treated with a few drops of methanol, concentrated under reduced pressure, diluted with aqueous ammonium sulfate, and extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate, dried, and concentrated to leave 954 mg. of white solid containing[16] two components, lactone 16 and a second unidentified material, in approximately equal amounts. Fractional crystallization from methanol separated 354 mg. (23%) of the pure lactone 16, m.p. 130–131.5°, identified with a subsequently described sample by a mixture melting point determination and comparison of infrared spectra. No other pure material was isolated from either the neutral or acidic portions of the reaction products.

In another experiment, 9.00 ml. of a tetrahydrofuran solution containing 8.51 mmoles of diborane was treated with 1.158 g. (17.02 mmoles) of 2-methyl-2-butene to prepare di(3-methyl-2-butyl)borane.[20] After this solution had been stirred at 0° for 3 hr., it was added to a solution of 2.00 g. (7.40 mmoles) of the unsaturated ester 15 in 5 ml. of tetrahydrofuran. The resulting solution was stirred for 2 hr. at 0° and 20 hr. at room temperature. The mixture was treated successively with 2 ml. of water and a solution of 4.90 g. of sodium dichromate hexahydrate and 3 ml. of concentrated sulfuric acid in 25 ml. of water, and then stirred for 30 min. at 0° and at room temperature for 5 hr. After the reaction mixture had been diluted with aqueous ammonium sulfate and extracted with ether, the ethereal extract was washed with aqueous sodium bicarbonate, dried, and concentrated. The crude neutral oil (1.943 g.) contained[16] two major products, the lactone 16 and a second unidentified material, as well as some starting material. A solution of the neutral product in 75 ml. of ether was stirred with a solution of 4.0 g. of sodium hydroxide in 50 ml. of water for 45 min. at room temperature to selectively saponify part of the γ-lactone 16. Acidification of the aqueous layer followed by appropriate manipulation afforded 287 mg. (16%) of the crude lactone 16, m.p. 128–131°, which was recrystallized from aqueous methanol to give 210 mg. of the pure lactone as white needles, m.p. 131.2–132.2°. This product has infrared absorption[18] at 1775 and 1760 (shoulder) cm.$^{-1}$ (γ-lactone C=O) and at 1705 (C=O); ultraviolet maxima[14] at 252 mμ (ε 12,800) and 300 (2320); and a series of n.m.r. peaks[15] in the region 2.3–3.0 τ (3H, aryl C–H) as well as a multiplet centered at 5.04 (1H, CH–O), a singlet at 7.35 (3H, aryl CH_3), a multiplet centered at 6.79 (1H, benzylic C–H), a pair of doublets (J = 17 c.p.s.) centered at approximately 7.1 and 7.6 (2H, CH_2 of lactone), and complex absorption in the region 7.6–8.9.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.87; H, 6.31.

Reductive Cleavage of the Diketone Lactone 19. A. With Zinc and Acetic Acid.—A mixture of 1.092 g. (4.03 mmoles) of lactone 19, 2.00 g. of zinc dust, 3 ml. of water, and 30 ml. of acetic acid was refluxed with stirring for 7 hr. at which time all the zinc had dissolved. An additional 2.05-g. portion of zinc was added and refluxing and stirring were continued for an additional 14 hr. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure, diluted with aqueous ammonium sulfate, and extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate, dried, and concentrated to leave 309 mg. of neutral oil which contained[16] at least five components, one of which corresponded in R_f value to the starting material. The aqueous bicarbonate layer was acidified, saturated with ammonium sulfate, and extracted with ether. After this ether solution had been dried and concentrated, the crude acidic fraction (1.408 g.) was esterified with ethereal diazomethane to give, after appropriate manipulation, 812 mg. of a neutral oil which contained two major components, 20 and 22. After an involved sequence of chromatography and fractional crystallization, a small amount of the keto ester 20 was separated from ether at low temperatures as white prisms, m.p. 93–94° The product has infrared absorption[18] at 1710 cm.$^{-1}$ (C=O) with a shoulder at *ca.* 1725 (ester C=O); ultraviolet maxima[14] at 252 mμ (ε 12,900) and 300 (2320); and a series of n.m.r. peaks[15] in the region 2.3–2.9 τ (3H, aryl C–H) with a singlet at 6.39 (3H, O–CH_3) superimposed on a multiplet (1H, benzylic C–H), and a single peak at 7.33 (8H, aryl CH_3 and two $-CH_2-$ groups next to multiple bonds), as well as complex absorption in the region 7.4–8.2

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.22; H, 6.40.

The combined mother liquors from this separation were subjected to preparative thin layer chromatography on silica gel to separate the second component, the keto ester 22, which crystallized from an ether–petroleum ether mixture as white prisms, m.p. 81–82°. This product has infrared absorption[18] at 1710 cm.$^{-1}$ (C=O) and 1725 (ester C=O) with no absorption in the 3-μ region indicative of a hydroxyl function. The product has weak ultraviolet maxima[14] at 265 mμ (ε 494) and 273 (454).

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.94; H, 7.42.

B. With Chromium(II) Chloride.—To a solution of 3.680 g. (13.6 mmoles) of keto lactone 19 in 200 ml. of acetone was added the aqueous solution of chromium(II) chloride prepared from 15.0 g. (56.2 mmoles) of chromium(III) chloride hexahydrate by reduction with zinc amalgam.[10a] After the resulting solution had been stirred at room temperature under a carbon dioxide atmosphere for 5 hr., the mixture was concentrated under reduced pressure, diluted with aqueous sodium chloride, and extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate, dried, and concentrated to leave 3.130 g. of the crude acid 21 as a white solid which was esterified with ethereal diazomethane. Recrystallization of the resulting crude ester (3.099 g.) from an ethyl acetate–hexane mixture afforded 2.509 g. (65%) of the pure keto ester 20 as white prisms, m.p. 92.5–94°. This product was identified with the previously described sample by a mixture melting point determination and comparison of infrared spectra.

Treatment of the Diketo Ester 20 with Sodium Methoxide.—A solution of 300 mg. (1.05 mmoles) of diketo ester 20 in methanolic sodium methoxide, prepared from 5 ml. of methanol and 60 mg. (2.6 mg.-atoms) of sodium was refluxed for 48 hr. The neutral product separated from 1-ml. aliquots withdrawn from this refluxing solution after 2 and 8 hr. exhibited only a single peak on gas chromatography[17] corresponding in retention time to the starting ester 20. The solution remaining after 48 hr. was diluted with ether and washed with aqueous sodium bicarbonate. The crude acid, isolated from the aqueous extract in the usual way, was esterified with diazomethane and, after recombination with material removed as 1-ml. aliquots, the crude ester (277 mg.) was distilled in a short-path still (180-200° at 0.05, mm.) to separate 179 mg. (59.7%) of the crude ester 20 as a yellow oil which crystallized on standing, m.p. 82–86°. This crude product, which has infrared absorption[18] and behavior on thin-layer[16] and gas chromatography[17] identical with the starting diketo ester, was recrystallized from a hexane–ethyl acetate mixture to separate 109 mg. (36.4%) of the pure diketo ester 20 91.5–93°, which was identified by a mixture melting point determination.

(20) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 1241 (1961).

The Transformation of 22,26-Oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol to 17-Iso,20-isocholestane Derivatives

MALCOLM J. THOMPSON,[1a] GOVINDAN V. NAIR,[1b] AND ERICH MOSETTIG[1c]

The National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda 14, Maryland

Received June 6, 1963

The reduction of 22,26-oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol in acidic media yields three 17-isocholestane derivatives. The major reduction product is a 17-iso,20-isocholestane-3β,16ξ-27-triol (IIIa). The conversion of IIIa to 17-iso,20-isocholestan-16ξ-ol (V), 17-iso,20-isocholestan-3β-ol (IXb), and 17-iso,20-isocholestane (IXa) is described.

In a previous publication[2] the structure of 22,26-oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol (I) was established. While ascertaining the structure of I, it was observed that the hydrogenation of I did not yield the expected 22,26-oxidocholestane-3β,16ξ-diol as the major product. Instead, three compounds were obtained, including a 22,26-oxido compound that was sterically different from the two epimeric 22,26-oxidocholestane-3β,16ξ-diols.[3] This paper is concerned with the hydrogenation of 22,26-oxido-$\Delta^{17(20)}$-cholestane-3β,16ξ-diol (I) and the proof of structure of the compounds so obtained. The transformation of the major reduction product, 17-iso,-20-isocholestane-3β,16ξ,27-triol (IIIa) to the formerly unknown 17-iso,20-isocholestan-3β-ol (IXb) and 17-iso,20-isocholestane (IXa) also is described.

Catalytic hydrogenation of I (PtO_2, 90% ethanol–acetic acid) gave II, IIIa, and IIIb in 23, 58, and 3% yields, respectively. Compound II obviously resulted from the saturation of the 17,20-double bond. It readily gave a diacetate indicating the presence of two hydroxyl groups and an inert ether oxygen. Oxidation of II with chromic acid gave the diketone XIII showing strong bands at 1712 and 1736 cm.$^{-1}$ of the 3- and 16-carbonyl bands. Since it may be assumed for steric reasons that the pyran ring in I is *trans* to the steroid skeleton, if hydrogen attacked from the back, II should be a 17-normal,20-isocholestane derivative.[4] The value of optical rotation of XIII indicates a 17-iso-compound (see Table I). The formation of such derivative (*i.e.*, 17-iso,20-normal) necessitates a front side attack of hydrogen on I. Compound II cannot be further reduced under the conditions employed. Furthermore XIII is sterically different from the two epimeric 22,26-oxidocholestane-3,16-diones[3] (see Table I). The mode of formation of these latter epimers demonstrated that they have the normal configuration at C-17 and C-20.

Our key compound IIIa, the major reduction product of I, is formulated as a 17-iso,20-isocholestane derivative because of its physical properties and a number of transformations elaborated later.[5] Acetylation of IIIa readily yielded a triacetate. Oxidation with chromic acid (acetone at 20°) gave 25-carboxy-17-iso,20-iso-26-norcholestane-3,16-dione (X), showing strong bands at 1709 (25-carboxy and 3-carbonyl groups) and 1733 (16-ketone), and the typical broad absorption of the carboxylic groups at 2500–2700 cm.$^{-1}$.

Apparently 16-keto steroids (see Table I) with a β-oriented side chain give high negative rotations. Therefore, the specific rotation +39° of XIII and +2° of X supports the assumption of the 17-iso configuration of these two compounds and consequently of II and IIIa.

Attempts to prepare the 17-iso,20-isocholestane-16ξ-ol derivative from IIIa *via* selective tosylation and subsequent lithium aluminum hydride reduction gave in good yields predominately the Δ^{16}-20-isocholestene (IVa). It should be remembered that under identical conditions, cholestane-3β,16β,27-triol gave cholestan-16β-ol.[6] When the tosylation of IIIa was carried out at 0°, subsequent reduction of the tosylate mixture with lithium aluminum hydride gave a mixture of at least four compounds. In order of their increasing adsorption on alumina Δ^{16}-20-isocholestene (IVa), 17-iso,-20-isocholestan-16ξ-ol (V), Δ^{16}-20-isocholesten-3β-ol (IVb), and 17-iso,20-isocholestane-3β,16ξ-diol (VI) were

TABLE I

Compound	$[\alpha]_D$, deg.	Compound	$[\alpha]_D$, deg.
17-Iso,20-isocholestan-16-one (VIIa)	+2	Cholestan-16-one	−117[a]
		Coprostan-16-one	−121[b]
		5-Cholestene-3β,27-diol-16-one	−156[c]
25-Carboxy-17-iso,20-iso-26-norcholestane-3,16-dione (X)	+2	25-Carboxycholestane-3,16-dione	−97[c]
22,26-Oxido-20ξ-methyl-17-isocholestane-3,16-dione (XIII)		22,26-Oxidocholestane-3,16-dione	−107[d]
	+39	22,26-Oxido-22-isocholestane-3,16-dione	−104[d]

[a] See ref. 9. [b] See ref. 6. [c] I. Scheer, M. J. Thompson, and E. Mosettig, *J. Am. Chem. Soc.*, **78**, 4733 (1956). [d] See ref. 3.

(1) (a) Insect Physiology Laboratory, Agricultural Research Center, Beltsville, Md.; (b) visiting scientist; (c) deceased, May 31, 1962.

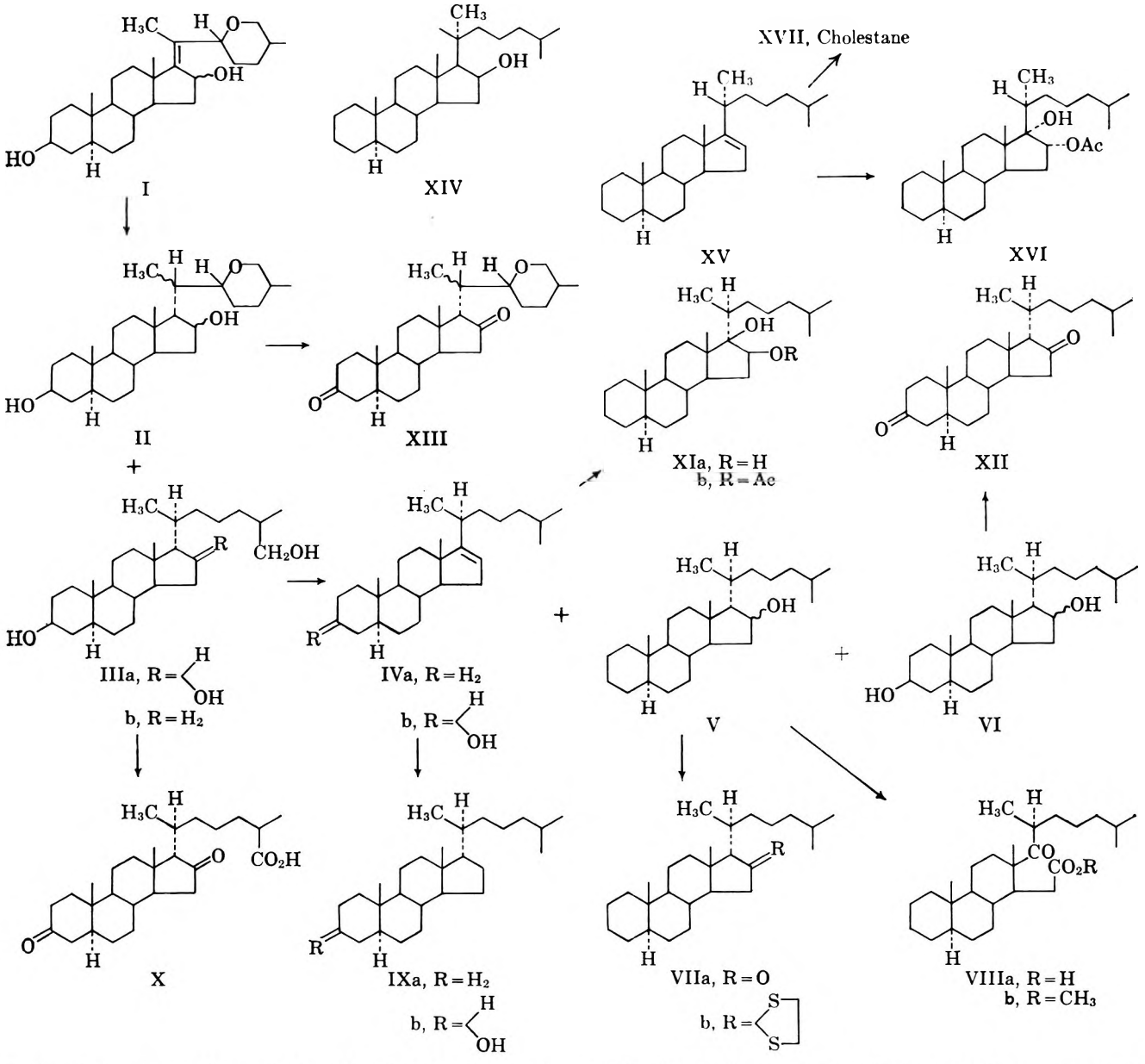
(2) M. J. Thompson, J. Moore, and E. Mosettig, *J. Org. Chem.*, **27**, 4108 (1962).

(3) I. Scheer, M. J. Thompson, and E. Mosettig, *J. Am. Chem. Soc.*, **79**, 3218 (1957).

(4) The configuration assignment at C-22 is arbitrary.

(5) The formation of IIIa from I may take place through: (A) opening of the pyrano ring (facilitated by the 17,20-double bond), and subsequent saturation of the double bond of an intermediate $\Delta^{17(20)}$-cholestene derivative; (B) 1,4-addition of hydrogen to the allylic ether and subsequent saturation of an intermediary $\Delta^{17(22)}$-cholestene derivative. No intermediate compound in the reduction of I and II has been detected. Pathway A necessitates the assumption of a *cis* *n*-hexyl side-chain and frontal attack of hydrogen at the C-17,C-20 double bond. For pathway B again one has to assume (in the first step) a frontal attack of hydrogen at C-17. The saturation of the 20,22-double bond can lead then either to a 17-iso,20-normal, or 17-iso,20-iso configuration.

(6) I. Scheer and E. Mosettig, *J. Am. Chem. Soc.*, **77**, 1820 (1955).



obtained in respective yields of 13, 35, 13, and 11%.[7]

Compound V gave a monoacetate (acetic anhydride, pyridine, steam bath). Treatment with chromic acid in acetone for only 2 min. gave quantitatively 17-iso,20-isocholestan-16-one (VIIa). A strong band at 1736 cm.$^{-1}$ and the low specific rotation of +2° support the assigned structure. When V was treated with an excess of chromic acid for 30 min., the keto acid VIIIa was obtained. Its methyl ester VIIIb exhibited two sharp bands in the carbonyl region at 1739 (ester carbonyl) and 1712 cm.$^{-1}$ (ketone). Oxidation of 16β-hydroxycholestane under similar conditions gave cholestan-16-one.

The optical rotatory dispersion curve of VIIa exhibits a weak negative single Cotton effect (α_{310} −249°, $\alpha_{272.5}$ +241°).[8] The rotatory dispersion curve of cholestan-16-one exhibits a very strong negative single Cotton effect (α_{320} −2900°, α_{277} + 3100°). While the troughs and peaks are nearly at the same wave lengths, the amplitude of the latter curve is more than ten times that of the former.[9] Analogous relations prevail in regards to the 17α-epimeric methyl-D-homoanalones.[10]

Compound VI readily gave a diacetate and brief treatment with chromic acid gave in good yield the dione which showed strong absorption bands at 1712 and 1736 cm.$^{-1}$.

The location of the double bond in IVa was confirmed through n.m.r. spectra and integration of the olefinic proton area, as well as chemically by hydroxylation and subsequent acetylation. Chromatography of the reaction product yielded as the sole product the hydroxy acetoxy derivative XIb which was not attacked by chromic acid. The Δ^{16}-hydrocarbon also was obtained by heating under reflux the tosylate of V in collidine. We then converted under identical conditions cholestan-16β-ol (XIV)[6] to Δ^{16}-cholestene (XV).[11] Compounds XV and IVa proved to be different. The 17-normal,20-

(7) The ease of dehydration to Δ^{16}-compounds (IVa and IVb) suggests α-orientations in IIIa and consequently in V and VI.

(8) We are obliged to Professor Djerassi for providing these data.

(9) C. Djerassi, O. Galpern, G. R. Pettit, and G. H. Thomas, *J. Org. Chem.*, **24**, 1 (1959); see also C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 45.

(10) 17a,α-Methyl-D-homoandrostan-3β-ol-17-one, α_{320} −463°, α_{281} +195°; 17aβ-methyl-D-homoandrostan-3β-ol-17-one, α_{316} −1723°, α_{275} +1308; see C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

(11) N.m.r. spectra and integration of the olefinic proton area showed only one proton indicating a trisubstituted double bond, *viz.*, $\Delta^{16(17)}$.

normal configuration of XIV appears to be reasonably well established through its relation to cholestane.[6,12]

The C-20 in IVa must have an iso configuration, which consequently must be true for all compounds experimentally linked to it. Hydroxylation of XV and subsequent acetylation as applied in IVa, yielded after chromatography the hydroxy acetoxy derivative (XVI), $[\alpha]D$ −47°, differing considerably in the specific rotation from XIb, $[\alpha]D$ +35°. This difference suggests that the side chain of XIb is α-oriented[13] or, in other words, that hydroxylation of IVa has taken place at the front side, in contrast to the hydroxylation of XV.

Catalytic hydrogenation of IVa yields apparently as the only product a crystalline, saturated hydrocarbon IXa, m.p. 99.5–100.5°, $[\alpha]D$ −2°, which again means that hydrogen has entered from the front side; otherwise the 17-normal cholestane would have been formed.[14] Hydrogenation of the Δ^{16}-cholestene (XV) under identical conditions gave cholestane (XVII). The reduction of IVb gave the 17-iso,20-isocholestan-3β-ol (m.p. 165–166°, $[\alpha]D$ −7°). The structure of 17-iso,20-isocholestane is assigned to IXa and IXb. This is further supported by comparison with 20-isocholestane which was synthesized in this laboratory[15] (m.p. 67–68°, $[\alpha]D$ +7.6°). Mixture melting point of IXa and 20-isocholestane showed an appreciable depression.

It is interesting, at this stage to confirm the observations made by Sondheimer and Mechoulam[13] and Plattner and Pataki[16] in their 20-iso series; the trend of optical rotation is towards negative values as epimerization proceeds *via* >20-iso, >17-iso, 20-iso series (see Table II).

TABLE II

Compound	M.p., °C.	$[\alpha]D$, deg.	MD, deg.
5α-Cholestane (17-*n*,20-*n*)	80	+25.9	+96.5
5α-Cholestane (17-*n*,20-iso)	68–69	+7.6[15]	+28.3
5α-Cholestane (17-iso,20-iso) IXa	99–100	−2.0	−7.5
5α-Cholestan-3β-ol (17-*n*,20-*n*)	144–145	+25.0	+97.7
5α-Cholestan-3β-ol (17-*n*,20-iso)	160–161	+6.0	+23.3
5α-Cholestan-3β-ol (17-iso,20-iso) IXb	165–166	−6.6	−28.8

[a] See ref. 15.

The physical properties and a number of transformations elaborated in the manuscript demonstrate that our key compound IIIa and the various compounds derived from IIIa are 17-iso,20-isocholestane derivatives and are structurally presented as the same in the scheme. The specific rotation +39° of XIII supports the assignment of the 17-iso configuration of XIII and consequently of II. Since the configuration at C-20 of these two compounds was not proven and could not be arrived at solely on mechanistic grounds, the configuration at C-20 is given the uncertain designation, namely "20ξ-methyl."

The physical properties, especially the $[\alpha]D$ of 17-iso,-20-isocholestane derivatives should be of significant help in determining the correct stereochemistry at C-17 of naturally occurring C_{27} sterols and steroids. It should be mentioned that the synthesis of the 17-iso,20-isocholestane derivatives leaves only one of the four possible isomers of the cholestane side chain to be synthesized, namely, the 17-iso,20-normal cholestane.

Experimental[17]

Reduction of 22,26-Oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol (I).—A mixture of 2.0 g. of 22,26-oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol (I), 0.5 g. of Adams catalyst, 275 ml. of 95% ethanol, and 25 ml. of glacial acetic acid was shaken with hydrogen at room temperature and atmospheric pressure for 24 hr. Approximately 2.2 molecular equivalents of hydrogen was absorbed. The catalyst was removed by filtration and the solution was concentrated to dryness *in vacuo*. The residue recrystallized from ethyl acetate–methanol to give 1.16 g. of **17-iso,20-isocholestane-3β,16ξ,27-triol (IIIa)** as rods, m.p. 243–247°. A second recrystallization raised the melting point to 246–248°, $[\alpha]D$ +20°.

Anal. Calcd. for $C_{27}H_{48}O_3$: C, 77.09; H, 11.50. Found: C, 76.92; H, 11.22.

The triacetate of IIIa (acetic anhydride–pyridine, steam bath, 2 hr.) was obtained as rectangular plates from dilute methanol, m.p. 119–120°, $[\alpha]D$ +6°.

Anal. Calcd. for $C_{33}H_{54}O_6$: C, 72.59; H, 9.96; acetyl, 23.6. Found: C, 72.53; H, 9.67; acetyl, 23.1.

20ξ-Methyl,22,26-oxido-17-isocholestane-3β,16ξ-diol (II).—The mother liquor from the catalytic hydrogenation of the 22,26-oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol (I), described before, was concentrated to dryness *in vacuo* and the residue was chromatographed on benzene-washed alumina (activity grade II). The crystalline fractions eluted with benzene–chloroform (9:1) and (6:1) and exhibiting identical infrared spectra were combined and recrystallized from acetone to give 0.46 g. of II as spears, m.p. 191–194°, $[\alpha]D$ +25°. Prolonged drying under high vacuum at 140° was required to free II of solvent.

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.30; H, 10.82.

Further elution of the column with benzene–chloroform (3:1) yielded 60 mg. of **17-iso,20-isocholestane-3β,27-diol (IIIb)** as needles from acetone, m.p. 194–195°, $[\alpha]D$ +3°.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.13; H, 11.95. Found: C, 80.42; H, 11.84.

The diacetate of II (acetic anhydride–pyridine, 18 hr., 25°) was obtained as rectangular plates from dilute methanol, m.p. 171–173°, $[\alpha]D$ +5°.

Anal. Calcd. for $C_{31}H_{50}O_5$: C, 74.06; H, 10.02. Found: C, 74.21; H, 9.79.

20ξ-Methyl,22,26-oxido-17-isocholestane-3,16-dione (XIII).—To a stirred solution of 50 mg. of 20ξ-methyl,22,26-oxido-17-isocholestane-3β,16ξ-diol (II) in 5 ml. of acetone at 10° was added, dropwise, an 8 *N* solution of chromic acid in dilute sulfuric acid (*ca.* 40%) until a persistent orange-brown coloration indicated oxidation was completed.[18] The mixture was kept at 10° for 15 min., diluted with water, and the white crystalline precipitate was collected, washed with water, and dried to yield 40 mg. of XIII, m.p. 161–165°. Recrystallization from dilute acetone gave elongated needles, m.p. 173–175°, $[\alpha]D$ +39°, ν^{CHCl_3} 1736 (16-ketone) and 1712 (s, 3-ketone) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.42; H, 10.26.

(12) R. E. Marker and D. L. Turner, *J. Am. Chem. Soc.*, **63**, 767 (1941).

(13) The difference between cholesterol and 20-isocholesterol, *i.e.*, the contribution of the 20-methyl to optical rotation, is apparently quite small: see (a) F. Sondheimer and R. Mechoulam, *ibid.*, **80**, 3087 (1958); (b) R. Hayatsu, *ibid.*, **77**, 823 (1957); (c) K. Tsuda, R. Hayatsu, Y. Kishida, and S. Akagi, *ibid.*, **80**, 921 (1958).

(14) Attempts to arrive at IXa *via* VIIb failed, presumably because of partial inversion of VIIa during formation of the thioketal. The infrared spectra of IXa and the hydrocarbon mixture (m.p. 76–78°, $[\alpha]D$ +4°) obtained by desulfurization differed only slightly. Ketone VIIa, $[\alpha]D$ +2°, was isomerized by refluxing for 2 hr. with 5% methanolic potassium hydroxide to a product of m.p. 89° and $[\alpha]D$ −60°, which is either 20-isocholestan-16-one or a mixture of the latter and 17-iso,20-isocholestan-16-one (VIIa).

(15) G. V. Nair and E. Mosettig, *J. Org. Chem.*, **27**, 4659 (1962).

(16) P. A. Plattner and J. Pataki, *J. Chim. Acta*, **36**, 1241 (1943).

(17) All melting points were determined on the Kofler block. Rotations were determined in approximately 1% solutions in chloroform at 20°. Infrared spectra were obtained with a Perkin-Elmer Model 21 double beam spectrophotometer with sodium chloride prism and cells. N.m.r. spectra were obtained with a Varian HR-60 spectrometer. Deuteriochloroform was used as solvent and all data are reported in cycles per second referred to tetramethylsilane as an internal reference.

(18) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem Soc.*, 2548 (1953).

25-Carboxy-17-iso,20-iso-26-norcholestane-3,16-dione (X).—To a stirred solution of 120 mg. of 17-iso,20-isocholestane,3β,16ξ,-27-triol (IIIa) in acetone at 20° was added a slight excess of an 8 *N* solution of chromic acid in dilute sulfuric acid and stirring was continued for 2 min. The mixture was diluted with water and the crystalline precipitate was collected, washed with water, and dried to yield 100 mg. of X, m.p. 194–196°. Recrystallization from dilute acetone gave rectangular plates, m.p. 195–197°, $[\alpha]_D$ +2°; ν^{CHCl_3} 2700–2500 (wb), 1709 (s, 3-ketone and carboxy carbonyl), and 1733 (s, 16-ketone) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.30; H, 9.83. Found: C, 75.56; H, 9.66.

Tosylation and Subsequent Lithium Aluminum Hydride Reduction of 17-Iso,20-isocholestane-3β,16ξ,27-triol (IIIa).—To a solution of 2.2 g. of IIIa in 67 ml. of dry pyridine at 0° was added 3.4 g. of *p*-toluenesulfonyl chloride. The solution was allowed to stand overnight at 0°, was poured into ice and water, and the precipitate was extracted with ether. The ethereal solution was washed with cold 5% hydrochloric acid, water, 2% sodium bicarbonate solution, water, and dried over sodium sulfate. On evaporation *in vacuo* a semicrystalline residue was obtained. The residue was dissolved in 400 ml. of dry ether and 2.0 g. of solid lithium aluminum hydride was added. The mixture was refluxed overnight, cooled, treated with a few drops of ethyl acetate, water, and 20 ml. of 4 *N* hydrochloric acid. The ether layer was separated and washed with 5% bicarbonate solution and water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. The semicrystalline residue was chromatographed over 9:1 benzene–petroleum ether (b.p. 60–70°) washed alumina (activity grade II). The first two fractions eluted with benzene–petroleum ether (9:1) crystallized from ether–methanol to give 0.25 g. of **$\Delta^{16(17)}$-20-isocholestene (IVa)** as spears, m.p. 87–90°, $[\alpha]_D$ −33°. This material gave a positive tetranitromethane test. N.m.r. intergration of the olefinic proton area showed only one proton indicating a trisubstituted double bond.

Anal. Calcd. for $C_{27}H_{46}$: C, 87.49; H, 12.51. Found: C, 87.67; H, 12.08.

Further elution of the column with benzene–petroleum ether (9:1) afforded after crystallization from methanol 0.7 g. of **17-iso,20-isocholestan-16ξ-ol (V)**, m.p. 181–183°, $[\alpha]_D$ +19°.

Anal. Calcd. for $C_{27}H_{48}O$: C, 83.43; H, 12.44. Found: C, 83.70; H, 12.13.

The acetate of V (acetic anhydride–pyridine, 1 hr., steam bath) was obtained as plates, m.p. 141–142°, $[\alpha]_D$ +20°.

Anal. Calcd. for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 81.09; H, 11.31.

Elution of the column with benzene after the separation of V yielded, after crystallization from methanol, needles of **$\Delta^{16(17)}$-20-isocholesten-3β-ol (IVb)**, 0.26 g., m.p. 165–167°, $[\alpha]_D$ −26°. This compound gave a positive tetranitromethane test.

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.86; H, 11.99. Found: C, 83.77; H, 11.85.

Continued elution of the column with benzene–chloroform (3:1) yielded 0.25 g. of **17-iso,20-isocholestane-3β,16ξ-diol (VI)**, m.p. 221–222°, $[\alpha]_D$ +21°.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96. Found: C, 80.07; H, 12.01.

The diacetate of VI (acetic anhydride–pyridine, 1 hr., steam bath) was obtained as needles from dilute methanol, m.p. 116–120°, with resolidification and remelting at 134–137°. After prolonged drying under high vacuum at 110°, the melting point was 137–139°, $[\alpha]_D$ +7°.

Anal. Calcd. for $C_{31}H_{52}O_4$: C, 76.18; H, 10.72. Found: C, 76.44; H, 10.31.

17-Iso,20-isocholestan-16-one (VIIa).—To a stirred solution of 0.3 g. of 17-iso,20-isocholestan-16ξ-ol (V) in 30 ml. of acetone at 15° was added a slight excess of 8 *N* solution of chromic acid in dilute sulfuric acid, and after 2 min. the mixture was diluted with water. The precipitate was collected, washed with water, and dried. The dried material (0.28 g.) was dissolved in benzene–petroleum ether (3:1) and filtered through a layer of Florisil. The solvent was removed *in vacuo* and the residue recrystallized from ethanol yielded as needles 0.25 g. of VIIa, m.p. 137–138°, $[\alpha]_D$ +2°; ν^{CS_2} 1736 (s, 16-ketone) cm.$^{-1}$; R.D. (*c* 0.09, methanol) trough at α_{310} −249°, peak at α_{272} +241°.

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.97; H, 11.73.

When the alcohol (V) in acetone at 25° was treated with an excess of 8 *N* solution of chromic acid in dilute sulfuric acid for 30 min., the **keto acid (VIIIa)** was obtained, m.p. 197–199°, $[\alpha]_D$ +90°.

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.25; H, 11.02.

Treatment of VIIIa with diazomethane in the usual manner gave the **methyl ester (VIIIb)**, m.p. 184–187°, $[\alpha]_D$ +96° ν^{CS_2} 1739 (ester carbonyl) and 1712 (ketone) cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{48}O_3$: C, 77.72; H, 11.19. Found: C, 77.34; H, 10.91.

17-Iso,20-isocholestan-16-one 16-Ethylenethioketal (VIIb).—To a solution of 70 mg. of 17-iso,20-isocholestan-16-one (VIIa) in 2 ml. of acetic acid was added 0.2 ml. of ethanedithiol and 0.2 ml. of boron fluoride in ether. The mixture was allowed to stand overnight at room temperature diluted with water and precipitate collected. Recrystallization from ether–methanol gave 50 mg. of VIIb as needles, m.p. 183–186° and 190–194°, $[\alpha]_D$ +8°.

Anal. Calcd. for $C_{29}H_{50}S_2$: C, 75.25; H, 10.85. Found: C, 75.05; H, 10.84.

Isomerization of VIIa.—A mixture of 53 mg. of 17-iso,20-isocholestan-16-one (VIIa, $[\alpha]_D$ +2°) and 10 ml. of 5% methanolic potassium hydroxide was refluxed for 2 hr. The mixture was diluted with water and extracted with ether. The ethereal solution was washed with water and dried over sodium sulfate. The solution was concentrated to dryness *in vacuo*. Crystallization from methanol gave 40 mg. of plates, m.p. 88–91°, $[\alpha]_D$ −60°; ν^{CS_2} 1736 (s, 16-ketone) cm.$^{-1}$.

17-Iso,20-isocholestane-3,16-dione (XII).—Oxidation of 100 mg. of 17-iso,20-isocholestane-3β,16ξ-diol (VI) as was described for the preparation of VIIa gave 95 mg. of XII as needles, m.p. 170–175°. Two recrystallizations from ethanol gave 70 mg. of material, m.p. 174–176°, $[\alpha]_D$ +18°; ν^{CS_2} 1712 (s, 3-ketone) and 1736 (s, 16-ketone) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.68; H, 10.81.

Hydroxylation and Subsequent Acetylation of $\Delta^{16(17)}$-20-Isocholestene (IVa).—A mixture of 100 mg. of $\Delta^{16(17)}$-20-isocholestene (IVa), 10 ml. of dry ether, 100 mg. of osmium tetroxide, and two drops of pyridine was allowed to stand for 24 hr. at room temperature. Hydrogen sulfide was passed through the mixture and the black precipitate of osmium sulfide was collected. The ether was evaporated *in vacuo* to a crystalline residue, which was dissolved in 10 ml. of benzene and chromatographed over Florisil. The first 25-ml. fraction of benzene yielded 30 mg. of starting material IVa. The column was then eluted with benzene–chloroform (1:1) to yield crystalline material. This material was acetylated (acetic anhydride–pyridine, steam bath, 2 hr.). The crystalline material was chromatographed over neutral alumina (activity grade II). The fraction eluted with 6:1 benzene–petroleum ether (b.p. 60–70°) upon recrystallization from dilute methanol yielded 65 mg. of XIb as elongated needles, m.p. 167–169°; after drying at 100° under high vacuum, m.p. 179–180°, $[\alpha]_D$ +35°; ν^{CS_2} 1745 (s, acetate) and 3571 (hydroxyl) cm.$^{-1}$. This material was not attacked by chromic acid solution under mild conditions.

Anal. Calcd. for $C_{29}H_{50}O_4$: C, 77.97; H, 11.28. Found: C, 78.19; H, 11.18.

The Glycol (XIa).—Saponification of XIb with 2% methanolic potassium hydroxide solution gave the glycol XIa in 90% yield, needles from dilute methanol, m.p. 201–203°, $[\alpha]_D$ +10°.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.13; H, 11.96. Found: C, 80.36; H, 12.09.

$\Delta^{16(17)}$-Cholestene (XV).—A mixture of 650 mg. of cholestan-16β-ol (XIV) and 1.1 g. of *p*-toluenesulfonyl chloride was allowed to stand overnight at room temperature. The mixture was poured into ice and water, and extracted with ether. The ethereal solution was washed with water, 2% sodium bicarbonate solution, water, dried over sodium sulfate, and concentrated to dryness *in vacuo*. To the oily tosylate was added 50 ml. of dry collidine and the mixture was refluxed for 30 min. The collidine was removed *in vacuo* and the residue was treated with petroleum ether. The insoluble residue was removed by filtration and the petroleum ether filtrate was passed through a column of activity grade II alumina. The first two fractions eluted with petroleum ether yielded 418 mg. of an oily hydrocarbon. Crystallization from acetone gave 206 mg. of $\Delta^{16(17)}$-cholestene (XV), m.p. 65–66°, $[\alpha]_D$ +6°. The infrared spectra of XV and IVa were different. N.m.r. integration of the olefinic proton area showed one olefinic proton, indicating a trisubstituted double bond, *viz.*, $\Delta^{16(17)}$.

Anal. Calcd. for $C_{27}H_{46}$: C, 87.49; H, 12.51. Found: C, 87.65; H, 12.34.

Hydroxylation and Subsequent Acetylation of $\Delta^{16(17)}$-Cholestene (XV).—As in the prior preparation of XIb, 50 mg. of $\Delta^{16(17)}$-cholestene and 100 mg. of osmium tetroxide were allowed to stand at room temperature overnight. The crystalline glycol thus obtained was acetylated (acetic anhydride–pyridine, steam bath, 2 hr.). Careful chromatography of the crystalline acetate yielded 44 mg. of the hydroxy acetate (XVI) as the only product, m.p. 174–175°, $[\alpha]D$ −47°; ν^{CS_2} 1745 (s, acetate) and 3571 (hydroxyl) cm.$^{-1}$. The infrared spectra of XIb and XVI were different.

Anal. Calcd. for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 78.26; H, 11.33.

17-Iso,20-isocholestane (IXa).—A mixture of 0.3 g. of $\Delta^{16(17)}$-20-isocholestene (IVa), 1.0 g. of 10% palladium on charcoal, 25 ml. of ethyl acetate, and 10 ml. of acetic acid was shaken with hydrogen at room temperature and pressure for 2 hr. The crystalline residue obtained from the reaction gave 250 mg. of plates, m.p. 98–99°. A second recrystallization from ether–methanol gave 235 mg. of IXa, m.p. 99.5–100.5°, $[\alpha]D$ −2°, negative tetranitromethane test.

Anal. Calcd. for $C_{27}H_{48}$: C, 87.02; H, 12.98. Found: C, 87.10; H, 12.71.

Hydrogenation of $\Delta^{16(17)}$-cholestene (XV) under similar conditions gave cholestane (XVII), m.p. 78–79°. Mixture melting point with an authentic sample of cholestane showed no depression. The compounds had identical infrared spectra.

The Raney nickel reduction of the 17-iso,20-isocholestan-16-one 16-ethylenethioketal (VIIb) afforded plates from ether–methanol, m.p. 76–78°, $[\alpha]D$ +4°. The infrared spectra of this material and the substance obtained from catalytic hydrogenation of IVa were different.

17-Iso,20-isocholestan-3β-ol (IXb).—A mixture of 100 mg. of $\Delta^{16(17)}$-20-isocholesten-3β-ol (IVb), 50 ml. of ethyl acetate, 5 ml. of acetic acid, and 50 mg. of platinum oxide was shaken with hydrogen at room temperature and pressure. The crystalline residue crystallized from ethanol gave needles, m.p. 160–163°. The material recrystallized twice from ethanol gave 60 mg. of needles, m.p. 165–166°, $[\alpha]D$ −6.6°. Mixture melting point with 20-isocholestan-3β-ol (m.p. 160–161°)[15] showed a depression, m.p. 130–137°.

Anal. Calcd. for $C_{27}H_{48}O$: C, 83.43; H, 12.45. Found: C, 83.70; H, 12.22.

Acknowledgment.—The authors are indebted to Dr. G. Rosenkranz, Syntex, S. A., Mexico, for a generous supply of kryptogenin. Microanalyses are by the Analytical Service Laboratory of this Institute, under the direction of Mr. H. G. McCann. We wish to thank Dr. Edwin Becker of this Institute for the n.m.r. data. Infrared spectra were determined by Mr. H. K. Miller, Mrs. A. Wright, and Mr. R. T. Brown.

Telomerization by Free-Radical Mercaptan Chain Transfer. II. Telomers of Acrylate Esters with Simple Thiols[1,2]

GEORGE P. SCOTT, CHIA CHU SOONG, WANN-SHENG HUANG, AND JON L. REYNOLDS

Department of Chemistry, University of South Dakota, Vermillion, South Dakota

Received August 14, 1963

Preparation and characterization of ten telomers formed from acrylate esters in reactions with methyl and ethyl mercaptans are reported. Determination of the first three telomerization chain transfer constants and the polymerization chain transfer constant for the methyl acrylate–ethanethiol system is also described. The two-unit transfer constant is about equal to the polymerization constant, but the three-unit constant is substantially higher than either. This suggests that a reactivity minimum exists for the three-unit radical such as has been reported for bromotrichloromethane telomers. A possible explanation is suggested.

Studies of telomerization of several monomers with bromotrichloromethane[3] have yielded evidence for an unexplained reactivity minimum in radical chains three or four units long. Propagation rate constants (k_p) are reported to be significantly lower for these lengths than for shorter or longer chains. Rate constants for chain transfer (k_d) are much less reduced; hence the Mayo chain transfer constants ($C_n = k_d/k_p$) show a corresponding maximum.

Some exchange reaction or interaction involving the chain end seems implied by these findings, but its nature is still obscure. Kirkham and Robb[3b] suggested a "semibond" interaction between a terminal chlorine atom and the radical-bearing carbon. In three- and four-unit chains these are eight and ten atoms apart respectively, which are usually considered improbable intervals for maximum direct interaction. However, there is some uncertainty about the chain sizes involved since the experiments on which these results are based do not involve quantitative separation of telomer products.

Kharasch and Fuchs[4] showed that methyl acrylate yields mixtures of volatile telomers when it reacts with ethanethiol in the presence of a free-radical initiator; hence acrylate esters and low molecular weight thiols appear to be promising systems for telomerization studies involving discrete separations of products by gas chromatography. This paper reports identification and characterization of ten acrylate ester telomers with methyl and ethyl mercaptans. Determination of several chain transfer constants in the methyl acrylate–ethanethiol system, which show some evidence for a reactivity minimum, also are described.

A procedure for obtaining telomer chain transfer constants similar to that described by Scott and Wang[2] was employed. This has the advantage that only ratios of successive telomer concentrations formed at low conversion and varying monomer to thiol ratios need to be measured. Chances for experimental errors are thereby minimized. The polymerization chain transfer

(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research; (b) presented in part at the 144th National meeting of the American Chemical Society, Division of Polymer Chemistry, Los Angeles, Calif., April, 1963

(2) Paper I in this series, G. P. Scott and J. C. Wang, *J. Org. Chem.*, **28**, 1314 (1963).

(3) (a) J. C. Robb and E. Senogles, *Trans. Faraday Soc.*, **58**, 708 (1962); (b) W. J. Kirkham and J. C. Robb, *ibid.*, **57**, 1757 (1961); (c) J. C. Robb and D. Vofsi, *ibid.*, **55**, 558 (1959); (d) W. I. Bengough and R. A. M. Thompson, *ibid.*, **57**, 1928 (1961); (e) **56**, 407 (1960).

(4) M. S. Kharasch and C. F. Fuchs, *J. Org. Chem.*, **13**, 97 (1948).

TABLE I

ACRYLATE ESTER TELOMERS AND DERIVATIVES

	Physical[a] constants	Formula	Analysis,[b] % Calcd.	Found
Methyl acrylate–methanethiol				
One-unit telomer[c]	B.p. 118–119° (2 mm.)	$C_6H_{10}O_2S$	*h*	
	$n^{25}D$ 1.4668			
One-unit sulfone	M.p. 96.5°	$C_6H_{10}O_4S$	*h*	
Two-unit telomer[d]	B.p. 158–160° (2 mm.)	$C_9H_{16}O_4S$	C 49.05	49.20
	$n^{25}D$ 1.4759		H 7.27	7.63
Two-unit sulfone	M.p. 71.0–72.0°	$C_9H_{16}O_6S$	C 42.46	42.48
			H 6.35	6.95
			S 12.69	12.70
Methyl acrylate–ethanethiol				
One-unit telemer[e]	B.p. 73.0–75.0° (1.5 mm.)	$C_6H_{12}O_2S$	C 48.62	48.67
	$n^{28}D$ 1.4589		H 8.16	8.00
One-unit acid sulfone[i]	M.p. 115–116°	$C_5H_{10}O_4S$	C 36.13	36.25
			H 6.07	6.23
			S 19.29	19.40
One-unit benzylamide	M.p. 50–51°	$C_{12}H_{17}ONS$	C 64.53	64.67
			H 7.67	7.88
			S 14.36	14.53
Two-unit telomer[f]	B.p. 110–112° (0.3 mm.)	$C_{10}H_{18}O_4S$	C 51.26	51.45
	$n^{28}D$ 1.4664		H 7.74	7.71
Two-unit benzylamide	M.p. 138–139°	$C_{22}H_{28}O_2N_2S$	C 68.71	68.50
			H 7.34	7.12
			S 8.34	8.10
Three-unit telomer[g]	B.p. 164–166° (0.2 mm.)	$C_{14}H_{24}O_6S$	C 52.48	52.42
	$n^{28}D$ 1.4692		H 7.55	7.46
			S 10.01	9.87
Ethyl acrylate–ethanethiol				
One-unit telomer[e]	B.p. 53–55° (0.3 mm.)	$C_7H_{14}O_2S$	C 51.82	52.00
	$n^{27}D$ 1.4543		H 8.70	8.88
Two-unit telomer[f]	B.p. 123–125° (0.5 mm.)	$C_{12}H_{22}O_4S$	C 54.93	54.77
	$n^{27}D$ 1.4593		H 8.12	8.48
Three-unit telomer[g]	B.p. 177–179° (0.2 mm.)	$C_{17}H_{30}O_6S$	C 56.33	56.39
	$n^{27}D$ 1.4615		H 8.35	8.49
			S 8.85	8.95
Isopropyl acrylate–ethanethiol				
One-unit telomer[e]	B.p. 41–43 (0.4 mm.)	$C_8H_{16}O_2S$	C 54.51	54.49
	$n^{26}D$ 1.4517		H 9.15	9.18
Two-unit telomer[f]	B.p. 101–103° (0.3 mm.)	$C_{14}H_{26}O_4S$	C 57.90	58.24
	$n^{26}D$ 1.4517		H 9.02	9.12

[a] Melting points and boiling points are uncorrected. [b] Microanalyses are by Galbraith Laboratories, Knoxville, Tenn., and Mikrotech Laboratories, Skokie, Ill. [c] 3-Thiomethylpropionic acid methyl ester. [d] 2-Thiomethylethylglutaric acid dimethyl ester. [e] 3-Thioethylpropionic acid methyl, ethyl, and isopropyl esters. [f] 2-Thioethylmethylglutaric acid dimethyl, diethyl, and diisopropyl esters. [g] 6-Thioethyl-1,3,5-hexanetricarboxylic acid trimethyl and triethyl esters. [h] Sulfone m.p. 94.0–94.6° reported; A. J. Haagen-Smit, J. G. Kirchner, C. L. Deasy and A. N. Prater, *J. Am. Chem. Soc.*, **67**, 1651 (1945). [i] *Cf.* ref. 4.

constant C_∞ was determined by the method of Gregg, Alderman, and Mayo.[5]

Experimental

Materials.—Commercial grade thiols and acrylate esters were redistilled twice just prior to each experiment; fractions boiling over a 1° range were used. Other materials of best commercial grades were used without further purification.

Preparation and Isolation of Telomers.—Mixtures of ester and thiol in mole ratios (ester/thiol) of 0.9 to 1.3 were sealed with 0.1 to 0.5 mole % of azobisisobutyronitrile (AIBN) in 30-ml. Pyrex tubes and heated at 50° for periods of 2.0 to 24 hr. After removing unchanged thiol and ester with a water aspirator, mixtures were fractionated at low pressures. Major fractions were redistilled and the purity of the resulting samples checked by gas chromatography. Additional distillations were carried out when necessary.

Sulfones.—In each case esters were treated with excess 30% hydrogen peroxide in glacial acetic acid. Attempts were made to crystallize the resulting oils from various solvents. Ester sulfones formed from the methanethiol telomers. The one-unit sulfones from the ethanethiol telomers hydrolyzed to the acid sulfone before crystallizing. The higher ethanethiol telomers gave only oils.

Benzylamides.—A mixture of methyl acrylate–ethanethiol one-unit telomer (1.0 g.), 3.0 ml. of benzylamine, and 0.1 g. of powdered ammonium chloride was heated for 1 hr. in an oil bath under a gentle reflux. The resulting mixture was washed with water and crystallized in the presence of a little hydrochloric acid. The product was recrystallized twice from a mixture of petroleum ether (b.p. 70–90°) and a little ethyl acetate.

Preparation of the benzylamide from the two-unit telomer was carried out in the same way except that the relative amount of benzylamine was twice as great. The yield of this amide was small.

Determination of Telomer Chain Transfer Constants.—Mixtures of methyl acrylate and ethanethiol of varying mole ratios totaling 4 to 6 g. containing AIBN (0.1–0.4 mole % of the thiol) were sealed in acid-washed, nitrogen-filled 8-ml. Pyrex tubes and heated 0.5 to 4.5 hr. in a constant temperature bath at 50.0 ± 0.5°. Gas chromatograms of the resulting mixtures were run at 100° on a 0.5 in. × 5 ft. column containing 60/80 firebrick coated with 20% GE-SF-96 silicone oil using methanol as an internal standard to determine per cent of methyl acrylate consumed. If more than 10% had been consumed, the run was rejected. The column was then heated to 250° and several chromatograms

(5) R. A. Gregg, D. M. Alderman, and F. R. Mayo, *J. Am. Chem. Soc.*, **70**, 3740 (1948).

run, interspersed with chromatograms of prepared standard mixtures of one- and two-unit telomers similar in ratio to the sample, to calculate the one- to two-unit telomer ratios formed in each reaction. Relatively large injections (up to 60 μl.) were required for each chromatogram owing to the high per cent of starting material present. Reaction mixtures were stored in Dry Ice and acetone to avoid further reaction and analyzed as soon as possible.

In runs used for measurement of ratios of two- to three-unit telomers, the same procedure was followed except that a 0.25 in. × 15 ft. column containing 60/80 firebrick coated with 20% SE-30 silicone oil was used and the column temperature was raised to 300°.

Determination of Polymerization Chain Transfer Constants.—Mixtures of methyl acrylate containing 0.0145 mole of ethanethiol and 0.00029 mole of AIBN per mole of ester were sealed in 30-ml. acid-washed, nitrogen-filled Pyrex tubes and heated in a constant temperature bath at 50.0 ± 0.5° until the polymerization had proceeded to the desired extent as indicated by an increase in viscosity of the mixture. Tubes were then stored at −20° until they could be analyzed for thiol and ester remaining.

The per cent of ethanethiol remaining was measured by amperometric titration.[6] To avoid appreciable interference by methyl acrylate, the following procedure was used. Aliquots of only 0.50 ml. were injected into a titration cell containing 100 ml. of methanol, 2 ml. of 5 *M* ammonium nitrate, and 1.5 ml. of 4 *M* ammonium hydroxide vigorously stirred by a magnetic stirrer (as well as the rotating platinum electrode) in an ice bath maintaining the temperature below 10°. Titration with 0.0035 *N* silver nitrate was carried out as rapidly as possible guided by a rough preliminary titration to determine the approximate end point.

Determination of the per cent methyl acrylate remaining was carried out by gas chromatography as described in the preceding section except that acetone was used as the internal standard instead of methanol.

Results

Telomers and Derivatives.—Properties of telomers and derivatives prepared so far are listed in Table I.

All telomers were colorless liquids; the increase in viscosity for the higher telomers was very noticeable. Attempts to prepare satisfactory solid derivatives to characterize these products have been only partially successful because of the reluctance of many of the usual products to crystallize. The three-unit telomers were presumably mixtures of isotactic and syndiotactic diastereomers (two *dl* pairs); however, in attempts to separate these forms of the methyl acrylate three-unit telomer on a 15-ft. column, it behaved like a pure compound. Telomers higher than three-unit have not been separated owing to their high boiling points.

These products are quite stable. Heating the one-unit methyl acrylate telomer 24 hr. at 50° in the presence of 1 mole % AIBN (as described in ref. 2) indicated that less than 1% had decomposed to give back methyl acrylate and ethanethiol. No decomposition at all was noted in the two-unit telomer under the same conditions.

Chain Transfer Constants.—Data for determination of telomer chain transfer constants are listed in Table II. The telomer ratios at less than 10% conversion are assumed[2] to closely approximate the left side of eq. 1

$$\frac{d[B - M_n - A]}{d[B - M_{n+1} - A]} = C_n[AB]/[M] + C_n/C_{n+1} \qquad (1)$$

where [AB] and [M] are the monomer and thiol concentrations, respectively, and C_n and C_{n+1} refer to C_1 and C_2, or C_2 and C_3. The linear slopes of one- to two-unit telomer ratios (runs 1 through 6) and two- to three-unit telomer ratios (runs 7 through 11) obtained by least squares calculations are equal to C_1 and C_2, respectively (see Fig. 1). The intercepts equal C_1/C_2 and C_2/C_3. From these a check value for C_2 and a value for C_3 are calculated.

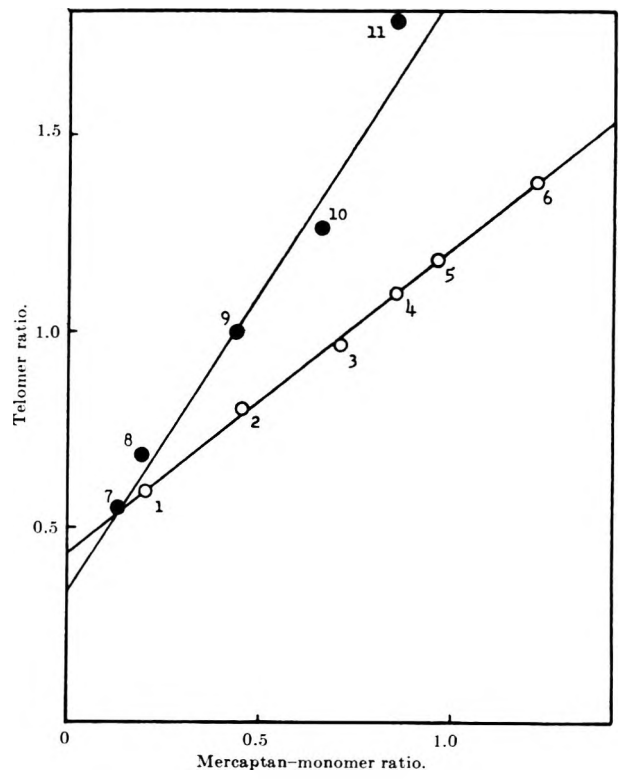


Fig. 1.—One-unit to two-unit telomer mole ratio, ○, and two-unit to three-unit telomer mole ratio, , plotted against ethanethiol to methyl acrylate mole ratio.

TABLE II

DATA FOR CALCULATION OF TELOMER CHAIN TRANSFER CONSTANTS FOR METHYL ACRYLATE AND ETHANETHIOL AT 50°

Run no.	Mole ratio EtSH–acrylate	Mole % AIBN (compared to EtSH)	Time, hr.	Methyl acrylate consumed, %	Mole ratio, one-unit–two-unit	Mole ratio, two-unit–three-unit
1	0.202	0.28	3.2	5.4	0.590	
2	.457	.26	2.0	7.4	.801	
3	.712	.25	1.1	3.3	.969	
4	.854	.28	1.0	5.0	1.100	
5	.960	.21	1.0	10.0	1.182	
6	1.220	.27	0.6	9.4	1.385	
7	0.130	.38	4.5	4.7		0.550
8	.189	.34	2.7	5.1		.715
9	.444	.25	1.4	2.8		.995
10	.655	.22	1.5	8.6		1.270
11	.842	.12	1.0	9.8		1.810

Determination of the polymerization chain transfer constant C_n was complicated by the fact that methyl acrylate interferes seriously with the amperometric titration method of Kolthoff and Harris[6] under the usual conditions presumably because of the rapid base-catalyzed addition of mercaptan to acrylate on mixing with ammonia. It was found, however, that in mixtures containing enough mercaptan to titrate with small aliquots, results within 2% of the values found in the absence of acrylate could be obtained consistently by

(6) I. M. Kolthoff and W. E. Harris, *Ind. Eng. Chem., Anal. Ed.*, **18**, 161 (1946).

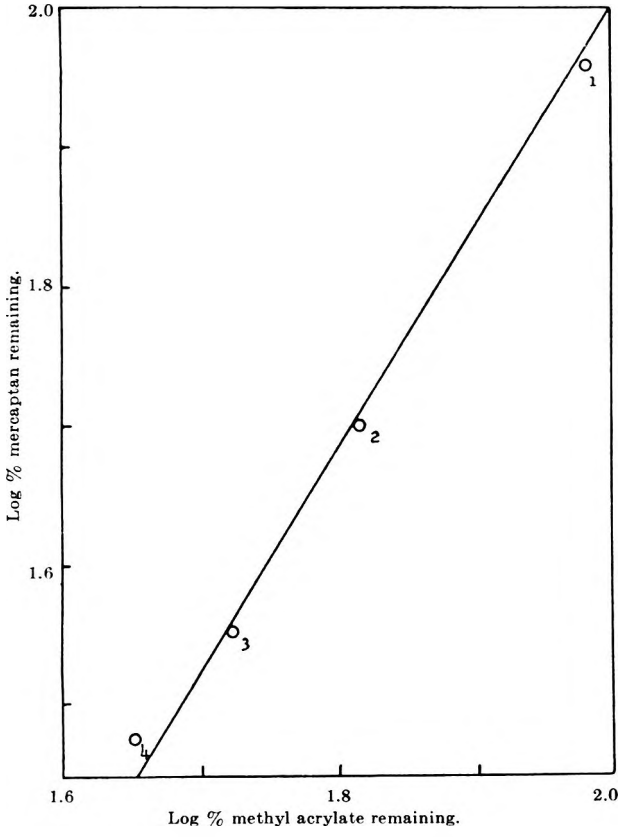


Fig. 2.—Data for determination of polymerization chain transfer constant.

rapid titration below 10° using reduced base concentration (see Experimental). Data for this are recorded in Table III and plotted in Fig. 2.

TABLE III

DATA FOR CALCULATION OF C_∞ FOR METHYL ACRYLATE AND ETHANETHIOL AT 50°

Run no.[a]	Methyl acrylate remaining, %	Log % methyl acrylate remaining	Ethanethiol remaining, %	Log % ethanethiol remaining
1	97.0	1.986	91.0	1.959
2	65.9	1.819	50.2	1.702
3	53.2	1.726	35.7	1.553
4	45.0	1.654	30.4	1.477

[a] Mixtures contained 0.0145 mole of thiol per mole of monomer.

Values of the chain transfer constants together with statistical estimates of their reproducibility are summarized in Table IV.

Discussion

The value reported here for C_∞ agrees well with the value of 1.69 reported by Walling[7] for methyl acrylate and butanethiol on the basis of measurements using radioactive sulfur. The value for C_1 appears to be smaller by the same order of magnitude as in the case of styrene and ethanethiol.

The values for C_2 are consistent with each other. They are also remarkably close to C_∞ and suggest that

TABLE IV

SUMMARY OF CHAIN TRANSFER CONSTANT DATA ON METHYL ACRYLATE AND ETHANETHIOL AT 50°

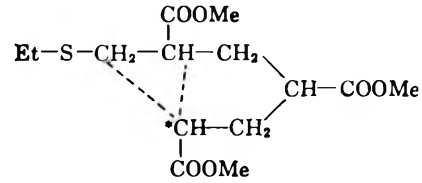
Constant		Fig.	Table	Value[a]	Standard deviation	Estimated error[b]
C_1	Slope	1	II	0.78	0.0111	±0.03
	Intercept	1	II	0.434	0.0109	± .030
C_2			II	1.79		± .15[c]
C_2	Slope	1	II	1.61	0.111	± .35
	Intercept	1	II	0.33	0.082	± .26
C_3			II	5		−2.0 +19[c]
C_∞[d]	Slope	2	III	1.57	0.043	±0.18

[a] Values are based on least squares calculation assuming linearity. [b] 5% probability level. [c] Based on intercept limits. [d] One fixed point assumed with 100% of both reactants remaining.

the two-unit radical is not appreciably less active than the polymer radical in spite of the fact that the active end should be most favorably placed to interact directly with the sulfur.

The high value for C_3 strongly suggests a reactivity minimum for the three-unit radical similar to that reported for the styrene bromotrichloromethane system.[3b] Unfortunately, the data does not give so reliable a value for C_3 as for C_2, and some apparent increase may arise from the small decrease in the monomer to thiol ratio during the reaction. This means that points should be plotted a little further to the left in Fig. 1 raising the intercept slightly. However, a value of C_3 as low as C_3 and C_∞ would require an intercept of unity, which seems to be exceedingly improbable.

In considering possible explanations, it should be pointed out that the reactive end of the three-unit radical appears favorably placed to abstract a hydrogen



reversibly from either the first or second carbon atom along the chain from the sulfur. In either case a more stable radical having less relative tendency to propagate might result. It seems conceivable that the proximity of sulfur or other polarizable end-group atoms having available orbitals might facilitate such exchanges. Since our data gives no information on C_4, it is possible that the chain transfer constant maximum and the reactivity minimum may be further down the chain (*cf.* ref. 3a and 3d). Such a finding would be harder to explain. There is need for more data on relative and absolute rates of formation of individual telomers as well as termination rates for individual radicals of known length. Such studies are planned in this laboratory.

The two- and three-unit telomers have potential interest as synthetic intermediates (*cf.* cyclic compounds from similar products[8]). We currently are studying cotelomers formed from acrylate esters with styrene and other monomers to extend these possibilities.

(7) C. Walling, *J. Am. Chem. Soc.*, **70**, 2561 (1948).

(8) G. Schreyer and T. Voelker, *Makromol. Chem.*, **63**, (1963).

Steric Effects in Ambident Ions. The Acylation of Cyclic β-Keto Esters[1]

JAMES P. FERRIS, CHARLES E. SULLIVAN,[2] AND BETH GEORGE WRIGHT

Department of Chemistry, Florida State University, Tallahassee, Florida

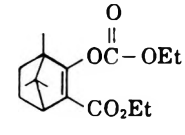
Received February 4, 1963

Acylation of five-, six-, and seven-membered cyclic β-keto esters with ethyl chloroformate yields both carbon- and oxygen-acylated products. The greatest proportion of carbon-acylation was observed with the seven-membered ring compound and the least in the six-membered ring compound. The preponderance of oxygen-acylated product in the 2-carbethoxycyclohexanone reaction is ascribed to hindrance to axial attack of the ethyl chloroformate on the carbocyclic ring. Such hindrance, due to the ring hydrogens, is less in the five- and seven-membered rings, thereby accounting for the greater proportion of carbon-acyl product.

The alkylation of ambident ions has been the topic of extensive recent investigation and the reaction conditions which direct alkylation on carbon or oxygen have been well defined in certain systems.[3] The corresponding acylation reaction has not been studied in a systematic manner, although in several instances it is known that solvent, reaction temperature, and the cation accompanying the anion exert considerable effect on the proportion of carbon- and oxygen-acylation.[4-6] It was hoped that a systematic investigation of the acylation of β-keto esters would clarify previous literature reports, point to a method of obtaining better yields of the synthetically more useful carbon-acylated product, and contribute to the general understanding of the factors which direct the point of attack in an ambident ion.[7]

We chose to study the reaction of ethyl chloroformate with cyclic β-keto esters. The anions of the cyclic compounds would be expected to be planar about the carbon atoms joined to the ester and carbonyl groups so that the most favored conformation of the ring would be the same as that in the corresponding cycloalkenes. The latter have been investigated extensively and the most stable conformations are known.[8] The mechanism of the reaction of ethyl chloroformate with various nucleophiles has been examined and it was found to be a second-order reaction displacement in every instance.[9] This combination of reactants requires a transition state which involves axial attack[10] of the ethyl chloroformate on the anion of the keto ester. Equipped with this knowledge it should be possible to discern the more subtle factors which effect the geometry of the transition state so as to tilt the balance in favor of either carbon- or oxygen-acylation. In this work we planned to explore the effect of systematically changing the ring size of the β-keto ester.

A few literature reports are available describing the acylation of cyclic β-keto esters. Komppa and Talvitie[11] reported the preparation of 2,2-dicarbomethoxycyclopentanone (II, Et = Me) by the reaction of the sodium salt of 2-carbomethoxycyclopentanone with methyl chloroformate. Hydrolysis of this product yielded adipic acid. However, an equally plausible reaction product, consistent with the structure proof given, is the enol carbonate III (Et = Me). The report that ethyl camphorcarboxylate yields the oxygen-acylated product (XIII) on treatment with ethyl chloroformate[12] would provide a precedent for structure III.



XIII

More recently Plesek[13] has reported that carbon-acylated products are formed from the reaction of the magnesium salt of 2-carbethoxycyclopentanone with various acid chlorides. However, the acylated product was not isolated, but instead the cyclopentanone ring of the crude product was cleaved to the corresponding keto acid with sodium carbonate. This reaction does not prove that the carbon-acylated product was initially obtained since there remains the possibility that the oxygen-acylated product was originally formed and

(1) Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(2) Abstracted in part from the M.S. thesis of C. E. Sullivan.

(3) Recent developments in this area have been reviewed by C. F. Hobbs, C. K. McMillin, E. P. Papdopoulos, and C. A. VanderWerf, *J. Am. Chem. Soc.*, **84**, 43 (1962).

(4) The older literature on the alkylation and acylation of β-keto esters is reviewed by A. Brändström, *Arkiv Kemi*, **6**, 155 (1953).

(5) H. D. Murdoch and D. C. Nonhebel, *J. Chem. Soc.*, 2153 (1962); D. C. Nonhebel, *ibid.*, 738 (1963).

(6) W. J. Barry, *ibid.*, 670 (1960).

(7) A recent review has pointed out the need for such a study: D. P. N. Satchell, *Quart. Rev.* (London), **17**, 161 (1963) (see especially pp. 194–195).

(8) K. Pitzer and W. G. Dauben, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 38; N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 5729 (1959).

(9) H. K. Hall, Jr., *ibid.*, **77**, 5993 (1955); **79**, 5438 (1957); H. K. Hall, Jr., and P. W. Morgan, *J. Org. Chem.*, **21**, 249 (1956).

(10) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301 (1953); G. Stork and S. D. Darling, *ibid.*, **82**, 1512 (1960).

(11) G. Komppa and A. Talvitie, *Ann. Acad. Sci., Fennicae Ser.*, **A57**, **No. 15**, 3 (1941); *Chem. Abstr.*, **38**, 5496 (1944).

(12) J. W. Bruhl, *Ber.*, **24**, 3391, 3709 (1891).

(13) J. Plesek, *Collection Czech. Chem. Commun.*, **21**, 1312 (1956); **22**, 49 (1957); **22**, 1661 (1957).

then rearranged to the carbon-acylated product before ring cleavage.[14]

The results of our study, summarized in Table I, show that the proportion of carbon-acylation decreases as the ring size changes from C_7 to C_5 to C_6. The relative proportion of carbon- and oxygen-acylated product was determined by vapor phase chromatography (v.p.c.) and by the extinction coefficient of the α,β-unsaturated ester chromophore (oxygen-acylated product) in the ultraviolet spectrum. Pure samples of the carbon- and the oxygen-acylated products of IV and X were not obtained, but the composition of the reaction mixture may be calculated from the extinction coefficient of the mixture, if one makes the reasonable assumption that the pure oxygen-acylated derivatives would have the same extinction coefficients as the oxygen-acylated derivatives of I and VII.

TABLE I

PRODUCTS OF THE REACTION OF ETHYL CHLOROFORMATE WITH CYCLIC β-KETO ESTERS

Keto ester	Temp., °C.	Solubility of chelate salt	Total yield, %	% C- and O-acylation Ultraviolet C:O	% C- and O-acylation V.p.c. C:O
I	80	Insoluble	62	24:76	23:77
I	R.T.[a]	Insoluble	57	19:81	17:83
IV	80	Soluble	68	20:80	10:90
VII	110	Insoluble	60		1:99
VII	R.T.[a]	Insoluble	61		1:99
X	80	Soluble	67	57:43	50:50[b]
X	R.T.[a]	Soluble	54	62:38	50:50[b]

[a] Room temperature. [b] Peaks were of equal height but overlapped so that accurate integration was not possible.

The reactions were carried out at room temperature and at reflux temperatures (with the exception of IV which reacted at reflux only) with no appreciable variation in the yield or proportion of carbon- and oxygen-acylated product. The composition of the crude reaction products and the distilled product were shown to be the same by comparison of infrared spectra and vapor phase chromatograms before and after distillation. The distilled products were shown to be stable when heated for 30 min. at 200° in sealed tubes. These data show that oxygen-acylated material was not rearranging to carbon-acylated material either during the reaction or in any of the subsequent work-up and analysis steps.[15]

The structures of the reaction products were proved by spectral and chemical means. The oxygen-acylated product exhibited maxima ascribed to the enol carbonate carbonyl and double bond at 1765 and 1660 cm.$^{-1}$, respectively. The carbonyl group for the α,β-unsaturated ester appeared at 1720 cm.$^{-1}$. In the cases where appreciable amounts of carbon-acylated product were formed the maxima for the ring carbonyl also was observed. The ultraviolet spectra of the products all exhibited maxima in the 220–230-mμ region consistent with the enol ester chromophore.[16] The carbon-acylated product would not be expected to have appreciable absorption in that region of the ultraviolet.

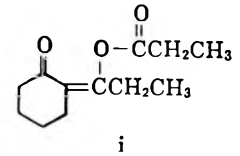
We carried out some degradative reactions on the product obtained from the acylation of 2-carbethoxycyclopentanone to verify the aforementioned spectral assignments. Acid- and base-catalyzed ethanolysis (the product was stable in ethanol alone) yielded diethyl adipate as the principal product. Diethyl carbonate as well as trace amounts of 2-carbethoxycyclopentanone also were found in the base-catalyzed reaction. More definitive evidence for the enol carbonate structure (III) was obtained by reaction with sodium borohydride in ethanol, a procedure which is known to cleave enol esters.[17] Diethyl carbonate was observed as a product of this reaction, a result consistent with the proposed structure. The reaction of sodium borohydride with the carbon-acylated product would not be expected to give diethyl carbonate under such mild reaction conditions.[18]

A sample of the pure III was prepared using pyridine as the reaction solvent.[19] The v.p.c. retention times for the principal product (93%) of this reaction and that from the reaction of the sodio derivative with ethyl chloroformate were identical. The infrared and ultraviolet spectral data of the two products were quite similar except for a more intense ultraviolet absorption for the product from the pyridine reaction and the presence of a weak carbonyl maxima in the infrared at 1740 cm.$^{-1}$ (cyclopentanone carbonyl from product of sodium in benzene reaction). Surprisingly, only starting material was recovered when the acylation of 2-carbethoxycycloheptanone was attempted in pyridine solution. Attempted preparation of pure samples of the carbon-acylated products by treatment of the magnesium salts[20] of 2-carbethoxycyclopentanone and 2-carbethoxycyclohexanone with ethyl chloroformate yielded only starting material and diethyl carbonate.

All this evidence clearly shows that the principal product obtained from the reaction of ethyl chloroformate with 2-carbethoxycycloheptanone is that of oxygen-acylation and not the carbon-acylated product reported by Komppa and Talvitie.[11]

Discussion

The mechanism of the reactions studied must involve axial attack[10] of the ethyl chloroformate on the π-electron system of the anion of the β-keto ester. This is essentially an irreversible process since nonpolar solvents were used and no evidence was found for rearrangements when the reactions were carried out at higher temperatures and longer reaction times. In some cases the salt of the β-keto ester was insoluble in



i

(14) H. Henecka, *Ber.*, **81**, 196 (1948). This possibility currently is being investigated in our laboratory.

(15) F. Gogan, A. E. O'Brian, E. M. Philbin, N. S. O'Connor, F. R. F. Timoney, and T. S. Wheeler, *Tetrahedron*, **3**, 140 (1958).

(16) The enol acetate of ethyl acetoacetate has a maximum at 212 mμ (log ϵ 3.90); R. Richter, *Helv. Chim. Acta*, **35**, 1115 (1952). Compound i has a maximum at 234 mμ (ϵ 7800); S. Hunig, E. Benzing, and L. Lucke, *Ber.*, **90**, 2833 (1957).

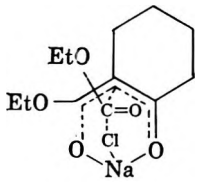
(17) W. G. Dauben, R. A. Micheli, and J. F. Eastham, *J. Am. Chem. Soc.*, **74**, 3852 (1952).

(18) Mr. C. Crawford recently has prepared 2,2-dicarbethoxycyclopentanone. It exhibits strong bands in the infrared at 1773 and 1739 cm.$^{-1}$ and a λ_{max} at 287 mμ (ϵ 54) in the ultraviolet. No diethyl carbonate is formed when it is treated with sodium borohydride (see Experimental).

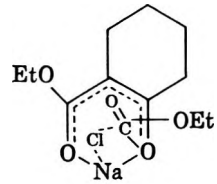
(19) L. Claisen and E. Hasse, *Ber.*, **33**, 1242 (1900); P. E. Wright and W. E. McEwen, *J. Am. Chem. Soc.*, **76**, 454 (1954).

(20) M. Viscontini and N. Merckling, *Helv. Chim. Acta*, **35**, 2280 (1952).

benzene and in others it was soluble. One might expect that a different mechanism would be operative in the two different cases.[21] However, essentially the same proportion of carbon- and oxygen-acylation was obtained when 2-carbethoxycyclopentanone was acylated, the sodium salt of which is insoluble in benzene, as was obtained from diethyl cyclopentanone-2-carboxylate-5-β-propionate (IV),[22] the sodium salt of which is soluble in benzene. If the heterogeneous reactions were proceeding by a mechanism that was considerably different from the homogeneous reactions one would expect to see a significant difference in the reaction products.[23] Other factors found by previous workers to effect course of reaction of an ambident ion—*e.g.*, solvent[21,24] and the metal ion used[25]—were held constant in this work so that the principal factor which governs the course of these acylations must be the different steric requirements of the anions being acylated.[5]



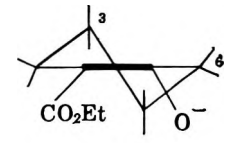
XIV



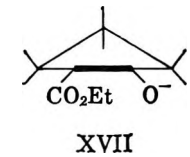
XV

Brändström[4] originally postulated that the transition state for the carbon-acylation reaction is best represented by XIV. The attack of the acylating agent is facilitated by polarization of the carbon–halogen bond by the metal of the chelate ring. Nonhebel,[5] using Brändström's model, suggested, as shown in XV, that the oxygen-acylation reaction involves a four-centered transition state for carbon acylation. Therefore, one would expect that only a small change in the steric requirements of the anion being acylated would change the nature of the transition state from one favoring carbon-acylation to one favoring oxygen-acylation.

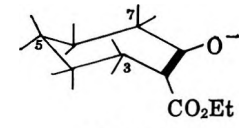
Models of the anions studied reveal that axial attack on the 2-carbethoxycyclohexanone chelate XVI (shown without the chelated metal ion for clarity) is highly hindered by the axial hydrogen at C-4 and the quasi-axial hydrogen at C-6. This hindrance is somewhat less in the cyclopentanone chelate (XVII) where the ring hydrogens are not perpendicular to the plane of the ring and, therefore, are not in direct interference with an entering group. One finds the least hindrance of all in the cycloheptanone ring where the plane described by the chelate system (XVIII) is inclined away from any interference with the quasi-axial hydrogens at C-3, C-5, and C-7.



XVI



XVII



XVIII

The rate of nucleophilic displacement at carbon should be faster than that at oxygen[26] so that the carbon-acylated product would be expected to form more rapidly. However, as the hindrance in the vicinity of the carbon atom increases, the acylation takes place on the more accessible oxygen atom.[27]

Experimental[29]

Reaction of 2-Carbethoxycyclopentanone with Ethyl Chloroformate. A. At Room Temperature.—2-Carbethoxycyclopentanone (31.2 g., 0.2 mole) was added dropwise with stirring and heating to 4.6 g. (0.2 g.-atom) of powdered sodium in 600 ml. of dry benzene. The mixture was refluxed and stirred for 5 hr. with the formation of a white pasty solid. Ethyl chloroformate (33.0 g., 0.3 mole) was added dropwise with stirring to the mixture; it was then stirred at room temperature for 4 hr. The benzene solution was washed twice with water, dried over sodium sulfate, and the benzene distilled *in vacuo*. Distillation of the residue at 82–84° (0.05 mm.) yielded 26 g. (57%); λ_{max} 228 mμ (ε 7420); ν_{max} 1765, 1725, 1660, 1740 (shoulder) cm.$^{-1}$; v.p.c. retention times for the crude reaction mixture, 4.3 (4%), 5.7 (16%), and 6.8 (78%) min. A peak with the retention time of 2.5 min. was observed for the starting β-keto ester. The distilled product had peaks of retention time, 5.4 (17%) and 6.6 (83%) min.

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.65; H, 7.21.

B. In Refluxing Benzene.—The sodium salt of 2-carbethoxycyclopentanone (31.2 g., 0.2 mole) was prepared as previously described. Ethyl chloroformate (33 g., 0.3 mole) was added dropwise with stirring to the sodium salt at room temperature and the mixture was then refluxed and stirred for 5 hr. After the usual work-up, 28.2 g. (62%) of product distilled at 82–84° (0.05 mm.), λ_{max} 228 mμ (ε 7010). The crude reaction product exhibited v.p.c. retention times of 5.7 (23%), 6.7 (73%), and 8.1 (2%) min. A peak with retention time of 2.3 min. was observed for starting β-keto ester. The distilled product had peaks of retention time, 5.6 (20%), 6.7 (79%), and 7.9 (1%) min.

C. With Sodium Hydride in Refluxing Benzene.—The sodium salt of 2-carbethoxycyclopentanone (144 g., 0.9 mole) was pre-

(21) N. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, **81**, 2705 (1959).

(22) N. N. Chatterjee, B. K. Das, and G. N. Barpujari, *J. Indian Chem. Soc.*, **17**, 161 (1941).

(23) Evidence has been cited[4,5] which suggests that the sodium salts of β-keto esters and β-diketones have the sodium bound in a chelate ring and not as the enolate salt. We have assumed the sodium to be chelated even though it has been suggested that such salts may be recognized by solubility in nonpolar solvents and the predominent formation of carbon-acylated products on treatment with acid halides. We feel that the binding in the salts of I and IV should be the same (chelate) even though one is soluble and the other insoluble in benzene. The greater solubility of the salt of IV in nonpolar solvents is undoubtedly only a reflection of its greater molecular weight. The preponderance of oxygen-acylation with these chelates is dealt with later in this paper.

(24) N. Kornblum, P. Berrigan, and W. Le Noble, *J. Am. Chem. Soc.*, **82**, 1257 (1960).

(25) D. Y. Curtin, R. J. Crawford, M. Wilhelm, *ibid.*, **80**, 1391 (1958); I. Forsblad, *Arkiv Kemi*, **15**, 403 (1960).

(26) E. S. Gould, "Mechanism and Structure in Organic Chemistry," H. Holt and Co., New York, N. Y., 1959, p. 259.

(27) Brändström[4] explains the formation of oxygen-alkylated products with 2-cyanocyclohexanone and exclusive formation of carbon-alkylated products of 2-cyanocyclopentanone on the greater degree of enolization of the former. Such rationalization is inconsistent with our data as it would predict that 2-carbethoxycycloheptanone (12% enolized[28]) would give more oxygen-acylation than 2-carbethoxycycloheptanone (5% enolized[28]), but actually the opposite is observed.

(28) G. Schwarzenbach, M. Zimmerman, and V. Prelog, *Helv. Chim. Acta*, **34**, 1954 (1951).

(29) Infrared spectra were determined on a Perkin-Elmer Model 137 in carbon tetrachloride. Ultraviolet spectra were determined on a Cary Model 14 in 95% ethanol by Mrs. K. Osmond, Mrs. D. DeTar, and Mrs. P. Ward. V.p.c. analyses were performed on an F and M Model 500 chromatograph equipped with Disc Integrator. A 2-ft. silicone rubber column was used with helium flow rate of 50 ml./min. The column was programmed at 11 deg./min. starting at 90°. Powdered sodium was prepared in toluene and then the toluene was decanted and the solvents and reactants listed were added. In each acylation the infrared spectrum of the reaction product before distillation was determined and it was found to be virtually identical with that of the distilled product. Analyses were performed by F. Pascher, Bonn, West Germany; Midwest Microlab, Indianapolis; and Scandanavian Microanalytical Laboratory, Copenhagen, Denmark.

pared by refluxing with 50 g. (1 mole) of 53% sodium hydride–mineral oil dispersion in 2 l. of dry toluene. Ethyl chloroformate (108 g., 1 mole) was added dropwise with stirring and the mixture was stirred and refluxed an additional 5 hr. Distillation after the usual work-up yielded 153 g. (75%) of a product that was identical in all respects with that prepared in B.

D. **In Pyridine[19] at Room Temperature.**—2-Carbethoxycyclopentanone (31.2 g., 0.2 mole) was dissolved in 32 g. of pyridine, ethyl chloroformate (32.4 g., 0.3 mole) was added slowly, and the mixture was allowed to stand at room temperature for 2 days. Water was added and the mixture was extracted with ether, the ether extracts were washed with cold 10% potassium hydroxide, dried over sodium sulfate, and the ether distilled to yield 12.3 g. of a red oil. Vacuum distillation at 84–86° (0.1 mm.) yielded 4.0 g.; λ_{max} 228 mμ (ε 9115); ν_{max} 1765, 1725, and 1660 cm.$^{-1}$; v.p.c. retention times, 5.4 (7%) and 6.6 (93%) min.

E. **With Magnesium Ethoxide.**[20]—Magnesium turnings (13.25 g.-atom) were converted to magnesium ethoxide by refluxing with 200 ml. of absolute ethanol. Dry ether (500 ml.) was then added to the solution followed by dropwise addition of 78 g. of 2-carbethoxycyclopentanone. The mixture was stirred for an hour, ethyl chloroformate (54 g.) was added dropwise, and the stirring was continued overnight. Acetic acid and water were added to the mixture and the ether layer was separated and washed with water. The ether solution was dried over sodium sulfate, concentrated, and the residue was vacuum distilled to yield 5 g. of diethyl carbonate and 40 g. of starting keto ester (identified *via* the infrared spectra).

Reaction of Diethyl Cyclopentanone-2-carboxylate-5β-propionate[22] with Ethyl Chloroformate.—The title compound (111 g., 0.43 mole) was added dropwise with stirring to 10 g. (0.44 g.-atom) of powdered sodium suspended in 0.5 l. of toluene and 1 l. of benzene. The solution was stirred and refluxed for 5 hr. The solution was cooled to room temperature and 57 g. (0.53 mole) of ethyl chloroformate was added; then the mixture was stirred and refluxed for an additional 5 hr. The benzene solution was washed with water and sodium carbonate solution, dried over sodium sulfate, and the solvent removed *in vacuo*. The residue distilled at 155–157° (0.2–0.3 mm.) to yield 95.5 g. (68%). A sample was redistilled for analysis at 155° (0.25 mm.); λ_{max} 229 mμ (ε 6371); ν_{max} 1765, 1740, 1725 (shoulder), and 1650 cm.$^{-1}$; v.p.c. retention times, 10.3 (10%) and 12.7 (90%) min.

Anal. Calcd. for $C_{16}H_{24}O_7$: C, 58.52; H, 7.37. Found: C, 58.75; H, 7.43.

Reaction of 2-Carbethoxycyclohexanone with Ethyl Chloroformate. A. At Room Temperature.—The sodium salt (34 g., 0.2 mole) of 2-carbethoxycyclohexanone was prepared by refluxing with 4.6 g. (0.2 mole) of powdered sodium for 10 hr. Ethyl chloroformate (33 g., 0.3 mole) was added to the cooled solution and the mixture was stirred at room temperature for 4 hr. The mixture was washed with water, dried over sodium sulfate, and the benzene distilled. Distillation of the residue at 97–98° (0.05 mm.) yielded 29.5 g. (61%); λ_{max} 222 mμ (ε 8558); ν_{max} 1765, 1720, 1660 cm.$^{-1}$. The v.p.c. of the crude reaction mixture exhibited peaks of retention time, 6.1 (1%) and 7.9 (99%) min. A peak of retention time of 3.4 min. was observed for starting material. The distilled product exhibited only one peak with a retention time of 7.2 min.

Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.89; H, 7.51.

B. **In Refluxing Toluene.**—The aforementioned reaction was carried out by refluxing in toluene for 35 hr. A 60% yield of product was obtained that was identical in all respects with that prepared in A.

C. **With Magnesium Ethoxide.**[20]—Magnesium turnings (2.7 g., 0.11 g.-atom) were converted to magnesium ethoxide with 15 ml. of ethanol. Ether (100 ml.) was added and then 17.4 g. (0.1 mole) of 2-carbethoxycyclohexanone in 20 ml. of ether. The mixture was stirred at room temperature for 30 min., then 10.9 g. (0.1 mole) of ethyl chloroformate in 20 ml. of ether was added, and the mixture was allowed to stir at room temperature overnight. At the end of this time the mixture was refluxed for 1 hr., ice and dilute sulfuric acid were added until the water solution was distinctly acid, and the ether layer was separated, washed with water, dried over sodium sulfate, and concentrated. The crude reaction product exhibited v.p.c. peaks of 0.4 (27%), 3.7 (62%), and 11.4 (11%) min. The peaks at 0.4 and 3.7 min. were shown to be diethyl carbonate and 2-carbethoxycyclohexanone, respectively. Distillation of the residue yielded 10 g. of starting keto ester as well as diethyl carbonate. Both were identified *via* infrared spectra.

Reaction of 2-Carbethoxycycloheptanone[30] with Ethyl Chloroformate. A. At Room Temperature.—The sodium salt (31.8 g., 0.17 mole) of 2-carbethoxycycloheptanone was prepared by refluxing with 4.6 g. (0.2 g.-atom) of powdered sodium for 5 hr. Ethyl chloroformate (33 g., 0.3 mole) was added dropwise with stirring to the solution of the sodium salt and the mixture was stirred for 4 hr. at room temperature. The benzene solution was washed with water, dried with sodium sulfate, and the benzene was distilled. The residue distilled at 105–108° (0.3 mm.) to yield 23.9 g. (54%); λ_{max} 223 mμ (ε 3590); ν_{max} 1760, 1730, 1715 (shoulder), and 1660 cm.$^{-1}$. The crude reaction mixture exhibited v.p.c. peaks of retention time, 0.8 (7%), 7.7 (45%), and 7.8 (45%) min. A peak of retention time 4.1 min. was observed for the starting material. The distilled product had peaks of retention time, 8.6 (50%) and 8.8 (50%), min.

Anal. Calcd. for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 61.40; H, 8.09.

B. **In Refluxing Benzene.**—The sodium salt (92 g., 0.5 mole) of 2-carbethoxycycloheptanone was prepared by refluxing with 13.8 g. (0.6 g.-atom) of powdered sodium suspended in 0.5 l. of toluene and 1 l. of benzene for 4 hr. The reaction mixture was allowed to cool to room temperature and 64.8 g. (0.6 mole) of ethyl chloroformate was added and the mixture was refluxed for an additional 4 hr. The solution was then washed with water, dried over sodium sulfate, and the solvent distilled *in vacuo*. Distillation of the residue at 99–100° (0.1 mm.) yielded 86 g. (67%) of product (λ_{max} 223 mμ, ε 4100) that was identical with that from the room temperature reaction.

C. **In Pyridine at Room Temperature.**—The reaction was carried out in exactly the same way as with 2-carbethoxycyclopentanone, but only starting material was isolated on work-up.

Hydrolysis of the Reaction Product Obtained from the Acylation of the Sodium Salt of 2-Carbethoxycyclopentanone. A. With Acetic Acid.[31]—The reaction product (8 g.) was dissolved in a solution of 100 ml. of water, 100 ml. of glacial acetic acid, and 5 ml. of hydrochloric acid, and stirred at room temperature overnight. The solution was poured into 1 l. of water and extracted thoroughly with ether. The ether extracts were combined and washed with water and sodium carbonate solution, dried over sodium sulfate, and the ether removed under vacuum. An infrared spectrum of the residue showed it to be starting material.

B. **With Hydrochloric Acid.**—The reaction product (16 g.) was dissolved in a mixture of 75 ml. of concentrated hydrochloric acid and 200 ml. of ethanol and stirred at room temperature overnight. Work-up as in A gave 5 g. of an oil whose infrared spectrum was identical with that of diethyl adipate.

C. **With Sodium Ethoxide.**—The reaction product (16 g.) was added to 250 ml. of 0.28 *M* sodium ethoxide and the mixture was refluxed overnight. The dark brown solution was cooled and poured into 200 ml. of concentrated hydrochloric acid. Water (1.5 l.) was then added and the mixture extracted with ether. The ether extracts were washed with water and sodium carbonate solution, dried over sodium sulfate, and the ether removed on the steam bath. Distillation of the residue at atmospheric pressure yielded 2 g. of a liquid whose infrared spectrum was identical with that of diethyl carbonate. The remainder was too badly charred for further investigation.

A repetition of this experiment followed by distillation under vacuum yielded two fractions. Fraction 1 gave a positive ferric chloride test (violet color) and its infrared spectrum showed it to be mainly diethyl adipate with some 2-carbethoxycyclopentanone (weak infrared bands at 1760, 1660, and 1620 cm.$^{-1}$). Fraction 2 did not give a positive ferric chloride test and its infrared spectrum identified it as diethyl adipate.

Sodium Borohydride Reduction of the Reaction Product Obtained from the Acylation of the Sodium Salt of 2-Carbethoxycyclopentanone.—The reaction product (8 g., 0.035 mole) was added dropwise with stirring to 2.6 g. (0.07 mole) of sodium borohydride in 250 ml. of absolute ethanol and the mixture was stirred for 24 hr. at room temperature. Dilute hydrochloric acid (1 l.) was added and the aqueous solution was extracted with ether. The ether extract was washed with sodium carbonate solution, dried over sodium sulfate, and the ether was distilled to yield 0.96 g. of product. The infrared spectrum of this

(30) Prepared by an unpublished procedure of Professor W. Herz and L. Glick.

(31) J. C. Sheehan and C. E. Mumaw, *J. Am. Chem. Soc.*, **72**, 2127 (1950).

material was essentially that of diethyl carbonate; v.p.c. analysis confirmed the presence of diethyl carbonate by a peak of retention time 0.4 (13%) min. However the following peaks also were present, 1.5 (1%), 2.4 (11%), 3.3 (53%), 3.7 (1%), 4.7 (15%), 6.3 (1%), 7.3 (3%), and 8.0 (1%) min.

Sodium Borohydride Reduction of 2,2-Dicarbethoxycyclopentanone.[18]—2,2-Dicarbethoxycyclopentanone (8 g., 0.035 mole) was added dropwise with stirring to 2.6 g. (0.07 mole) of sodium borohydride in 250 ml. of absolute ethanol and the mixture was stirred for 24 hr. at room temperature. Dilute hydrochloric acid (1 l.) was added and the aqueous solution was extracted with ether. The ether extract was washed with sodium carbonate solution, dried over sodium sulfate, and the ether was distilled to yield 0.85 g. of product. The infrared spectrum of this material was not at all similar to diethyl carbonate and no peak in the v.p.c. corresponding in retention time to this compound was observed. Peaks of retention times of 4.5 (11%), 6.2 (10%), 7.9 (74%), and 8.3 (5%) min. were observed.

Attempted Thermal Rearrangement of the Acylation Products.—One-milliliter samples of the acylation products of 2-carbethoxycyclopentanone, 2-carbethoxycyclohexanone, and 2-carbethoxycycloheptanone were heated in sealed tubes at 200° for 30 min. V.p.c. and infrared analysis indicated no rearrangement took place.

Acknowledgment.—The authors wish to thank Professor Werner Herz and Mr. Laverne Glick for communicating the results of unpublished work and for determining several of the vapor phase chromatograms.

Highly Substituted Aromatics. The Synthesis and Nuclear Magnetic Resonance Spectrum of 2,4,6-Tri-*t*-butyl-3-fluorophenol[1]

BRUCE RICKBORN, DONALD A. MAY, AND ANTONI A. THELEN

The Department of Chemistry, University of California, Santa Barbara, California

Received August 16, 1963

The low steric requirements of the fluoro substituent allow the insertion of a *t*-butyl group in the 2-position of 3-fluorophenol, as evidenced by the preparation of the title compound. The n.m.r. spectra of this material and some analogs were used for structure proof; long-range H–F spin-spin coupling between the protons of the 2- and 4-*t*-butyl groups and the adjacent fluorine was observed.

The large steric requirement of the *t*-butyl group has been the subject of a great deal of experimental and theoretical chemistry. The bulk effect of this substituent may be used to advantage or it may be the source of extreme synthetic difficulties. The latter are exemplified in the recent syntheses of *o*-di-*t*-butylbenzenes.[2] The strain energy involved in these systems, demonstrated by the apparent distortion of the benzene ring,[2a] supports Brown's earlier suggestion that these compounds are not to be expected from Friedel–Crafts type alkylation reactions.[3]

Extending the question of *ortho* steric effects of the *t*-butyl group, it is noted that innumerable compounds have been prepared by classical aromatic substitution methods which bear one substituent *ortho* to the bulky group.[4] In contrast, very few materials are known in which the *t*-butyl substituent is flanked by two groups other than hydrogen. Among these compounds are the "synthetic musks," in which both *ortho* groups are nitro.[5] Nitration appears generally to be less susceptible to bulk effects than many other electrophilic substitution reactions.[6] Kaeding[7] recently has prepared 4,6-dibromo-2-chloro-3-*t*-butylphenol. This compound, in which the *t*-butyl group is adjacent to bromine and chlorine, represents an extreme for halogenation.

In these examples the *ortho* groups were added after formation of a suitable *t*-butylbenzene derivative. The converse production of highly substituted aromatic *via* *t*-butylation was the object of the present study. The literature contains three reports of di-*ortho*-substituted *t*-butylbenzenes presumably prepared by direct alkylation. Katsui and Kuyama are quoted[8] as having examined the effect of 2,4-di-*t*-butylresorcinol on stabilization of vitamin A; the original literature indicates that the compound in question is the 4,6-derivative, instead, and that an error in translation is involved.

Dacre[9] has reported the preparation of 3,5-di-*t*-butyl-2,4-dihydroxytoluene from 2,4-dihydroxytoluene, but the only structure proof given was an acceptable carbon and hydrogen analysis. This, of course, would be identical for an isomeric O-butylated product, which is more likely the correct structure.[10]

Using the aluminum phenoxide-catalyzed alkylation reaction, which is noted for preferential *ortho* substitution,[11] Stroh, Seydel, and Hahn have reported the formation of 2,6-di-*t*-butyl-3-methylphenol from *m*-cresol.[12] However, it was subsequently shown that no substitution had taken place in the hindered *ortho* position and that the product was in reality 2,4-di-*t*-butyl-5-methylphenol.[13] Thus there are no clear-cut examples in the literature in which a *t*-butyl group has

(1) Work done in part at the University of California, Berkeley, Calif.

(2) (a) A. W. Burgstahler and M. O. Abdel-Rahman, *J. Am. Chem. Soc.*, **85**, 173 (1963); (b) L. R. C. Barclay, C. E. Milligan, and N. D. Hall, *Can. J. Chem.*, **40**, 1664 (1962); (c) E. M. Arnett, M. E. Strem, and R. A. Friedel, *Tetrahedron Letters*, 658 (1961); (d) C. Hoogzand and W. Hübel, *ibid.*, 637 (1961).

(3) H. C. Brown and K. L. Nelson, *J. Am. Chem. Soc.*, **75**, 24 (1953).

(4) For a summary of the pertinent information, see G. S. Hammond and M. F. Hawthorne, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chap. 3.

(5) R. J. W. LeFevre, *J. Chem. Soc.*, 977 (1933).

(6) (a) P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Am. Chem. Soc.*, **76**, 2349 (1954); (b) W. Rundel, *Ber.*, **96**, 636 (1963); (c) K. Ley and E. Müller, *ibid.*, **89**, 1402 (1956).

(7) W. W. Kaeding, *J. Org. Chem.*, **26**, 4851 (1961).

(8) G. Katsui and H. Kuyama, *Vitamins* (Kyoto), **5**, 342 (1952); *Chem. Abstr.*, **47**, 8316.

(9) J. C. Dacre, *Biochem. J.*, **78**, 758 (1961).

(10) Resorcinol itself gives a complex mixture of products under these reaction conditions. Although these have not been completely identified, some are definitely ethereal (unpublished results).

(11) (a) A. J. Kolka, J. P. Napolitano, and G. G. Ecke, *J. Org. Chem.*, **21**, 712 (1956); (b) A. J. Kolka, J. P. Napolitano, A. H. Filbey, and G. G. Ecke, *ibid.*, **22**, 642 (1957).

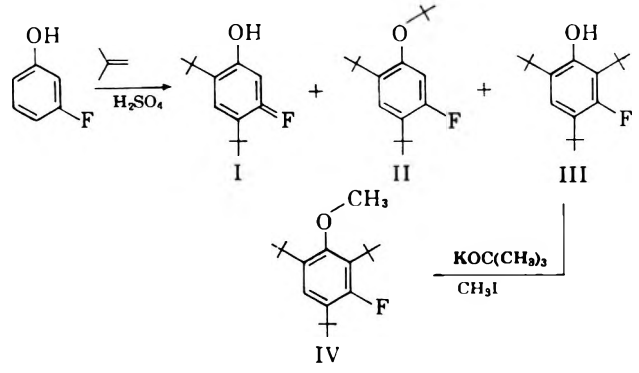
(12) R. Stroh, R. Seydel, and W. Hahn, *Angew. Chem.*, **69**, 699 (1957).

(13) R. Stroh, personal communication; see also R. Stroh, R. Seydel, and W. Hahn, "Neuer Methoden der Präparativen Organischen Chemie," Band II, Verlag Chemie, Weinheim, 1960, p. 231.

been directly substituted between two groups on an aromatic ring.[14]

A number of sources of the *t*-butyl group are available and have been used in Friedel–Crafts alkylation. Isobutylene undergoes a rapid reaction (acid-catalyzed) with phenol to give in high yield 2,4,6-tri-*t*-butylphenol.[15] Highly substituted phenols of this type have been explored extensively, mainly because of their effectiveness as antioxidants.[16,17] Bowman and Stevens[18] pointed up the large steric requirements of the butylation reaction when they observed the complete lack of reaction of 3,5-dimethylphenol.

In our hands, butylation failed to give reaction at the hindered *ortho* position (between hydroxyl and *meta* substituent) of *m*-cresol, *m*-chlorophenol, and 3,4-xylenol.[19] The small van der Waals radius of fluorine suggested that it might be suitable as a *meta* substituent,[20] and this was indeed found to be the case. *m*-Fluorophenol, as a neat liquid containing a small amount of concentrated sulfuric acid, undergoes vigorous reaction with isobutylene to yield principally the three products shown (I–III). Methylation gave the anisole derivative IV of the very hindered phenol III.[21]



A fourth product was obtained in small yield during the butylation procedure; this material could be made to predominate by prolonged treatment at higher temperatures. Its structure has not as yet been determined.[22]

Of primary interest from our standpoint is the formation of the highly substituted 2,4,6-tri-*t*-butyl-3-fluorophenol (III). The formation of this material adds a third class to the two already known in which the bulky alkyl group is flanked by two groups other than hydrogen, and further represents the first preparation of such a compound by direct *t*-butylation.[23] The yield of this material was quite sensitive to temperature changes; at 0° the rate of formation of III was prohibitively slow, while at 80° the equilibrium amount of this product was quite small. Optimum conditions were determined at approximately 45°, where the yield of 2,4,6-tri-*t*-butyl-3-fluorophenol increased steadily for approximately three hours, after which an equally steady decline was noted. The exact course of the reaction has not been determined, but it has been demonstrated that the over-all yield in terms of the four products noted previously is essentially quantitative. The decrease in III appears to be associated with the formation of the as yet unidentified fourth product.[22]

The *t*-butyl ether (II) of 2,4-di-*t*-butyl-5-fluorophenol is formed very rapidly and then decreases with increasing time. At the point where III is maximized, the yield of ether has been substantially diminished.[24] We have not as yet demonstrated whether I or II is the direct precursor of the tri-*t*-butylphenol (III), although it is tempting to speculate on an intramolecular rearrangement of the ether. The formation of products such as the *t*-butyl ether (II) appears to be possible only because the O-alkyl group is able to swing away from the bulky *ortho* substituent. Anisole itself, for instance, undergoes rapid *t*-butylation to give 2,4-di-*t*-butylanisole, with no evidence of the trialkylated product.[25]

The variation in the yield of 2,4,6-tri-*t*-butyl-3-fluorophenol stresses the fact that the *m*-fluoro group is indeed borderline between hydrogen (high yield by rapid reaction) and chlorine (no trialkylated product) for the butylation reaction. Under optimum conditions the yields obtained were I, 32%; II, 21%; and III, 25%.

The n.m.r. spectra of these materials, besides proving invaluable for structure determinations in this study, show interesting and clear-cut cases of long-range H–F spin–spin coupling. The data are shown in Table I. A number of examples of long-range hydrogen–fluorine nuclear magnetic interactions are found in the literature.[26] The mechanism of the transmission of these effects is still open to question. Spatial proximity[26b] and required bond geometry[26a] have both been stressed.

In the present case we note an essentially invariant H–F spin-coupling constant between 3-fluorine and the protons of the 4-*t*-butyl group (1 c.p.s.), irrespective of the other ring substituents. The 2-*t*-butyl group, in

(14) R. A. Benkeser, R. F. Grossman, and F. S. Clark [*J. Org. Chem.*, **27**, 3728 (1962)] have demonstrated that 2,3,5-trimethylphenol is not tritylated by triphenylcarbinol and sulfuric acid as reported previously by N. P. Buu-Hoi and R. Rips [*ibid.*, **22**, 666 (1957)]. This lack of reaction is in agreement with the available data in the literature and the results of the present study.

(15) G. H. Stillson, D. W. Sawyer, and C. K. Hunt, *J. Am. Chem. Soc.*, **67**, 303 (1945).

(16) For an excellent discussion, see G. Scott, *Chem. Ind.* (London), 271 (1963).

(17) The preferred catalyst for the butylation reaction is still an open question, and one which is being actively investigated by many workers. V. N. Ipatieff, H. Pines, and B. S. Friedman [*J. Am. Chem. Soc.*, **60**, 1495 (1938)] found phosphoric acid at 100° to give mainly 4-*t*-butyl- and 2,4-di-*t*-butylphenol. More recently, E. V. Alisova and S. V. Zavgorodnii [*Zh. Obshch. Khim.*, **32**, 3502 (1962)] have used mixed boron trifluoride–phosphoric acid in the alkylation reaction and found it to be an effective catalyst. In our hands, sulfuric acid gave quite reproducible results and was used exclusively in this study.

(18) R. S. Bowman and D. R. Stevens, *J. Org. Chem.*, **15**, 1172 (1950).

(19) Unpublished results with Denes Turcsanyi.

(20) F = 1.4 Å. (H = 1.2 Å., Cl = 1.8 Å.): E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, New York, N. Y., 1959, p. 51. As can be seen from the discussion in this reference, the van der Waals radius is not a particularly meaningful number for comparing bulk effects in a reaction such as aromatic substitution, since the electrophile comes nowhere near the distended cloud of the substituent. Hence these values are noted only as a point of departure.

(21) Methylation is the only satisfactory O-alkylation reaction that has been investigated for 2,6-di-*t*-butylphenols: see Experimental section and N. Kornblum and R. Seltzer, *J. Am. Chem. Soc.*, **83**, 3668 (1961).

(22) One interesting possibility which has been ruled out by n.m.r. is the *t*-butyl ether of III. Work is continuing to elucidate the nature of this material.

(23) One interesting exception is 2,4,6-tri-*t*-butylphenol-3-*d*, prepared by E. Muller, A. Rieker, and K. Scheffler, *Ann.*, **645**, 92 (1961), for e.p.r. studies.

(24) Acid-catalyzed and thermal decompositions and rearrangements of alkyl phenyl ethers are well known: (a) R. S. Bowman, D. R. Stevens, and W. E. Baldwin, *J. Am. Chem. Soc.*, **79**, 87 (1957); (b) R. A. Smith, *ibid.*, **54**, 1068 (1932); **53**, 272 (1931).

(25) Unpublished results with A. A. Thelen.

(26) (a) A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **84**, 3784 (1962); **84**, 1736 (1962); (b) M. Takahashi, D. R. Davis, and J. D. Roberts, *ibid.*, **84**, 2935 (1962).

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA

Compound	Group position[a] and absorption, p.p.m.[b] 2-*t*-Butyl	4-*t*-Butyl	6-*t*-Butyl	O-Alkyl	2-Proton	6-Proton
I		1.35 (1.0)	1.40		6.35(13)	7.20 (9.5)
II		1.35 (~1)[c]	1.36	1.54	6.70(15)	7.18 (10)
III	1.58 (2.9)	1.37 (1.1)	1.42			7.10 (9)
IV	1.51 (1.5)	1.35 (1.0)	1.40	3.60		7.09 (10)
2,4,6-tri-*t*-butylanisole	1.45	1.31	1.45	3.69		7.27

[a] In each case the fluorine is assigned the 3-position for simplicity of comparison. [b] The internal standard was tetramethylsilane with deuteriochloroform as solvent. The figure in parentheses is the coupling constant between the proton(s) in question and the fluorine nucleus, c.p.s. [c] Half of this doublet appeared with the 6-*t*-butyl absorption.

which the protons are removed from fluorine by the same number of bonds and which possesses the same relative geometry to the fluorine nucleus as does the 4-*t*-butyl group, shows a different and somewhat higher coupling constant. Two possibilities are suggested to account for this behavior: (1) the hydroxyl (or methoxyl) group may be disturbing the aromatic ring current sufficiently to allow this difference, or (2) a buttressing effect of the hydroxyl group may be forcing the 2-*t*-butyl group relatively closer to the fluorine nucleus than the 4-alkyl group. This latter possibility seems to be negated by the observation that the conversion of hydroxyl to methoxyl causes a decrease in the coupling constant, rather than the anticipated increase.

The data in Table I are compatible only with the structures suggested; long-range coupling by two of the three *t*-butyl groups marks them as *ortho* to the fluorine. This information taken in conjunction with the magnitude of the aryl hydrogen–fluorine coupling constant[27] and the absence of aryl hydrogen–aryl hydrogen magnetic interactions fully designates the structures given for I–IV. The data for 2,4,6-tri-*t*-butylanisole are included for comparison. The added fluorine has only small effects on the resonance peak positions, but fortunately these shifts are sufficient to identify the *t*-butyl groups individually.

Experimental

***m*-Fluorophenol.**—This material was prepared from *m*-fluoroanisole, which had in turn been synthesized from *m*-anisidine, by procedures which have been reported previously.[28]

***t*-Butylation of *m*-Fluorophenol.**—The reaction vessel used for butylation was a flat-bottomed 35-mm. tube which contained a magnetic stirring bar. The top was sealed by a stopper containing an exit tube and an inlet capillary tube which extended to the bottom of the flask. The inlet was connected through a drying tube containing 4A Molecular Sieves to the isobutylene tank.[29]

m-Fluorophenol, 2.0 g. (0.018 mole), was placed in this vessel and the isobutylene flow started. The temperature was maintained at 45 ± 2° by a water bath held on combined hot plate–magnetic stirrer. After thermal equilibration sulfuric acid (0.17 g., 0.0017 mole), was added. A vigorous reaction ensued during which the volume of solution increased substantially. Small samples were withdrawn at intervals, shaken with pentane and water, and the pentane evaporated to give a residue which was examined by v.p.c. A 2-m. silicone column was used at 200°; retention times were I, 8 min.; II, 10 min.; and III, 12 min.

The yield of 2,4,6-tri-*t*-butyl-3-fluorophenol reached a maximum after approximately 2.5 hr. The solution was mulled with a few grams of activated alumina,[30] and the entire slurry was then added to a basic alumina column (Harshaw 90% alumina which had been activated by heating at 300° for 0.5 hr. and cooled in a desiccator was used).

***t*-Butyl 4,6-Di-*t*-butyl-3-fluorophenyl Ether.**—Using pentane as eluting liquid, the *t*-butyl ether (II, 1.05 g., 21%) was obtained. Recrystallization from aqueous methanol gave material with m.p. 65–67°.

Anal.[31] Calcd. for $C_{18}H_{29}FO$: C, 77.1; H, 10.4. Found: C, 77.0; H, 10.4.

2,4,6-Tri-*t*-butyl-3-fluorophenol.—Gradual transition from pentane to ether as solvent caused the elution of 2,4,6-tri-*t*-butyl-3-fluorophenol, 1.25 g. (25%). After recrystallization from aqueous methanol, it had m.p. 147–148°; this white solid developed the blue tinge characteristic of 2,4,6-tri-*t*-butyl-phenol on standing.

Anal. Found: C, 77.2; H, 10 6.

4,6-Di-*t*-butyl-3-fluorophenol.—After the tri-*t*-butylated materials had been recovered, the chromatography column was stripped with methanol to give crude 4,6-di-*t*-butyl-3-fluorophenol, 1.3 g. (32%). A small sample was purified by collection from v.p.c.; it was obtained as a colorless liquid which rapidly developed a straw color on contact with air.

Anal. Calcd. for $C_{14}H_{21}FO$: C, 75.0; H, 9.4. Found: C, 74.7; H, 9.5.

Methyl 2,4,6-Tri-*t*-butyl-3-fluorophenyl Ether.—A sample of 2,4,6-tri-*t*-butyl-3-fluorophenol (0.27 g., 0.00095 mole) was dissolved in 5 ml. of tetrahydrofuran which had been dried and purified by distillation from lithium aluminum hydride. To this solution was added 0.46 g. (0.0041 mole) of potassium *t*-butoxide; after stirring 0.5 hr., 2 ml. of methyl iodide was added and the mixture stirred overnight.

Following a typical washing and extraction procedure, the residue was taken up in a small amount of pentane and subjected to column chromatography. Pentane elution gave 0.24 g. (87%) of the desired ether. The melting point was 126–127°, following recrystallization from aqueous methanol.

Anal. Calcd. for $C_{19}H_{31}FO$: C, 77.5; H, 10.6. Found: C, 77.3; H, 10.7.

Acknowledgment.—The authors wish to express their appreciation to Mr. Henry E. Gauthier of Varian Associates for his assistance both in obtaining and interpreting many of the n.m.r. spectra.

(27) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 86.

(28) C. M. Suter, E. J. Lawson, and P. G. Smith, *J. Am. Chem. Soc.*, **61**, 763 (1939).

(29) Phillips Petroleum 99% "Pure" grade isobutylene was used.

(30) This treatment prevented an exothermic initial reaction with the alumina chromatography column.

(31) Microanalysis by C. F. Geiger, 312 E. Yale St., Ontario, Calif.

Acid-Catalyzed Isomerization of 3-Ethylpentane. Steric Hindrance of Hydride Transfer

WILLIAM D. HUNTSMAN AND EUGENE A. EGGERS

Department of Chemistry, Ohio University, Athens, Ohio

Received August 12, 1963

The isomerization of 3-ethylpentane in the presence of sulfuric acid at 25.0° has been studied. 2-Methylhexane and 3-methylhexane are the initial products, with the dimethylpentanes being formed more slowly. The rate of isomerization of 3-ethylpentane is significantly lower than that of 3-methylpentane; this is interpreted as being due to steric hindrance of hydride transfer from 3-ethylpentane. The ratio of the methylhexane isomers formed shows significant variations when different hydrocarbons are present along with 3-ethylpentane in the reaction mixture. This variation also can be rationalized in terms of hydride donating ability of the added substances. Rate constants were calculated for the isomerization of 3-ethylpentane and 3-methylpentane in admixture and for 3-ethylpentane alone. 3-Ethylpentane has been detected as a minor product of isomerization of the methylhexanes in the presence of sulfuric acid.

The isomerization of most of the isomeric heptanes in the presence of sulfuric acid has been studied in some detail.[1-6] In accordance with the behavior of other homologs, isomers having at least one tertiary hydrogen rearrange rapidly by processes involving simple alkyl migration. Reactions which involve a change in degree of branching proceed much more slowly. Thus, 2- and 3-methylhexane are interconverted rapidly as are also 2,3- and 2,4-dimethylpentane. However, the dimethylpentanes are formed only very slowly from the methylhexanes, and 2,2,3-trimethylbutane is formed extremely slowly from the dimethylpentanes.

The isomerization of 3-ethylpentane has received only scant attention. In their study of the H–D exchange between alkanes and deuteriosulfuric acid, Stevenson and co-workers found that the rate was somewhat lower for 3-ethylpentane than for several other singly branched alkanes.[3] Thus, 3.3% of the 3-ethylpentane molecules suffered exchange in 2 hr., whereas with 3-methylhexane, 7% exchange occurred during 40 min. under the same conditions. The nature of the deuterated species formed from 3-ethylpentane deserves mention; d_{12} and d_{15}, with a possible trace of d_9, were the only species present. The unusual feature of these results is the absence of species with lower deuterium content. Mass spectrometric evidence also indicated that the deuterated compounds did not have the 3-ethylpentane skeleton.

Experimental

Materials.—3-Ethylpentane, b.p. 93.0–93.8°, n^{25}D 1.3907, was obtained by dehydrating 3-ethyl-3-pentanol over alumina at 370°, followed by hydrogenation of the resulting alkene over platinum oxide. This material was fractionated through a 60-cm. column packed with glass helices and then percolated over silica gel. Gas chromatography indicated a purity in excess of 99.9%, with the only contaminant being 3-methylhexane.

3-Methylpentane, b.p. 64.0–64.3°, n^{25}D 1.3738, was obtained from 3-methyl-3-pentanol by the same sequence of steps as used for 3-ethylpentane. Gas chromatography failed to reveal the presence of impurities.

A single bottle of reagent grade 96.4% sulfuric acid served as a stock solution for all reactions in which acid of this concentration was used. Acids of higher concentration were prepared from this stock solution by adding appropriate amounts of 15% fuming sulfuric acid (C.P. grade). All concentrations were determined by titration with standard sodium hydroxide.

Isomerization Reactions.—In the standard procedure, 0.5 ml. of hydrocarbon and 0.5 ml. of acid were placed in a water-jacketed tube and agitated by the "rapid-stirring" technique of Burwell and co-workers.[5] The water which was circulated through the jacket was maintained at a temperature of 25.0 ±0.1°. At the end of the reaction period, stirring was discontinued, and the mixture was allowed to stand until separation of layers occurred. A portion of the hydrocarbon layer was withdrawn by pipet and placed in a test tube containing a pellet of potassium hydroxide. Duplicate experiments were carried out in each case.

Product Analysis.—The products were analyzed by gas chromatography on a 50-ft. column packed with β,β′-oxydipropionitrile on Fisher Columpak and maintained at a temperature of 50°. Good resolution was achieved for all isomers encountered in the study, and the areas under the peaks were calculated by triangulation. The per cent composition of synthetic mixtures calculated by this method agreed with the known values to within 0.1.

Results

The results of the isomerization studies are summarized in Table I. As expected, 2- and 3-methylhexane were found to be the initial products of isomerization; the ratios of the concentration of these isomers in the products are listed in col. 5 of Table I. The reason for presenting the data in this fashion will become apparent below. The dimethylpentanes are formed at a much slower rate. For example, in experiment 15, approximately 0.1% of 2,4-dimethylpentane, and 0.05% of 2,3-dimethylpentane were formed, whereas the methylhexanes were present to the extent of 4.3%. Disproportionation products were not detected.

Mixtures of 3-ethylpentane and 3-methylpentane were used in the initial experiments (1–8) so that the rate for the former could be compared with that of a "methyl-shift" compound. Experiments 10–15 were conducted with 3-ethylpentane as the sole hydrocarbon to determine if the 3-methylpentane exerted a significant effect on the rate of isomerization of the former. The effect of a trace of olefin is illustrated by experiment 9, in which a small amount of 3-methyl-2-pentene was present.

The effect of doubling and tripling the acid to hydrocarbon ratio is illustrated by experiments 16 and 17. In experiment 18, a trace of 3-methyl-2-pentene was added to the 3-ethylpentane, and samples were withdrawn for analysis at the times indicated. The effect of methylcyclopentane on the rate of isomerization of 3-

(1) G. S. Gordon, III, and R. L. Burwell, Jr., *J. Am. Chem. Soc.*, **71**, 2355 (1949).

(2) V. I. Komarewsky and W. E. Ruther, *ibid.*, **72**, 2501 (1950).

(3) D. P. Stevenson, C. D. Wagner, O. Beeck, and T. W. Otvos, *ibid.*, **74**, 3269 (1952).

(4) A. K. Roebuck and B. L. Evering, *ibid.*, **75**, 1631 (1953).

(5) R. L. Burwell, Jr., R. B. Scott, L. G. Maury, and A. S. Hussey, *ibid.*, **76**, 5822 (1954).

(6) L. G. Maury, R. L. Burwell, Jr., and R. H. Tuxworth, *ibid.*, **76**, 5831 (1954).

TABLE I[a]

ISOMERIZATION OF 3-ETHYLPENTANE AT 25.0°

Expt. no.	Alkane	Time, hr.	% isomerization of 3 EP	Ratio of 2MH/3MH in product	% isomerization of 3 MP
			96.4% acid		
1	3EP, 3MP	1.0	0.8		2.3
2		1.5	1.3	1.2	3.9
3		2.0	1.8	1.2	5.5
4		2.5	2.3	1.2	6.6
5		3.0	2.7	1.2	7.5
6		3.5	3.4	1.3	9.6
7		4.0	4.0	1.3	11.3
8		5.0	4.8	1.3	13.0
9[b]		2.0	19.6	1.2	37.6
10	3EP	1.0	0.6	2.1	
11		2.0	1.5	1.9	
12		3.0	1.9	1.9	
13		4.0	2.8	1.9	
14		5.0	3.8	2.0	
15		6.0	4.4	2.0	
16[c]		2.0	2.8	2.1	
17[d]		2.0	3.9	2.1	
18[b,e]		0.25	0.9	1.1	
		0.50	3.3	1.5	
		1.0	9.3	1.7	
		1.5	12.2	1.7	
19[f]	3EP, MCP	18.0	1.5	0.2	
20[g]		5.0	0.3	0.5	
21[h]		5.0	0.4	0.7	
			98.7% acid		
22	3EP, 3MP	0.25	3.6	1.0	6.0
23		0.50	6.7	1.0	11.8
24		0.75	9.9	1.0	16.2
25		1.0	13.6	1.0	20.6
26		1.5	20.8	1.1	28.2
			99.4% acid		
27	3EP, 3MP	0.50	28.7	1.1	37.6

[a] These abbreviations are used: 3EP for 3-ethylpentane, 2MH and 3MH for 2- and 3-methylhexane, 3MP for 3-methylpentane, and MCP for methylcyclopentane. [b] One microliter of 3-methyl-2-pentene was added. [c] Acid–hydrocarbon volume ratio, 2:1. [d] Acid–hydrocarbon volume ratio, 3:1. [e] Samples were removed from reaction mixture at times indicated. [f] 50:50 mixture of 3EP and MCP by volume. [g] 10:1 mixture of 3EP and MCP by volume. [h] 20:1 mixture of 3EP and MCP by volume.

ethylpentane and on the ratio of the methylhexanes formed is illustrated by experiments 19–21. In agreement with the findings of others,[3] we did not detect isomerization of methylcyclopentane to cyclohexane.

Discussion

It is apparent from experiments 1–8 that 3-ethylpentane isomerizes at a decidedly lower rate than 3-methylpentane. Both reactions follow first-order kinetics, and rate constants, calculated by a least squares treatment of the data, are given in Table II. It has been shown that the rate of isomerization of isoparaffins depends greatly on the acid concentration.[4] Rate constants for reactions carried out with 98.7% acid (experiments 22–26) also are presented in Table II where it is seen that the proportional increase is greater for 3-ethylpentane than for 3-methylpentane. The possibility that, at a sufficiently high acid concentration, the rate for 3-ethylpentane might surpass that for 3-methylpentane is rendered unlikely by the results of experiment 27 where it is seen that, with 99.4% acid, 3-methylpentane still isomerizes at a substantially greater rate.

Although an exact comparison cannot be made, it does appear that our rate constants for 3-methylpentane

TABLE II

RATE CONSTANTS FOR ISOMERIZATION OF 3-ETHYLPENTANE AND 3-METHYLPENTANE IN ADMIXTURE, 25.0°

	k_1, hr.$^{-1}$[a]	
	96.4% acid	98.7% acid
3-Ethylpentane	0.0105 ± 0.0002	0.158 ± 0.004
3-Methylpentane	0.0308 ± 0.0008	0.238 ± 0.002

[a] The isomerization of 3-ethylpentane was treated as an irreversible reaction; that of 3-methylpentane was treated as a reversible reaction with equilibrium concentrations of 69% 2- and 31% 3-methylpentane (see ref. 4).

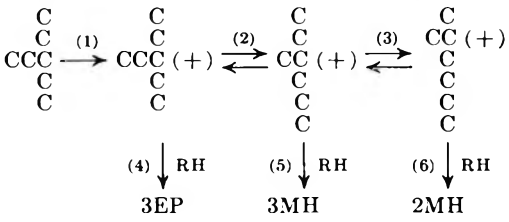
are somewhat larger than those that Roebuck and Evering found.[4] Thus, from the curve presented by these authors, one estimates $k_1 \simeq 0.15$ hr.$^{-1}$ for 98.7% acid, as compared with our value of 0.24 hr.$^{-1}$. The discrepancy is believed to be due to more efficient stirring of the reaction mixtures in the present study.[7]

When 3-ethylpentane alone is treated with sulfuric acid (experiments 10–15), the rate of isomerization, $k_1 = 0.0081 \pm 0.008$ hr.$^{-1}$, is slightly lower than when 3-methylpentane is present. The difference is small, how-

(7) Roebuck and Evering observed a decline in value of the first-order rate constants at increasing conversions. Burwell, *et al.*,[5] found that this did not occur with the "rapid-stirring" technique.

ever, and it may be concluded that 3-methylpentane does not exert a significant influence on the rate of isomerization of 3-ethylpentane.

The essential steps of the carbonium ion mechanism of isomerization of 3-ethylpentane are as follows. This scheme differs from the one presented by Burwell, *et al.*,[5]



for the methylhexanes only in that ethyl as well as methyl migration is included. In step 1, the chain-initiating step, oxidation of 3-ethylpentane to the carbonium ion state by sulfuric acid occurs, and, in steps 4, 5, and 6, the chain-carrying step, a new carbonium ion (not shown) is formed from RH, the hydride donor.

Stevenson, *et al.*, suggested that the absence of deuterated species with preserved carbon skeleton when 3-ethylpentane was treated with deuteriosulfuric acid might be due to (a) rapid migration of ethyl groups in the 3-ethylpentyl ion, or (b) an unusually long period of ionic residence, due perhaps to steric hindrance in the chain-carrying step.[3] The results of our study can be rationalized readily in terms of the latter postulate, *viz.*, the low reactivity of 3-ethylpentane as a hydride donor. This would result in a lowered rate for the chain-initiating and chain-propagating steps and an over-all reduction in rate of isomerization of 3-ethylpentane compared to 3-methylpentane.

The most striking difference between the experiments in which 3-methylpentane was present in the reaction mixture and those in which 3-ethylpentane alone was used is the difference in the relative amounts of the methylhexanes formed. The ratio of 2- to 3-methylhexane was approximately 1.25 when 3-methylpentane was present and 1.95 when it was absent. The postulation of low hydride donor tendency for 3-ethylpentane also provides an explanation for these differing ratios. The relative amounts of the methylhexanes formed would be expected to depend on the nature of the hydride donors present in the reaction mixture. When only reluctant donors are present—the situation that exists in the early stages of reactions involving 3-ethylpentane alone—a smaller fraction of the 3-methylhexyl ions will be converted to 3-methylhexane (step 5) than when a more efficient donor, *e.g.*, 3-methylpentane, is present.

It seems most likely that steric factors are responsible for the low hydride donor activity of 3-ethylpentane, and the situation is reminiscent of the findings of Brown and Taylor on the basicity of amines toward trimethylboron.[8] It was observed that basicity decreases in the series $EtNH_2 > Et_2NH \gg Et_3N$. Brown and Taylor proposed that at least one of the methyl groups of triethyl amine is held in a conformation in which it protrudes in front of the nitrogen, thus interfering with salt formation. A comparable situation may exist in 3-ethylpentane in which the methyl groups interfere with removal of the tertiary hydrogen. In support of this hypothesis may be cited the data on the exchange of ethylcyclopentane with deuteriosulfuric acid. This hydrocarbon exchanges very rapidly—35% in 2 hr. with 95% acid—as contrasted with 3.3% exchange for 3-ethylpentane in the same period of time.[3] Ethylcyclopentane can be visualized as an analog of 3-ethylpentane in which the accumulation of atoms in the region around the tertiary hydrogen has been reduced by tying two of the ethyl groups behind the carbon. The enhanced basicity of quinuclidine over that of triethylamine has been rationalized by a similar argument.[8]

To gain additional evidence concerning the relationship between the nature of the hydride donors present and the ratio of methylhexanes formed, experiments were carried out in which mixtures of methylcyclopentane and 3-ethylpentane were used (experiments 19–21). Methylcyclopentane, which can be considered as a cyclic analog of 3-methylpentane in which congestion around the tertiary hydrogen has been reduced by ring formation, has been shown to exchange very rapidly with deuteriosulfuric acid, *e.g.*, 9.5% in 40 min. and 63% in 120 min.[3] The presence of methylcyclopentane caused a marked reduction in the ratio of 2- to 3-methylhexane, *e.g.*, to a value of 0.2 when a 50:50 mixture was used. The ratio increased when smaller amounts of methylcyclopentane were used, but, even with a mixture of one part methylcyclopentane to twenty 3-ethylpentane, the ratio was only 0.7. Thus, these results support the postulate of the relationship between hydride donor ability and ratio of methylhexanes.

It is interesting to note the drastic reduction of rate of isomerization brought about by methylcyclopentane, *e.g.*, only 1.5% isomerization occurred in 18 hr. when a 50:50 mixture was used. This also may be related to the tendency of methylcyclopentane to donate hydride to an open-chain carbonium ion and thus decrease the rate of the chain-carrying step.

The methylhexane ratio is not affected greatly by the concentration of acid, although it does appear to be slightly lower at higher acid concentrations. Thus, for mixtures of 3-ethylpentane and 3-methylpentane with 98.7% acid, the ratio was approximately 1.0, and with 99.4% acid, the value was 1.1. The significance of the latter value can be questioned on the grounds that an extensive amount of isomerization occurred. The fact that the ratios do appear to be slightly lower for higher acid concentrations may reflect a higher concentration of hydride donors in the acid phase.

One experiment (no. 18) was performed in which a trace of 3-methyl-2-pentene was added to 3-ethylpentane, and the methylhexane ratio was determined periodically during the early stages of the reaction. Initially, the ratio was quite small, for 1.1 after 0.9% isomerization had occurred, but increased to a value of 1.7 after 9% isomerization. The low values observed initially are believed to result from a higher-than-usual concentration of hydride donors, *e.g.*, alkene, in the acid phase. As the reaction proceeds, the extra concentration diminishes because of polymerization, etc., and a corresponding increase in the methylhexane ratio is observed.

Small amounts of 3-ethylpentane are formed by isomerization of the methylhexanes, but the rate of formation is very low. For example, 3-ethylpentane was not detected after 4 hr. treatment with 96.4% acid, and less than 1.0% was present after 28 hr. with 98.7% acid.

(8) H. C. Brown, and M. D. Taylor, *J. Am. Chem. Soc.*, **69**, 1332 (1947).

Electrophilic Substitution of 4a-Methyl-1,3,9-triphenyl-4a*H*-fluorene[1]

HAROLD W. MOORE AND H. R. SNYDER

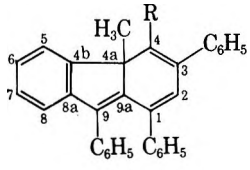
The Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois

Received August 5, 1963

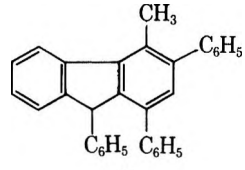
Electrophilic substitution reactions of the strongly basic hydrocarbon (Ia) are described. The new substitutions are chlorination with either thionyl chloride or phosphorus oxychloride in dimethyl sulfoxide, the Vilsmeier formylation with dimethylformamide and phosphorus oxychloride, and nitration with cupric nitrate in acetic anhydride. In each reaction substitution occurs in the 4-position. The intermediate iminium salt can be isolated easily in the Vilsmeier synthesis, and the salt is readily reduced to the tertiary amine. The 4-nitro compound is identical with a product obtained earlier from the hydrocarbon and nitrous acid in hot acetic acid.

In earlier papers of this series[2-4] it was shown that the lower melting hydrocarbon obtained from the polyphosphoric acid-catalyzed condensation of acetophenone is 4a-methyl-1,3,9-triphenyl-4a*H*-fluorene (Ia). It was shown also that protonation of this hydrocarbon occurs stereospecifically as position 4 to give a new stable carbonium ion which can be isolated as the perchlorate, fluoroborate, or bromide.[4] It has been shown[4] that hydrocarbon Ia is readily brominated when treated with dimethyl sulfoxide and ethyl bromide according to the method of Fletcher and Pan,[5] and the location taken by the entering bromine atom was deduced as position 4 (structure Ib). Part of the argument for this assignment rested on the fact that the deuterio compound (Ic), obtained from the bromide by conversion to the lithium compound and reaction of the latter with deuterium oxide, lost deuterium when subjected to rearrangement by hydrobromic acid in acetic acid, yielding 4-methyl-1,3,9-triphenylfluorene (II).

The facile protonation and mild bromination of Ia have prompted an investigation of other electrophilic substitutions of the hydrocarbon. One of the most interesting processes discovered is the essentially quantitative reaction of the hydrocarbon with either thionyl chloride or phosphorus oxychloride and dimethyl sulfoxide in benzene. The reaction presumably proceeds through the intermediate III previously proposed[6] as the precursor of the α-chlorosulfide formed from the sulfoxide and thionyl chloride.



I



II

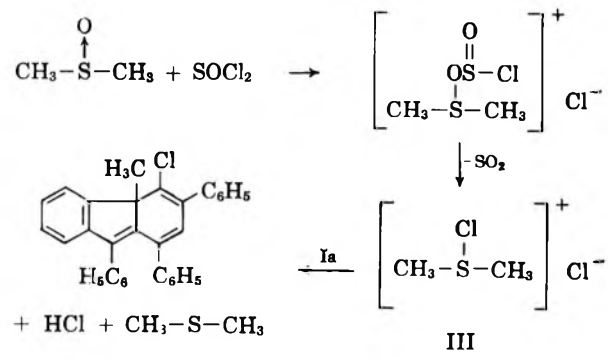
a, R = H e, R = CHO

b, R = Br f, R = $CH{=}\overset{+}{N}(CH_3)_2$

c, R = D g, R = $CH_2{-}N(CH_3)_2$

d, R = Cl h, R = NO_2

The infrared spectrum of the chloro compound (Id) was nearly identical with that of 4-bromo-4a-methyl-1,3,9-triphenyl-4a*H*-fluorene (Ib). The n.m.r. spectrum of the chloro compound showed, in addition to aromatic and methyl proton absorption, one vinyl proton absorption as a singlet at 3.60 τ. These spectral data show that the position of the chlorine atom in Id is the same as that of the bromine atom in Ib.



III

When the hydrocarbon (Ia) was treated with an equimolar amount of phosphorus oxychloride in dimethylformamide and the reaction mixture was worked up by the addition of water, an 86% yield of 4-formyl-4a-methyl-1,3,9-triphenyl-4a*H*-fluorene (Ie) was realized. The infrared spectrum of Ie showed strong absorption at 1655 cm.$^{-1}$ indicting a conjugated carbonyl group. The n.m.r. spectrum of Ie showed the absorption of a sharp singlet in the vinyl proton region at 3.52 τ. The aldehyde proton absorbed at 0.35 τ. Unambiguous proof that formylation had taken place in the 4-position was obtained by formylation of 4a-methyl-1,3,9-triphenyl-4a*H*-fluorene-4*d* (Ic). Since formylation of the deuterated hydrocarbon (Ic) in the 4-position would eliminate the deuterium from the compound, the n.m.r. spectrum of the product should be identical with the spectrum of the aldehyde obtained from the undeuterated hydrocarbon, *i. e.*, singlet vinyl absorption at 3.52 τ. The expected identity of the n.m.r. spectra of the two samples of the aldehyde was indeed observed.

The intermediate iminium salt (If) could be isolated when the hydrocarbon (Ia) was treated with equimolar amounts of dimethylformamide and phosphorus oxychloride in benzene. After vigorous stirring at room temperature for five minutes the reaction mixture became blood red and a beautiful red crystalline solid precipitated. This material was shown to be the dimethylimine salt (If). The infrared spectrum of If shows strong C=N absorption at 1640 cm.$^{-1}$. The n.m.r. spectrum of If shows that there is a great deal of double bond character to the carbon–nitrogen bond. The two methyl groups attached to the nitrogen are nonequivalent. These methyl group protons appear as singlets at 7.49 and 6.30 τ. The proton α to the nitrogen absorbs at -0.83 τ. The methyl group at the

(1) Grateful acknowledgment is made of partial support of this work by a grant from the National Science Foundation (G-6223) and of a Fellowship (1960–1962) to H. W. M. Provided by the Phillips Petroleum Co.

(2) H. W. Moore and H. R. Snyder, *J. Org. Chem.*, **28**, 535 (1963).

(3) R. W. Roeske, D. B. Bright, R. L. Johnson, W. J. DeJarlais, R. W. Bush, and H. R. Snyder, *J. Am. Chem. Soc.*, **82**, 3128 (1960).

(4) H. W. Moore and H. R. Snyder, *J. Org. Chem.*, **28**, 297 (1963).

(5) T. L. Fletcher and H. L. Pan, *J. Am. Chem. Soc.*, **78**, 4812 (1956); *Chem. Ind.* (London), 660 (1957).

(6) F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, **77**, 575 (1955).

4a-position absorbs at 7.85 and the vinyl proton at the 2-position gives a singlet at 3.45 τ.

Smith[7] showed that lithium aluminum hydride reduction of the iminium salt obtained as an intermediate in the Vilsmeier formylation of indole gave the known compound gramine. Lithium aluminum hydride reduction of the iminium salt (If) proceeded instantaneously to give 4-dimethylaminomethyl-4a-methyl-1,3,9-triphenyl-4a*H*-fluorene (Ig). The n.m.r. spectrum of Ig is in strict agreement with the proposed structure. The methyl groups attached to the nitrogen are now equivalent and show absorption as a singlet at 7.82 τ. The methyl at the 4a-position comes at 8.02 τ. Methylene absorption appears as a singlet at 6.37 and the one vinyl proton at the 2-position appears as a singlet at 3.52 τ.

An earlier attempt[8] to effect the nitration of the hydrocarbon Ia with fuming nitric acid at room temperature did not lead to a pure product. However, reaction with nitrous acid in hot acetic acid gave a pure substance having the composition of a mononitro derivative and believed to be an α,β-unsaturated nitro compound.[3] It is now found that nitration of the hydrocarbon Ia with cupric nitrate in acetic anhydride at 0°, according to the method of Anderson, Nelson, and Tazuma,[9] gives 4-nitro-4a-methyl-1,3,9-triphenyl-4a*H*-fluorene (Ih) in good yield. The infrared spectrum of the nitro compound (Ih) showed strong nitro group absorption at 1520 and 1345 cm.$^{-1}$. The n.m.r. spectrum showed methyl group absorption at 7.92 and the vinyl proton at the 2-position appeared as a singlet at 3.65 τ. The sample of the nitro compound prepared in this experiment was found to be identical with that prepared earlier[3] from nitrous acid by comparison of the infrared spectra and by mixture melting point determination.

It was of interest to determine the fate of substituents in the 4-position when compounds Ib and Ie containing them are subjected to the action of 48% hydrobromic acid in refluxing acetic acid, the conditions causing rearrangement of Ia to the fluorene (II). In a variation[2] of this rearrangement of the hydrocarbon (Ia) in which dimethyl sulfoxide was employed as the solvent, bromination at the 9-position evidently occurred, since the product obtained after treatment of the reaction mixture with water was the fluorenol having the structure of II but with a hydroxyl group in place of the hydrogen atom at position 9. A similar reaction occurred when the bromo compound (Ib) was heated with hydrobromic acid in acetic acid under conditions of moderate concentration (3 g. of Ia and 4 ml. of hydrobromic acid in 75 ml. of acetic acid); the principal substance isolated after recrystallization of the crude product from a mixture of ethanol and chloroform was 9-ethoxy-4-methyl-1,3,9-triphenylfluorene (38%). Only a little (7%) of hydrocarbon II was isolated, although it may have formed in considerably larger amounts, its separation from the mixture being rather difficult. Free bromine was detected as a product of the reaction. In a similar experiment in which the relative amounts of the bromo compound and hydrobromic acid were about the same (0.8 g. and 1 ml.) but the relative amount of acetic acid (150 ml.) was increased severalfold, only hydrocarbon II was isolated. Evidently the bromo compound (Ib) in acid solution is a source of positive bromine, perhaps through the elimination of a positive bromine ion from the protonated species to yield the parent hydrocarbon (Ia) which then protonates and rearranges to II, with the liberated bromine ion attacking either II or the hydrogen bromide in the solution.

A similar treatment of the aldehyde (Ie) gave only the rearranged hydrocarbon (II). Presumably the protonated form of the aldehyde expels carbon monoxide to generate the carbonium ion related to Ia, which then rearranges.

Experimental[10]

Preparation of 4-Chloro-4a-methyl-1,3,9-triphenyl-4a*H*-fluorene (Id).—Two grams (0.005 mole) of 4a-methyl-1,3,9-triphenyl-4a*H*-fluorene (Ia) was dissolved in 100 ml. of benzene and 20 ml. of dry dimethyl sulfoxide in a 250-ml. three-necked round-bottomed flask equipped with an automatic stirrer, $CaCl_2$-protected condenser, and a dropping funnel. To this yellow solution was added 1.18 g. (0.010 mole) of thionyl chloride over a period of 15 min. Immediately upon addition of the thionyl chloride the solution became dark blue-green, and the odor of dimethyl sulfide was very prevalent. The color faded to yellow after about 5 min. The addition of thionyl chloride caused an increase in temperature to 35°. The reaction solution was stirred for 3 hr. without any application of heat. The solvent was then removed by distillation at reduced pressure leaving 2.1 g. (94%) of 4-chloro-4a-methyl-1,3,9-triphenyl-4a*H*-fluorene, m.p. 206–208°.

Anal. Calcd. for $C_{32}H_{23}Cl$: C, 86.68; H, 5.19. Found: C, 86.42; H, 5.40.

Preparation of 4-Formyl-4a-methyl-1,3,9-triphenyl-4a*H*-fluorene (Ie).—Two grams (0.005 mole) of Ia was dissolved in 100 ml. of dry dimethylformamide in a 250-ml. three-necked round-bottomed flask equipped with a $CaCl_2$-protected condenser, automatic stirrer, and a dropping funnel. The solution was vigorously stirred at room temperature while 1.2 g. (0.007 mole) of $POCl_3$ was added slowly. Immediately upon addition of the $POCl_3$ the reaction solution turned a deep orange-red. This solution was heated on the steam bath for 1 hr. Water (50 ml.) was added to the hot solution, causing the precipitation of an orange-red solid. This aqueous mixture was heated on the steam bath for 1.5 hr. At the end of this time the solid was a brilliant orange in color. Recrystallization three times from absolute ethanol gave 1.9 g. (86%) of 4-formyl-4a-methyl-1,3,9-triphenyl-4a*H*-fluorene, m.p. 175–176°.

Anal. Calcd. for $C_{33}H_{24}O$: C, 90.82; H, 5.50. Found: C, 90.63; H, 5.80.

Repetition of the experiment on a smaller scale (1/20) but with the deuterio compound 4a-methyl-1,3,9-triphenyl-4a*H*-fluorene-4*d*[4] gave about 70% of a product identical with that just described in melting point, mixture melting point, and n.m.r. spectrum.

Preparation of the Iminium Salt (If).—Five grams (0.012 mole) of 4a-methyl-1,3,9-triphenyl-4a*H*-fluorene (Ia) and 1 g. (0.015 mole) of dimethylformamide was dissolved in 100 ml. of dry benzene in a 250-ml. three-necked round-bottomed flask equipped with an automatic stirrer and a $CaCl_2$-protected condenser. The yellow solution was vigorously stirred while 1.4 g. (0.015 mole) of $POCl_3$ was added in one portion. Immediately upon addition of the $POCl_3$ there was a flash of blue color; this blue color lasted only a few seconds and then the solution became yellow.

About 5 min. later the solution was blood red. This red solution was stirred at room temperature for 4 hr. At the end of this time a beautiful crystalline solid had precipitated. The solid was removed by filtration giving 5.3 g. (92%) of the salt If, m.p. 152–155° dec. Because of the instability of the salt in hot solutions, attempts to purify it for analysis were unsuccessful.

(7) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).

(8) Richard L. Johnson, Ph.D. thesis, University of Illinois, 1955.

(9) A. G. Anderson, J. A. Nelson, and J. J. Tazuma, *J. Am. Chem. Soc.*, **75**, 4980 (1953).

(10) Melting points are uncorrected. Microanalyses were carried out by Mr. J. Nemeth and his associates, University of Illinois.

Preparation of 4-Dimethylaminomethyl-4a-methyl-1,3,9-triphenyl-4a*H*-fluorene (Ig).—Two grams of the iminium salt was dissolved in 100 ml. of dry tetrahydrofuran in a 250-ml. round-bottomed three-necked flask equipped with an automatic stirrer and a $CaCl_2$-protected condenser. Lithium aluminum hydride was added in small portions over a period of 30 min. During this period of time, the color of the reaction solution changed from deep red to light yellow. The reaction mixture was stirred at room temperature for 2 hr. Fifty milliliters of wet ether was then slowly added to decompose the complex and any unchanged lithium aluminum hydride. The reaction mixture was filtered and the solvent was removed by distillation under reduced pressure. A yellow solid was obtained, which after recrystallization from a 1:1 mixture of ethanol and chloroform gave 1.5 g. (74%) of 4-dimethylaminomethyl-4a-methyl-4a*H*-fluorene, m.p. 192–193°.

Anal. Calcd. for $C_{35}H_{32}N$: C, 90.32; H, 6.66; N, 3.02. Found: C, 89.85; H, 6.83; N, 2.97.

Preparation of 4-Nitro-4a-methyl-1,3,9-triphenyl-4a*H*-fluorene (Ih).—One and one-half grams (0.0037 mole) of Ia was added to 100 ml. of freshly distilled acetic anhydride in a 250-ml. three-necked round-bottomed flask equipped with an automatic stirrer, a thermometer, and a $CaCl_2$-protected reflux condenser. The reaction solution was cooled to 5° by means of an ice–water bath and stirred vigorously while 0.5 g. (0.0045 mole) of cupric nitrate in 20 ml. of acetic anhydride was added over a period of 15 min. The solution immediately became dark blue-green upon addition of the cupric nitrate. The ice–water bath was removed and the dark blue-green reaction solution was allowed to warm to room temperature. The solution was then vigorously stirred at room temperature for 4 hr. At the end of this time the reaction mixture was still blue-green, but it was more like the color of cupric nitrate than it had been earlier in the reaction. Water (100 ml.) was added and the resulting mixture was stirred, with cooling, for 30 min. During this time the acetic anhydride hydrolyzed and a brilliant orange solid precipitated. This material was collected by filtration and recrystallized from a 1:1 mixture of ethanol and chloroform giving 1.1 g. (65%) of 4-nitro-4a-methyl-1,3,9-triphenyl-4a*H*-fluorene, m.p. 196–198°.

Anal. Calcd. for $C_{32}H_{23}NO_2$: C, 84.76; H, 5.07; N, 3.09. Found: C, 84.38; H, 5.15; N, 3.14.

Reaction of 4-Bromo-4a-methyl-1,3,9-triphenyl-4a*H*-fluorene with 48% Hydrobromic Acid in Glacial Acetic Acid Followed by Reaction with Ethanol.—Three grams of 4-bromo-4a-methyl-1,3,9-triphenyl-4a*H*-fluorene[4] was added to 75 ml. of glacial acetic acid in a flask equipped with a stirrer and a reflux condenser connected to a trap containing chloroform. Four milliliters of 48% hydrobromic acid was added and the mixture was stirred and heated. A deep blue-green color soon developed and then slowly faded to yellow after 3 hr. of reflux. The chloroform solution in the trap had a pale color (bromine) and it gave a definite iodine color when shaken with aqueous sodium iodide. The grey solid that separated when the reaction solution was cooled to about 0° was recrystallized four times from 1:1 chloroform–ethanol to give 1.2 g. (38%) of 9-ethoxy-4-methyl-1,3,9-triphenylfluorene, m.p. 150–152°, identical in melting point, infrared spectrum, and n.m.r. spectrum with the sample prepared from the 9-hydroxy compound as described subsequently.

Dilution of the acetic acid solution from which the foregoing crude product had been separated with about 100 ml. of water caused the separation of a solid. Four recrystallizations of this material from 1:1 ethanol–chloroform gave 0.2 g. (7.2%) of 4-methyl-1,3,9-triphenylfluorene[3] (II), m.p. 163–164°, identified by mixture melting point.

In a reaction in which 0.8 g. of the bromo compound (Id) was heated with 150 ml. of acetic acid and 1 ml. of 48% hydrobromic acid, only 4-methyl-1,3,9-triphenylfluorene (II, 0.4 g., 62%) was isolated.

Preparation of 9-Ethoxy-4-methyl-1,3,9-triphenylfluorene from 9-Hydroxy-4-methyl-1,3,9-fluorene.—A mixture of 0.20 g. of 4-methyl-1,3,9-triphenyl-9-fluorenol[2] and 50 ml. of concentrated hydrochloric acid was refluxed for 15 min. and then allowed to stand at room temperature for 12 hr. Filtration gave 180 mg. (90%) of white crystalline 9-chloro-4-methyl-1,3,9-triphenylfluorene, m.p. 192–195°. The material was very sensitive to moisture. Accordingly, a sample prepared in this way (4.3 g.) was heated under reflux for 1 hr. with 100 ml. of ethanol–chloroform and the solid remaining after removal of the solvent mixture under reduced pressure was recrystallized four times from 1:1 ethanol–chloroform to give 4.3 g. (95%) of the ethoxy compound, m.p. 150–152°. The n.m.r. spectrum showed the characteristic absorption of the ethyl group (triplet at 8.99 and a quartet at 6.82 τ with a coupling constant, $J = 7$ c.p.s., with the relative intensity of the quartet to the triplet being 2:3).

Anal. Calcd. for $C_{34}H_{28}O$: C, 90.26; H, 6.19. Found: C, 90.24; H, 5.98.

Reaction of 4-Formyl-4a-methyl-1,3,9-triphenyl-4a*H*-fluorene with 48% Hydrobromic Acid in Acetic Acid.—Four grams of 4-formyl-4a-methyl-1,3,9-triphenyl-4a*H*-fluorene was dissolved in 150 ml. of glacial acetic acid in a flask equipped with a stirrer and a reflux condenser. Two milliliters of 48% hydrobromic acid was added, giving a deep brown-yellow solution. The color changed as the solution was heated and stirred, becoming an intense blue-green as the boiling point was reached and then slowly fading to brown-yellow after 4 hr. at reflux. Dilution of the cooled solution with water gave a grey solid. After five recrystallizations from 1:1 ethanol–chloroform there remained 2.0 g. (52%) of 4-methyl-1,3,9-triphenylfluorene, m.p. 162–164°, identified by mixture melting point with an authentic sample.[3]

N.m.r. Spectroscopy.—The n.m.r. spectra were recorded by Mr. D. Johnson and his associates with a Varian Associates high resolution spectrometer (A-60) at a frequency of 60 Mc. per second. Spectra were obtained in 30% solutions with tetramethylsilane as an internal standard. Chemical shifts are expressed as shielding values (τ) as defined by G. V. D. Tiers.[11]

(11) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

p-Polyphenyl from Benzene–Lewis Acid Catalyst–Oxidant. Reaction Scope and Investigation of the Benzene–Aluminum Chloride–Cupric Chloride System[1]

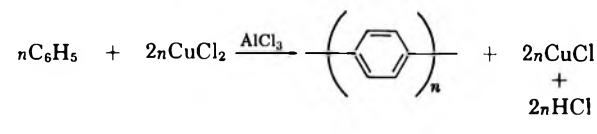
PETER KOVACIC AND JAMES OZIOMEK

The Department of Chemistry, Case Institute of Technology, Cleveland, Ohio

Received July 22, 1963

In the polymerization of benzene by aluminum chloride–cupric chloride, the yield of *p*-polyphenyl varied inversely with the amount of added water. Polymer yield attained a maximum value, almost quantitative, at an $AlCl_3$–$CuCl_2$ molar ratio of 2:1. The cuprous chloride formed by reduction of the oxidant is present as a C_6H_6·$AlCl_3$·CuCl complex. Large amounts of added cuprous chloride inhibited the reaction completely, whereas smaller quantities acted as a promoter. With cupric halide as oxidant, aluminum chloride, aluminum bromide, and antimony pentachloride exhibited catalytic activity. In the presence of aluminum halide catalyst, polymerization occurred with the oxidizing agents, cupric chloride, cupric bromide, lead dioxide, manganese dioxide, nitrogen dioxide, nitrogen trioxide, chloranil, and *p*-benzoquinone. There was evidence of chain termination by the nitrogen oxides and chloranil. The theoretical aspects are treated.

Recently, it was shown[2] that the aromatic nucleus can be polymerized smoothly in the system, aromatic monomer–Lewis acid catalyst–oxidant. This constituted the first case wherein an aromatic monomer functioned in a well defined polymerization leading to homopolymer. For example, benzene was converted to *p*-polyphenyl on treatment with aluminum chloride–cupric chloride under mild conditions.



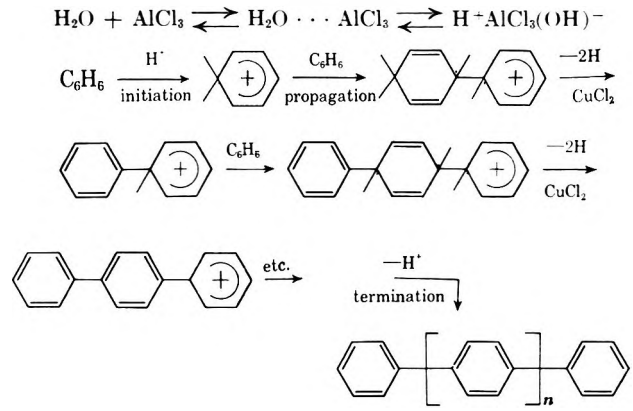
Also effective for the polymerization of benzene were molybdenum pentachloride[3] and ferric chloride.[4] These two metal halides apparently assume the dual role of catalyst and oxidant. Prior to these investigations Marvel and Hartzell[5] synthesized impure *p*-polyphenyl by the chloranil oxidation of poly-1,3-cyclohexadiene prepared by Ziegler polymerization.

The purpose of this study was to define the scope of benzene polymerization in the system, benzene–Lewis acid catalyst–oxidant. In particular, the reaction benzene–aluminum chloride–cupric chloride was explored, in order to determine the effect of water, cuprous chloride, and variation in catalyst–oxidant ratio. In addition, we were interested in obtaining information relative to the mechanistic aspects of this novel reaction.

Results and Discussion

Water Cocatalysis.—Previously, evidence was found in the benzene–ferric chloride reaction for cocatalysis by Brønsted acids, such as water, acetic acid, and nitroethane.[6] Subsequently, it was shown that the polymer yield passed through a maximum at a H_2O–$FeCl_3$ molar ratio of 1 for short reaction times. Furthermore, the most rapid rate of hydrogen chloride evolution was observed at this ratio.[7] These data indicate that ferric chloride monohydrate is the most active catalyst–cocatalyst complex.

In view of these results, we undertook an investigation of water as a potential cocatalyst in the benzene–aluminum chloride–cupric chloride reaction. The following working hypothesis was used.



Water was added to the system, C_6H_6–$AlCl_3$–$CuCl_2$ = 4:1:1 (2 hr. at 30–32°), in molar ratios of H_2O–$AlCl_3$ varying from 0 to 4. The results clearly show that polymer yield varies inversely with the amount of added water (Table I). This is in sharp contrast with

TABLE I

VARIATION OF WATER. EFFECT ON POLYMER YIELD[a,b]

H_2O, moles	Yield, %	*p*-Polyphenyl, % C	H	Cl	O	C–H, atomic ratio
0	64	92.29	5.03	2.47		1.53
0	66	91.79	5.07	2.29		1.50
0.05	60	93.43	5.05	1.62		1.54
0.05	56	92.21	5.00	2.40		1.54
0.25	29	91.48	5.04	2.43	0.49	1.51
0.25	30	92.66	5.07	1.79	0.22	1.52
0.5	17	93.32	5.38	1.38	0.31	1.44
0.5	18	92.25	5.05	1.42		1.52
1	8[c]	92.72	5.21	1.87		1.48
1	17	92.51	5.30	2.13	0.30	1.45
1	13	92.56	5.15	2.17	0.32	1.49
1.5	0.8[d]	84.00	4.74	1.95	1.37	1.47
1.5	3	91.17	5.37	2.01	0.46	1.41
2	0.13[e,f]	57.46	3.31	4.96	10.80	1.44
2	0.1[f]	26.45	2.57	3.07	2.75	0.83

[a] Benzene, 2 moles; aluminum chloride, 0.5 mole; cupric chloride, 0.5 mole. [b] 2 hr. at 30–32°. [c] 17°. [d] 25°. [e] 81°. [f] Probably contains a high per cent of contaminants from impurities in the metal halides.

(1) Paper VI. Polymerization of Aromatic Nuclei [undergraduate thesis of J. Oziomek, Case Institute of Technology, 1963] presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(2) P. Kovacic and A. Kyriakis, *J. Am. Chem. Soc.*, **85**, 454 (1963).

(3) P. Kovacic and R. M. Lange, *J. Org. Chem.*, **28**, 968 (1963).

(4) P. Kovacic and F. W. Koch, *ibid.*, **28**, 1864 (1963).

(5) C. S. Marvel and G. E. Hartzell, *J. Am. Chem. Soc.*, **81**, 448 (1959).

(6) P. Kovacic and C. Wu, *J. Polymer Sci.*, **47**, 45 (1960).

(7) P. Kovacic, F. W. Koch, and C. E. Stephan, *ibid.*, in press.

the data already cited for ferric chloride. A plausible interpretation involves the destruction of aluminum chloride by hydrolysis, on the assumption that large amounts of catalyst are required for high yields. It is evident that hydrolysis does occur at an appreciable rate under the standard conditions. When 0.25 mole of water was added, analysis indicated the evolution of 0.38 mole of hydrogen chloride, corresponding to a polymer yield of 14.4 g. However, only 5.7 g. of polymer was formed, which is equivalent to only 0.15 mole of hydrogen chloride. Consequently, hydrolysis must account for the remaining 0.23 mole of hydrogen chloride. Moreover, hydrogen chloride was generated when water was stirred with a cold mixture of benzene and aluminum chloride.

It is conceivable that some water is consumed in a chain termination reaction, which is in keeping with the presence of small amounts of oxygen in the polymers. However, there was no simple correlation which was apparent entailing oxygen content and the amount of added water.

Although no evidence was obtained for water cocatalysis, it is quite possible that small amounts of this or some other Brønsted acid are necessary for initiation. We have not yet investigated the reaction with rigorously purified reagents. The need of a Brønsted acid cocatalyst has been unequivocally establishd for many olefin polymerizations induced by Lewis acids.[8,9] In certain cases, only trace amounts of cocatalyst are needed. Furthermore, various studies point to an optimum quantity, with diminution in the activity of the catalyst–cocatalyst complex with added amounts of cocatalyst, presumably due to formation of more highly solvated entities.[8,10]

There are other reports which lend credence to these postulates. The rate curve for isobutylene polymerization leveled out at approximately equimolar proportions of catalyst and cocatalyst, as the amount of stannic chloride was increased at a fixed water concentration.[10] The effect on rate of varying the water concentration in the polymerization of styrene catalyzed by stannic chloride was determined by Overberger, Ehrig, and Marcus.[11] In a 30:70% mixture of nitrobenzene and carbon tetrachloride, the rate increased as the water concentration increased, reached a maximum at a 1:1 catalyst–cocatalyst molar ratio, and then decreased upon further addition of water. The system styrene-boron trifluoride–water is reported to give similar results.[8,9]

Variation in $AlCl_3$–$CuCl_2$.—In another series of experiments, the effect of variation in the $AlCl_3$–$CuCl_2$ molar ratio was investigated at temperatures of 30–32° for 2 hr. The yield of polymer rose rapidly with increasing molar ratio, reached a maximum at a 2:1 ratio and then remained essentially constant (Table II). It is noteworthy that yields approaching quantitative values were readily and reproducibly obtained. At the optimum ratio and with pulverized cupric chloride, the rapid polymerization produced *p*-polyphenyl in 98% yield based on the oxidant.

(8) "Cationic Polymerization and Related Complexes," P. H. Plesch, Ed., W. Heffer and Sons, Ltd., Cambridge, England, 1953.

(9) D. C. Pepper, *Quart Rev.* (London), **8**, 88 (1954).

(10) R. G. W. Norrish and K. E. Russell, *Trans. Faraday Soc.*, **48**, 91 (1952).

(11) C. G. Overberger, R. J. Ehrig, and R. A. Marcus, *J. Am. Chem. Soc.*, **80**, 2456 (1958).

TABLE II

VARIATION OF $AlCl_3$–$CuCl_2$ RATIO: EFFECT ON POLYMER YIELD[a]

		p-Polyphenyl			
		%			
$AlCl_3$–$CuCl_2$, molar ratio	Yield, %	C	H	Cl	C–H, atomic ratio
0.125:0.5	18	90.69	5.03	1.80	1.50
0.25:0.5	35	91.36	4.95	2.33	1.53
0.25:0.5[b]	34	89.04	4.74	4.02	1.56
0.5:0.5	64	92.29	5.03	2.47	1.53
0.5:0.5	66	91.79	5.07	2.29	1.50
1.5:1.5[c,d]	65	92.90	5.22	2.15	1.48
1.5:1.5[c,d]	63	92.31	5.10	2.25	1.51
0.5:0.25[e]	89	92.09	4.79	2.37	1.60
0.5:0.25	94	90.06	5.06	3.29	1.48
0.5:0.25[f]	91	91.15	5.00	1.75	1.52
0.5:0.25[g]	98	91.37	5.12	1.71	1.48
1.5:0.75[d]	91	92.40	5.28	2.71	1.46
1.5:0.75[d]	89[h]	91.75	5.10	1.73	1.50
1.5:0.75[d,i]	91	91.24	5.12	2.39	1.48
0.5:0.125	89	91.30	5.03	2.54	1.51

[a] Benzene, 2 moles; 2 hr.; 30–32°; no added water. [b] The aluminum chloride was pulverized in a blender with benzene. [c] By Richard Lewis, 30–36°; the cupric chloride was pulverized in a blender with benzene. [d] Benzene, 6 moles. [e] 1.5 hr. [f] 27.5 hr. [g] Pulverized cupric chloride. [h] 87% yield of hydrogen chloride. [i] By Vincent Marchionna.

Why the necessity for large quantities of the catalyst? In response to this question, we determined the influence of initially added cuprous chloride. Very strikingly, essentially no polymerization occurred, even at the reflux temperature, when cuprous chloride and aluminum chloride were used in an equimolar ratio.

At a CuCl–$AlCl_3$ molar ratio of 1:2, the yield (39%) corresponded closely to that (35%) obtained with half this amount of aluminum chloride in the absence of added cuprous chloride. These findings strongly support the thesis that cuprous chloride, generated during the course of the C_6H_6–$AlCl_3$–$CuCl_2$ reaction, acts as a powerful inhibitor by associating with aluminum chloride. The union apparently results in a 1:1 complex which contains the aluminum chloride in catalytically inactive form.

In further pursuit of this intriguing phenomenon, the benzene filtrate obtained from one of the reaction mixtures was examined. Addition of water to the dark green solution produced an exothermic reaction resulting in evolution of acid fumes and precipitation of copious amounts of cuprous chloride. Since the salt itself is very insoluble in benzene, this observation compellingly argues for the presence of cuprous chloride in complex form. Confirmation was readily obtained from solubility experiments (Table III). Although cuprous chloride and aluminum chloride individually were only slightly soluble (<3%) in benzene, a mixture containing equimolar amounts of the two salts dissolved almost completely at room temperature with formation of a yellow solution.

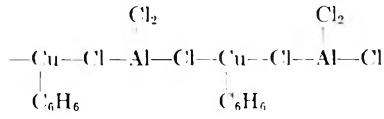
TABLE III

SOLUBILITY OF METAL HALIDES IN BENZENE[a]

$AlCl_3$		CuCl		Solid, g.	
g.	Mole	g.	Mole	Undissolved	Dissolved
16.66	0.125	0		16.00	0.42
0		12.40	0.125	12.25	0
16.70	0.125	12.40	0.125	1.4	27.1

[a] Benzene, 0.5 mole.

When our studies were essentially complete, Amma and Turner[12] presented their work on this hitherto unreported complex. A detailed X-ray analysis revealed that the compound was formed in the ratio, C_6H_6–CuCl–$AlCl_3$ = 1:1:1, and possessed this structure.



Cuprous bromide is known[13] to form similar complexes, such as $C_6H_5CH_3$·CuBr·$AlBr_3$. In related areas, Brown and Wallace[14] found evidence for the existence of arenonium-type entities, $ArH_2^+Al_2X_7^-$, which were solvated by the aromatic substrate. Quite thorough structural analyses have been made of the benzene–silver perchlorate complex.[15]

The reactions carried out at 30–32° in the absence of added water are characterized by induction periods varying from 15 to 25 min. Much to our surprise, we observed that cuprous chloride virtually eliminated the induction period when introduced in the ratio, CuCl–$AlCl_3$ = 1:2. Thus the cuprous chloride may function both as an inhibitor and a promoter. Although the precise nature of the promoting action is unknown, there are several conjectures deemed worthy of consideration. The cuprous chloride might be an efficient catalyst at some stage in the reaction sequence. Another possibility is that a cuprous–cupric complex[16] comprises the actual dehydrogenating agent. However, in one of the solubility experiments cupric chloride proved to be quite insoluble in benzene containing the C_6H_6·CuCl·$AlCl_3$ complex. It is significant that cuprous bromide exerts a similar accelerating effect in the bromination of toluene by cupric bromide.[17]

Essentially identical infrared spectra were exhibited by preparations of *p*-polyphenyl obtained under the various conditions. The C–H atomic ratios fell in the range, 1.41–1.60, with an average value of 1.50. These data compare favorably with the limiting ratio of 1.5 for $(-C_6H_4-)_n$.

Gas chromatographic analysis of the benzene filtrate from the reaction mixture revealed the presence of biphenyl and chlorobenzene in small quantities. Presumably, biphenyl derives from termination at the dimer stage of polymerization. Chloro aromatics might be formed through termination of the growing carbonium ion by chloride, or by chlorination effected by cupric chloride–aluminum chloride.[18]

One aspect of the mechanistic scheme[2] comprises transformation of dihydrobenzene structures to aromatic units. Previously, in investigations with the model compound, 1,4-cyclohexadiene, it was shown that benzene was readily formed on treatment with ferric chloride[4] or molybdenum pentachloride.[3] Analogous experiments were carried out with the metal halides present in our system (Table IV). Neither cupric chloride nor cuprous chloride produced detectable reaction with 1,4-cyclohexadiene. With aluminum chloride or aluminum chloride–cupric chloride, polymerization of the diene was the preferred route. However, using toluene as solvent, we found that benzene was formed with the reagents, aluminum chloride–cupric chloride–cuprous chloride and aluminum chloride–cuprous chloride. These data intimate that the Lewis acid catalyst participates in dehydrogenation by the oxidant. A more detailed discussion should be deferred until these preliminary results are expanded by additional studies. It is significant that 9,10-dihydroanthracene is smoothly dehydrogenated by cupric halides under mild conditions.[19]

TABLE IV

DEHYDROGENATION OF 1,4-CYCLOHEXADIENE[a]

Mole			Temp.,	Time,	
$AlCl_3$	CuCl	$CuCl_2$	°C.	min.	Results
0.01	0	0	10	~1	Polymerization
0	0.01	0	40	5	No reaction
0	0	0.01	40	5	No reaction
0.01	0	0.01	10	~1	Polymerization
0.01	0.011[b]	0	40	5	Benzene formed
0.01	0.011[b]	0.01[c]	40	5	Benzene formed[d]

[a] 1,4-Cyclohexadiene (1 ml.) in 15 ml. of toluene. [b] The toluene–aluminum chloride–cuprous chloride complex was formed before the addition of 1,4-cyclohexadiene. [c] Cupric chloride was added to the C_7H_8·CuCl·$AlCl_3$ complex before the 1,4-cyclohexadiene. [d] Hydrogen chloride was evolved.

Although we favor the oxidative cationic mechanism for the polymerization, alternative possibilities should also be considered. For example, the high degree of selectivity for 1,4-polymerization suggests that perhaps a surface effect involving metal halide plays an important role.

Benzene–Lewis Acid Catalyst–Oxidant.—A large number of candidate catalysts and oxidants were examined in an effort to ascertain the reaction scope. With cupric halide as the oxidant, polymerization to *p*-polyphenyl was accomplished only by those metal halides which possess rather high Lewis acid strength, namely, aluminum chloride, aluminum bromide, and antimony pentachloride (Table V). Ferric chloride[4] and molybdenum pentachloride[3] were previously shown to be active. It is interesting that antimony pentachloride alone, or in conjunction with aluminum chloride, gave only chlorinated benzenes.[20] A direct correlation apparently exists between ease of monomer polymerization and catalyst strength requirement. In contrast to the benzene reaction, cationic polymerization of olefins proceeds under very mild conditions, at −100° within a few seconds in the presence of a relatively weak catalyst such as boron trifluoride.

Specificity was evident relative to the nature of the oxidant. With aluminum halide as catalyst, polymer was generated by use of the following oxidizing agents: cupric chloride, cupric bromide, lead dioxide, manganese dioxide, nitrogen trioxide, nitrogen dioxide, chloranil, and *p*-benzoquinone (Table V).

Infrared spectral data (Table VI) and elemental analyses of the polymers were in agreement with a *p*-

(12) E. L. Amma and R. Turner, Abstracts of Papers, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1963, p. 12K.

(13) V. A. Plotnikov and Z. A. Yankelevich, *J. Gen. Chem. USSR*, **3**, 208 (1933); V. A. Plotnikov, Z. A. Yankelevich, and I. A. Sheka, *ibid.*, **3**, 802 (1933).

(14) H. C. Brown and W. J. Wallace, *J. Am. Chem. Soc.*, **75**, 6268 (1953).

(15) H. G. Smith and R. E. Rundle, *ibid.*, **80**, 5075 (1958).

(16) J. K. Kochi, *ibid.*, **77**, 5274 (1955); H. McConnell and N. Davidson, *ibid.*, **72**, 3168 (1950).

(17) K. Davis, unpublished work.

(18) J. C. Ware and E. E. Borchert, *J. Org. Chem.*, **26**, 2263, 2267 (1961).

(19) D. C. Nonhebel, *J. Chem. Soc.*, 1216 (1963).

(20) P. Kovacic and A. K. Sparks, *J. Am. Chem. Soc.*, **82**, 5740 (1960).

TABLE V

POLYMER FROM BENZENE–CATALYST–OXIDANT[a]

Catalyst	Oxidant	Time, hr.	Temp., °C.	Yield, g.	Polymer, % C	H	Halogen	N	O	C–(H + halogen), atomic ratio
$AlBr_3$	$CuBr_2$[b]	4.3	25	1.8[c]	87.77	5.17	6.81			1.39
$AlCl_3$	MnO_2	6	80	7.8[d,e,f]	67.71	3.65	21.10		4.10	1.33
$AlCl_3$	PbO_2	1	80	9.4[d,e,g]	79.58	4.22	14.07		2.00	1.44
$AlCl_3$	Chloranil	1	Reflux	8.3[c,h]	76.41	3.34	11.31		5.15	
$AlCl_3$	*p*-Benzoquinone	2	Reflux	1.7[h]	73.15	3.07	4.98		13.3	
$AlCl_3$	NO_2[i]	1	Reflux	2.5	85.07	4.40	4.55	0.87		1.56
$AlCl_3$	N_2O_3[j]	1	Reflux	1.2	85.09	4.41	4.15	0.84		1.57
$SbCl_5$	$CuCl_2$	4	5	1.9[j]	90.40	5.10	3.43			1.45

[a] Benzene, 2 moles; catalyst, 0.5 mole; oxidant, 0.5 mole. [b] Water cocatalyst, 0.025 mole; the assistance of F. J. Kohl is gratefully acknowledged. [c] Run at half-scale. [d] By A. Kyriakis. [e] Benzene, 1 mole; water, 1 ml. [f] *a*-Spacings: 4.22 and 9.30 Å., from X-ray powder pattern. [g] *d*-Spacings; 2.67, 4.35, and 7.75 Å., from X-ray powder pattern. [h] After exhaustive extraction with boiling ethanol. [i] The gas (undetermined amount) was introduced below the surface of the mixture. [j] Also C_6H_5Cl, $C_6H_4Cl_2$, and $C_6H_3Cl_3$.

TABLE VI

INFRARED SPECTRAL DATA FOR THE POLYMERS

p-Polyphenyl	Absorption maxima, cm.$^{-1}$ *para*	mono		Peak height ratios, *para*–(mono$_1$ + mono$_2$)
p-Terphenyl[a]	837	746	687	1:(1.12 + 1.0) = 0.47
p-Quaterphenyl[a]	825	752	687	1:(1.04 + 0.87) = 0.52
p-Quinquephenyl[a]	818	757	688	1:(1.0 + 0.79) = 0.56
p-Sexiphenyl[b]	811	756	682	1:(1.06 + 0.41) = 0.68
C_6H_6–$AlCl_3$–N_2O_3[c]	807	760	696	1:(0.83 + 0.75) = 0.63
C_6H_6–$AlCl_3$–NO_2[c]	806	762	697	1:(0.62 + 0.49) = 0.90
C_6H_6–$AlCl_3$–chloranil[d]	805	765	695	1:(0.51 + 0.25) = 1.32
C_6H_6–$AlCl_3$–$CuCl_2$	803	763	693	1:(0.18 + 0.04) = 4.55
C_6H_6–$AlBr_3$–$CuBr_2$	803	760	690	1:(0.14 + 0.02) = 6.25
C_6H_6–$SbCl_5$–$CuCl_2$	802	758	690	1:(0.09 + 0.03) = 8.35

[a] Data from A. Kyriakis. [b] Data from R. M. Lange. [c] Additional band at 1592 cm.$^{-1}$. [d] Additional minor bands at 740, 1425, 1324, 1213, and 933 cm.$^{-1}$.

polyphenyl structure, with the possible exception of the products derived from *p*-benzoquinone and chloranil. The dark polymer obtained from *p*-benzoquinone gave an ill-defined spectrum which, nevertheless, was suggestive of *p*-polyphenyl. In the case of chloranil, the product spectrum exhibited many absorption bands in addition to those characteristic of *p*-polyphenyl. It is conceivable that copolymers are formed from the benzene–quinone–aluminum chloride reactions. Nitrogen dioxide and nitrogen trioxide yielded polymers which were very similar to each other.

Examination of the infrared spectral data leads to the conclusion that the polymers prepared with the nitrogen oxides and chloranil possess lower molecular weights than the others. An approximate indication of relative molecular weights in the *p*-polyphenyl series may be obtained from the ratio, intensity (*para* band)–intensity (mono bands). The characteristic absorption maxima fall in the regions, 802–807 (*para*), 758–765 (mono), and 690–697 cm.$^{-1}$ (mono). As the molecular weight increases, this ratio becomes larger. The values for the polymers obtained with $AlCl_3$–$CuCl_2$, $AlBr_3$–$CuBr_2$, and $SbCl_5$–$CuCl_2$ lie in the range 4.5–8.4, as compared with 0.6–1.3 for the products from $AlCl_3$–NO_2, $AlCl_3$–N_2O_3, and $AlCl_3$–chloranil.

The inference can be drawn that the nitrogen oxides and chloranil also function as chain terminators. Brown and Mathieson[21] found that *p*-benzoquinone retarded or completely inhibited the cationic polymerization of styrene. Furthermore, the molecular weight of the polystyrene was decreased in proportion to the quinone concentration, which suggests interaction of quinone with the propagating carbonium ion. The 0.87% nitrogen in the *p*-polyphenyls generated with nitrogen oxides is most likely incorporated in nitro groups. On the assumption that one such group is present per molecule through chain termination, an average chain length of *ca.* eighteen benzene rings would apply. The position of the mono bands in the infrared spectrum points to a *p*-polyphenyl containing a *para* substituent. It may be that some nitro groups are situated along the backbone of the chain.

Since water is most likely generated in the nitrogen oxide systems, it is reasonable to consider a nitrogen-containing Brønsted acid as a possible terminator, in addition to the free nitrogen oxides. Of pertinence in this connection is the conversion of an alkyl halide to nitroalkane and nitrite ester by reaction with a nitrite salt.[22] By analogy, termination also could occur with formation of nitrite ester end groups which subsequently would be subjected to hydrolytic conditions. The literature contains evidence for retardation and inhibition of cationic polymerization by nitro bodies, such as nitrobenzene.[8,21]

Titov, who previously examined the benzene–nitrogen dioxide–aluminum chloride reaction under somewhat different conditions, was concerned primarily with aromatic nitration.[23] Good yields of simple nitrated products were reported from benzene, toluene, and chlorobenzene, with nitrosyl chloride[24] as a by-

(21) C. P. Brown and A. R. Mathieson, *J. Chem. Soc.*, 3612 (1957).

(22) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961 p. 128.

(23) A. I. Titov, *J. Gen. Chem. USSR*, **7**, 591 (1937).

(24) J. D. Archambault, H. H. Sisler, and G. E. Ryschkewitsch; *J. Inorg. Nucl. Chem.*, **17**, 130 (1961)

product. Nitration of aromatic nuclei also has been accomplished with boron trifluoride complexes[25] of dinitrogen tetroxide and nitrogen trioxide. In general, we did not investigate the low molecular weight fraction of the reaction mixtures.

Whereas the polyphenyl from cupric chloride contained only small amounts of chlorine (about 2%), halogenation was much more extensive (14–21%) with manganese dioxide and lead dioxide. Since these oxides readily oxidize hydrogen chloride,[26] subsequent catalytic chlorination of the *p*-polyphenyl most likely involves the generated chlorine. Hydrolysis of aluminum chloride, by water formed during polymerization, would serve as a plausible source of hydrogen chloride. The corresponding metal tetrahalides[27] might also arise *in situ* as reactive intermediates. In the case of the polymers (4% chlorine) synthesized with nitrogen oxides, nitrosyl chloride may be the halogenating species in view of its ability to chlorinate the aromatic nucleus.[28]

Experimental[29]

Benzene–Aluminum Chloride–Cupric Chloride. General Procedure.—A mixture of dry, thiophene-free benzene (2 moles) and anhydrous aluminum chloride (0.5 mole) was covered with an atmosphere of dry nitrogen. When water was used, addition was made dropwise to the stirred mixture at 6–10°. Then anhydrous cupric chloride (0.5 mole, dried at 120°) was added, and the mixture was heated to 30–32°. After an induction period of about 25 min., the contents assumed a purple-black color, and acid gas was evolved, which, in most cases, was followed by titration with standard caustic.

The reaction was allowed to proceed with efficient stirring for 2 hr. from the time of initiation. The mixture was then cooled to 15° and was either (1) added to 1.4 l. of ice-cold 18% hydrochloric acid, or (2) filtered, followed by addition of the residue to acid solution. The mixture of crude polymer and aqueous acid was heated at the boil, filtered, and the residue washed with water. After the solid was pulverized briefly in a blender with water, it was triturated with boiling 18% hydrochloric acid until the filtrate was colorless. Washing with boiling distilled water was continued until the test (silver nitrate) for chloride ion was negative. The product, dried at 120°, was a finely divided, light brown solid. Care was taken to avoid contamination.

A similar procedure was used with other catalyst–oxidant systems.

Average values for duplicate analyses are recorded in the tables. Maximum deviations were C, ± 0.2; H, ±0.15; Cl, ±0.2. Occasionally, an erratic analysis was obtained which was discarded after appropriate checking. Polymer yields (%) are based on cupric chloride.

Reaction Products. A. Cuprous Chloride.—The reaction mixture from benzene (2 moles)–aluminum chloride (0.5 mole)–cupric chloride (0.5 mole), 2 hr. at 31–32°, was filtered directly. Water was slowly added with stirring to the dark green filtrate until no further reaction occurred. After filtration, the white solid was washed under nitrogen with dilute hydrochloric acid and then with water. Drying was accomplished *in vacuo* at 100° to yield 21.8 g.

Anal. Calcd. for CuCl: Cu, 64.2. Found: Cu, 63.39.

The X-ray diffraction pattern[30] gave the *d*-spacings, Å.: 3.10, 1.90, 1.625, 0.891, and 0.861. Authentic cuprous chloride gave identical *d*-spacings. Essentially the same pattern is reported[31] for cuprous chloride.

B. Organic By-products.—The benzene solution from part A was separated from the aqueous portion, washed first with dilute acid and then with water, and dried over sodium sulfate. After distillation of the benzene through a helices-packed column, the residue was subjected to gas chromatography. Characterization was accomplished by retention times, infrared spectrum (for chlorobenzene product, identical with that of authentic material), and the ultraviolet spectrum (for biphenyl, λ_{max} 248 mμ, lit.[32] λ_{max} 248 mμ).

Benzene–Aluminum Chloride–Cupric Chloride–Cuprous Chloride. A.—After the addition of cupric chloride (0.25 mole) to a mixture of benzene (1 mole), aluminum chloride (0.25 mole) and cuprous chloride (0.25 mole) under nitrogen, stirring was maintained for 1 hr. at 31–32° and for 1 hr. at reflux. Work-up yielded only a trace of polymer.

B.—Cupric chloride (0.25 mole) was added to a mixture of benzene (1 mole), aluminum chloride (0.25 mole), and cuprous chloride (0.125 mole) at 25° with stirring under nitrogen. The reaction mixture immediately became dark and hydrogen chloride was evolved in a few seconds. After 2 hr. at 31–32°, the polymer was isolated by the usual procedure, 2.4 g. (39%).

Anal. Found: C, 90.72; H, 4.84; Cl, 3.37. Therefore, C–H = 1.56.

Solubility of Metal Halides in Benzene. A.—A mixture of the metal halide [aluminum chloride (0.125 mole), cuprous chloride (0.125 mole), or aluminum chloride (0.125 mole)–cuprous chloride (0.125 mole)] and benzene (0.5 mole) was stirred at reflux under nitrogen for 30 min. The mixture was allowed to cool to 25° and filtered. The amounts of undissolved and dissolved material were determined by vacuum drying of the solid at 80°, and by evaporation of the benzene filtrate *in vacuo* followed by drying of the residue. The results are summarized in Table III.

B.—A solution of the C_6H_6·CuCl·$AlCl_3$ complex was formed from benzene (1 mole), cuprous chloride (0.137 mole), and aluminum chloride (0.125 mole) by vigorous shaking for 5 min. After filtration from a small amount of undissolved solid, cupric chloride (8.40 g., 0.0625 mole) was added to the clear light-yellow filtrate. The mixture was shaken well, filtered, and the solid washed with benzene. The recovered material, which was dried at 110°, weighed 8.35 g.

Dehydrogenation of 1,4-Cyclohexadiene.—To a cooled mixture of toluene and the appropriate metal halides was added 1 ml. of 1,4-cyclohexadiene. If no noticeable reaction occurred, the mixture was warmed in a water bath at 40° for 5 min. with stirring. For those systems containing metal halides in solution, dilute hydrochloric acid was added to destroy the complex before gas chromatography. The other reaction mixtures were chromatographed directly after the metal salts had settled out.

In a control experiment with toluene and aluminum chloride, there was no evidence for the formation of benzene.

Benzene–Catalyst–Oxidant. No *p*-Polyphenyl.—Essentially no polymer was obtained from benzene–aluminum chloride at the reflux temperature with the following candidate oxidants ($AlCl_3$–oxidant ratio was usually 1): cuprous chloride, mercuric chloride, mercurous chloride, phosphorus pentachloride, nitrobenzene, nitromethane, sulfur, nitric oxide, antimony pentachloride, barium peroxide, and air.

The following catalyst–oxidant combinations (usually 1:1 molar ratio) failed to produce polymer with benzene at reflux: zinc chloride, titanium tetrachloride, stannic chloride, sulfuric acid, or boron trifluoride with cupric chloride; sulfuric acid, hydrogen chloride, phosphoric acid, or phosphorus pentoxide with manganese dioxide; hydrogen chloride–lead dioxide.

Acknowledgment.—We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. The contributions of Mr. Alexander Kyriakis are gratefully acknowledged.

(25) G. B. Bachman, H. Feuer, B. R. Bluestein, and C. M. Vogt, *J. Am. Chem. Soc.*, **77**, 6188 (1955); G. B. Bachman and T. Hokama, *ibid.*, **79**, 4370 (1957).

(26) N. V. Sidgwick, "The Chemical Elements and Their Compounds," Vol. I, Oxford University Press, Oxford, England, 1952, p. 600; Vol. II, p. 1272.

(27) H. F. Walton, "Inorganic Preparations," Prentice-Hall, Inc., Englewood Cliffs, N. J., p. 83.

(28) L. J. Beckham, W. A. Fessler, and M. A. Kise, *Chem. Rev.*, **48**, 319 (1951).

(29) Elemental analyses were done by Dr. Weiler and Dr. Strauss, Oxford, England, and by Geller Laboratories, Bardonia, N. Y. The infrared spectra were obtained by the potassium bromide pellet technique.

(30) We are grateful to R. M. Lange for the X-ray data.

(31) H. E. Swanson, R. K. Fuyat, and G. M. Ugrinic, "Standard X-Ray Diffraction Powder Patterns," National Bureau of Standards Circular 539, Vol. IV, p. 35.

(32) E. H. Smith, Polyphenyls: Literature Search, U. S. Atomic Energy Commision, ER-8098, 1956.

Hydrogenolyses with Chloroaluminum Hydrides. I. Diphenylallyl Alcohols

JAMES H. BREWSTER AND HORST O. BAYER[1]

Department of Chemistry, Purdue University, Lafayette, Indiana

Received June 7, 1963

The hydrogenolysis of *cis*- and *trans*-2,3-diphenyl-2-propen-1-ol and also of 1,2-diphenyl-2-propen-1-ol with mixtures of aluminum chloride and lithium aluminum hydride gives in each case, *cis*- and *trans*-α-methylstilbene and α-benzylstyrene. The relative amounts of the three olefins vary with the structure of the starting alcohol in a way that indicates that previous assignments of configurations to the olefins are correct. The results indicate that there is an appreciable, but not insurmountable, barrier to geometric interconversion of allylic carbonium ions in this system.

Mixtures of lithium aluminum hydride and aluminum chloride in ether show promise as selective reducing agents,[2] being less active than lithium aluminum hydride toward nitro groups,[3,4] simple halides,[2,3] and tosylates,[2] but more active in the hydrogenolysis[5] of acetals, ketals,[2,15,16] allylic and benzylic alcohols,[6-13] and ethers.[14] In addition, these reagents show interesting attributes in the epimerization of alcohols[2] and the reduction of epoxides.[2] It seems probable that the hydrogenolysis reactions involve the formation and reduction of carbonium ions,[2] the effective reagents being chloroaluminum hydrides[17]; the latter substances would be expected to behave both as Lewis acids and as hydride donors.

The possibility that the hydrogenolysis reactions involve the generation of carbonium ions[2] in the presence of hydride donors suggested that results of synthetic, theoretical, and stereochemical interest might be obtained from a broad study of them. Taken as a whole, the data presented in this series and in the earlier papers[2-16] would seem to leave little room for doubt that the formation of a carbonium ion is required if any significant reaction is to occur. Thus, aliphatic alcohols react only under the most vigorous conditions, and even then *n*-hexyl alcohol can be recovered unchanged[18]; with secondary and tertiary saturated alcohols the formation of olefins and rearranged products is prominent.[18] *p*-Methoxy groups produce a strong acceleration in reductions of benzyl alcohols.[19] The reduction of allylic alcohols gives mixtures of products which may be relatively rich in thermodynamically less stable isomers (following); such mixtures may be of synthetic interest as potential sources of olefins otherwise difficult of access. The reduction of allylic alcohols can occur with some inversion of geometric configuration at the original double bond, but there appears to be enough of a barrier to such interconversion[20] to permit the use of this reaction in the correlation of geometric configurations (following).

Our first studies in this field were aimed at confirming the configurations of the α-methylstilbenes[21] (*trans*, I; *cis*, II),[22] upon which rest the configurations assigned to the alcohols,[21] halides,[23] epoxides,[24] and diols[24] of the 1,2-diphenylpropane series. The configurations of the 2,3-diphenylacrylic acids (*trans*, IV; *cis*, V)[22] have been determined by chemical methods[25]; reduction of the two acids with lithium aluminum hydride gave *trans*

(1) The authors gratefully acknowledge the financial support of this research by the National Science Foundation (NSF-G 10051).

(2) For a review, see E. L. Eliel, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **22**, 129 (1961).

(3) R. F. Nystrom, *J. Am. Chem. Soc.*, **77**, 2544 (1955).

(4) See P. Newman, P. Rutkin, and K. Mislow, *ibid.*, **80**, 465 (1958), for an application of this reagent in reduction of a nitro acid.

(5) Certain aromatic carbinols undergo slow hydrogenolysis with excess lithium aluminum hydride alone at high temperatures. L. H. Conover and D. S. Tarbell, *ibid.*, **72**, 3586 (1950).

(6) B. R. Brown, *J. Chem. Soc.*, 2756 (1952).

(7) J. Broome and B. R. Brown, *Chem. Ind.* (London), 1307 (1956).

(8) A. J. Birch and M. Slaytor, *ibid.*, 1524 (1956).

(9) O. H. Wheeler and J. L. Mateos, *ibid.*, 395 (1957).

(10) R. Albrecht and C. Tamm, *Helv. Chim. Acta*, **40**, 2216 (1957).

(11) B. R. Brown and A. M. S. White, *J. Chem. Soc.*, 3755 (1957).

(12) R. F. Nystrom and C. R. A. Berger, *J. Am. Chem. Soc.*, **80**, 2896 (1958).

(13) J. Broome, B. R. Brown, A. Roberts, and A. M. S. White, *J. Chem. Soc.*, 1406 (1960).

(14) B. R. Brown and G. A. Somerfield, *Proc. Chem. Soc.*, 7 (1958).

(15) H. M. Doukas and T. D. Fontaine, *J. Am. Chem. Soc.*, **75**, 5355 (1953).

(16) E. L. Eliel and M. Rerick, *J. Org. Chem.*, **23**, 1088 (1958); E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Am. Chem. Soc.*, **84**, 2371 (1962); M. N. Rerick and E. L. Eliel, *ibid.*, **84**, 2356 (1962).

(17) Lithium aluminum hydride reacts with aluminum chloride in ether to form aluminum hydride [A. E. Finholt, A. C. Bond, Jr., and H. I. Schlesinger, *ibid.*, **69**, 1199 (1947)], presumably by way of intermediate chlorohydrides.

$$3LiAlH_4 + AlCl_3 \longrightarrow 3LiCl + 4AlH_3 \qquad (a)$$

The latter have been formed by reaction of aluminum chloride with aluminum hydride [E. Wiberg, *Angew. Chem.*, **65**, 16 (1953); E. Wiberg, K. Möedritzer, and R. U. Lacal, *Rev. acad. cienc. exact. fis.-quim. nat. Zaragoza*, [1] **9**, 91 (1954); *Chem. Abstr.*, **52**, 3584a (1958)] and have been isolated as etherates. On this basis, the commonly used 1:1 (ratio of aluminum chloride to lithium aluminum hydride) reagent conveniently may be considered to consist essentially of monochloroaluminum hydride (eq. b), while the 3:1 reagent which we have used extensively may be considered to consist essentially of dichloroaluminum hydride (eq. c).

$$AlCl_3 + LiAlH_4 \longrightarrow LiCl + 2AlClH_2 \qquad (b)$$

$$3AlCl_3 + LiAlH_4 \longrightarrow LiCl + 4AlCl_2H \qquad (c)$$

It is to be recognized that these are convenient oversimplifications since some mixtures are more strongly conducting than these equations would suggest they should be [G. G. Evans, J. K. Kennedy, Jr., and F. P. Del Greco, *J. Inorg. Nucl. Chem.*, **4**, 40 (1957)].

(18) J. H. Brewster, S. F. Osman, H. O. Bayer, and H. B. Hopps, *J. Org. Chem.*, **29**, 121 (1934).

(19) J. H. Brewster, H. O. Bayer, and S. F. Osman, *ibid.*, **29**, 110 (1964).

(20) See W. G. Young, S. H. Sharman, and S. Winstein, *J. Am. Chem. Soc.*, **82**, 1376 (1960).

(21) The higher melting isomer has been assigned the *trans*[22] configuration I on the ground that it is the more stable of the two [E. Ellingboe and R. C. Fuson, *ibid.*, **55**, 2964 (1933); D. J. Cram, F. D. Greene, and C. H. Depuy, *ibid.*, **78**, 790 (1956)]. The ultraviolet spectra of the two isomers are consistent with this assignment [D. J. Cram and F. A. Abd Elhafez, *ibid.*, **74**, 5828 (1952)], since they show differences similar to those observed with *cis*- and *trans*-stilbene [G. N. Lewis, T. T. Magel, and D. Lipkin, *ibid.*, **62**, 2973 (1940)].

(22) We are concerned in this paper with geometrical configurations about stilbenoid double bonds and use the terms *cis* and *trans* throughout to indicate the geometrical relationships of phenyl groups to one another about such bonds. The nomenclature of acids IV and V is thoroughly confused in the earlier literature, the more readily available and higher melting isomer V being called "α-phenyl-*trans*-cinnamic acid" in some sources (*e.g.*, Beilstein, "Handbuch der Organischen Chemie," IX, p. 691) and "*cis*-α-phenylcinnamic acid" in others [*e.g.*, L. F. Fieser, *J. Chem. Educ.*, **31**, 291 (1954)]. We, therefore, adopt the approach of *Chemical Abstracts* and term acid V, "*cis*-2,3-diphenylacrylic acid" and the alcohol VII, "*cis*-2,3-diphenylallyl alcohol" (*Chemical Abstracts* name, *cis*-2,3-diphenyl-2-propen-1-ol.).

(23) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5851 (1952).

(24) J. H. Brewster, *ibid.*, **78**, 4061 (1956).

(25) R. Stoermer, *Ann.*, **409**, 13 (1915).

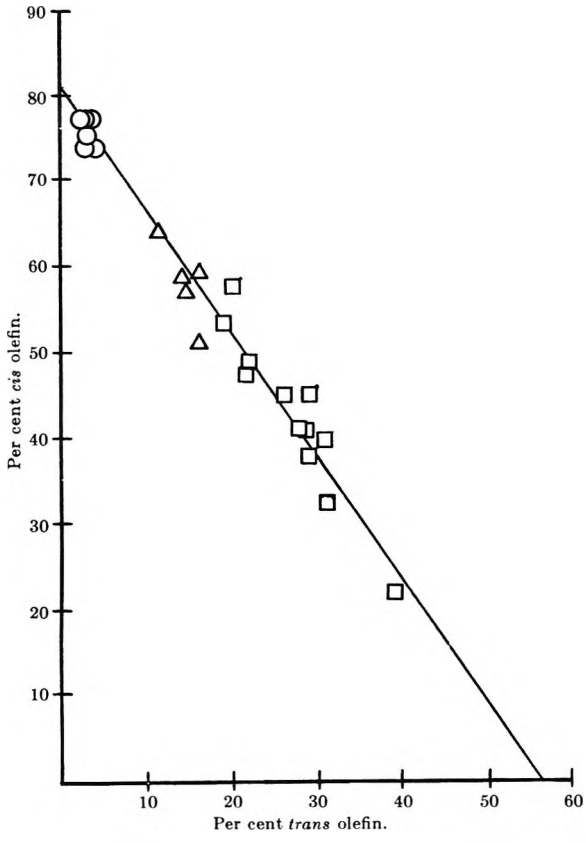
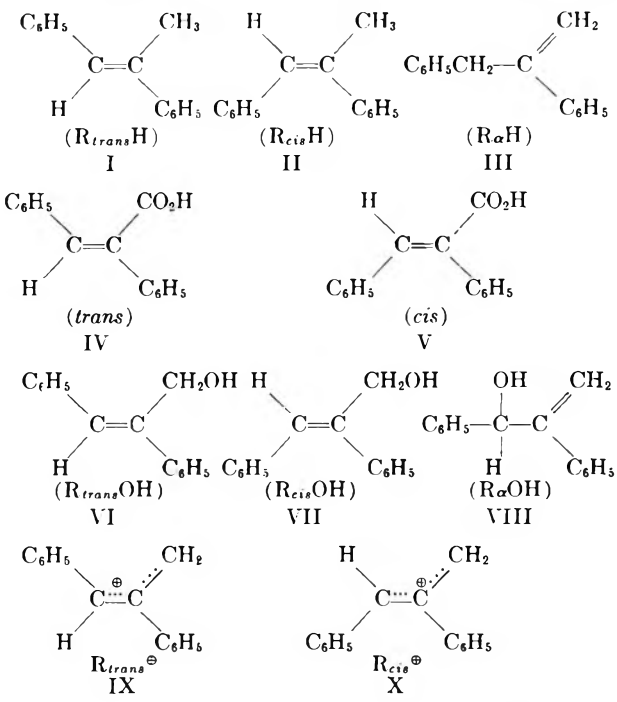


Fig. 1.—Composition of hydrocarbon mixtures from hydrogenolyses of diphenylallyl alcohols with "mixed hydride" reagents in ether. The per cent of *cis*- and *trans*-α-methylstilbenes in the hydrocarbon products is shown; the per cent of α-benzylstyrene in each case is that required to total 100%: ○, products from *cis*-2,3-diphenylallyl alcohol; □, products from *trans*-2,3-diphenylallyl alcohol; △, products from α-styrylphenylcarbinol.

alcohol[26] VI (λ_{max}^{EtOH} 273 mμ, ε 19,800) and *cis* alcohol[26] VII (λ_{max}^{EtOH} 222 mμ, ε 15,900; 257 mμ, ε 12,500), the ultraviolet spectra of which are very similar to those of, respectively, the more stable and the less stable of the α-methylstilbenes.[21,26] Although this seemed a satisfactory confirmation of the earlier assignments of configuration, we then attempted to buttress this argument by reduction of the alcohols with aluminum chloride–lithium aluminum hydride mixtures. Surprisingly, the less stable of the α-methylstilbenes was the predominant product in the reduction of *both* alcohols at or near room temperature. A third olefin, identified as α-benzylstyrene (III) by way of an independent synthesis, was always formed in amounts ranging from 20–40% of the hydrocarbon product. As seen from the data in Fig. 1, however, the less stable α-methylstilbene was formed in largest amounts (*ca.* 75% of the hydrocarbon product) from the *cis* alcohol (VII) while the more stable was formed in largest amounts (20–32% of the hydrocarbon product) from the *trans* alcohol (VI). Reduction in ether at 80° (sealed tube) gave a more decisive result since the *trans* alcohol (VI) gave 39% of the more stable and 22% of the less stable olefin, while the *cis* alcohol (VII) gave 2.4 and 69%, respectively. No simple pathway for specific inversion of geometric configuration being apparent, it must be concluded that the last-mentioned reductions occur with predominating retention of geometric configuration and that the more stable α-methylstilbene has, indeed, the *trans* configuration (I). It also must be concluded, however, from the results of reduction at room temperature, that a pathway for interconversion of geometrical isomers is available This pathway cannot involve equilibration of the olefins since it favors formation of the less stable α-methylstilbene and allows formation of quite large amounts of α-benzylstyrene (III), which should be the least stable of the three products. A control experiment showed that the olefins were not isomerized at all under the reaction conditions. It seems most likely that this interconversion involves the formation of some derivative of α-styrylphenylcarbinol (VIII). In this regard it is of interest to note that VIII is reduced more rapidly than the other two alcohols (Table I) and gives a distribution of olefins intermediate between those from VI and VII.



The olefin distribution in the product from the *trans* alcohol (VI) was found to be sensitive to the ratio of hydride to alcohol (Table II) and to the concentration of initial reactants (Table III); that from the *cis* alcohol (VII) was almost invariant. The rate of reduction increased markedly as the initial ratio of aluminum chloride to lithium aluminum hydride was increased

(26) The above-mentioned confusion in nomenclature[22] enters into the literature dealing with these alcohols. R. E. Lutz and E. H. Rinker, Jr., *J. Am. Chem. Soc.*, **77**, 366 (1955), reduced "*cis*-α-phenylcinnamic acid" (no melting point or literature cited, but indicated as having the *trans* configuration IV) to "*cis*-α-phenylcinnamyl alcohol," m.p. 73–74° (formula VI given) *which is described as having the ultraviolet spectrum to be expected of an α-substituted cis-stilbene* (λ_{max} 222, 258 mμ, ε 14,500). Our *cis* alcohol (VII), prepared from the more readily available *cis* acid (V, m.p. 172–173°) has properties agreeing closely with those reported for this substance (m.p. 72–73°), and there seems little reason to doubt that these alcohols are the same and that the formulas in the text of the paper of Lutz and Rinker are in error. H. E. Zimmerman, L. Singer, and B. S. Thyagarajan, *ibid.*, **81**, 108 (1959), have prepared this same alcohol from the corresponding aldehyde, the latter having been oxidized to the *cis* acid (V, m.p. 174–175°), but give m.p. 68–69° for the alcohol and regard it as different from that of Lutz and Rinker, apparently on the basis of the formulas and nomenclature of the latter workers. Zimmerman, Singer, and Thyagarajan also have prepared the *trans* alcohol (VI) from the *trans* acid (IV, m.p. 137°) and, on the basis of melting point (73–74°), conclude it is the same as the product of Lutz and Rinker. Our values for the melting point (77–78°) and the absorption spectrum (text) indicate that it is different from the product of Lutz and Rinker.

TABLE I

RELATIVE REACTIVITY[a] OF DIPHENYLALLYL ALCOHOLS

Alcohol[a]	Conversion,[b] %	—Product composition[b]— % $R_{cis}H$ (II)	% $R_{trans}H$ (I)	% $R\alpha H$ (III)
$R_{trans}OH$ (VI)	15	40	29	31
$R_{cis}OH$ (VII)	27	74	4	22
$R_{\alpha}OH$ (VIII)	72	51	16	33

[a] In diethyl ether, 4 hr. at 20°; 3:1 reagent; 0.5 mmole "$AlCl_2H$"/ml.; 0.05 mmole ROH/ml. [b] Determined by v.p.c. at 220° on polyadipate with naphthalene internal standard.

TABLE II

INFLUENCE OF REACTANT RATIO ON PRODUCT COMPOSITION (*trans* ALCOHOL VI)

Initial concentrations,[a] mmoles/ml. "$AlCl_2H$"[c]	$R_{trans}OH$	Conversion,[b] %	—Product composition[b]— % $R_{cis}H$ (II)	% $R_{trans}H$ (I)	% $R\alpha H$ (II)
0.4	0.2	62	71	15	14
.4	.133	85	48	22	30
.4	.10	82	45	29	26
.4	.089	75	41	29	30

[a] In diethyl ether; 16 hr. at 34°. [b] Determined by v.p.c. at 220° on polyadipate with naphthalene internal standard. [c] 3:1 reagent.

TABLE III

INFLUENCE OF CONCENTRATION ON CONVERSION AND PRODUCT COMPOSITION (*trans* ALCOHOL VI)

Initial concentrations[a] mmole/ml. "$AlCl_2H$"[c]	$R_{trans}OH$	Conversion,[b] %	—Product composition[b]— % $R_{cis}H$ (II)	% $R_{trans}H$ (I)	% $R\alpha H$ (III)
0.55	0.11	24.0	32.5	31.0	36.5
.30	.06	15.3	41.0	28.0	31.0
.20	.04	11.3	44.7	25.9	29.4
.15	.03	8.9	49.0	22.4	28.7
.10	.02	8.8	53.4	19.3	27.3

[a] In diethyl ether; 8 hr. at 20°. [b] Determined by v.p.c. at 220° on polyadipate with naphthalene internal standard. [c] Prepared from stock solutions of 3:1 reagent, assayed by hydrogen evolution as being 0.55 *N* and 0.069 *N* in hydride.

TABLE IV

EFFECT OF REAGENT COMPOSITION ON CONVERSION (*cis* ALCOHOL V)

Reagent[a] $AlCl_3$–$LiAlH_4$ (molar ratio)	—Concentrations, mmole/ml.— "H⁻"	ROH	Conversion,[b] %
1:1	0.30	0.060	0.6
2:1	.24	.048	15
3:1	.20	.040	34
4:1	.17	.034	48

[a] In diethyl ether; 16 hr. at 20°. [b] Determined by v.p.c. at 220° on polyadipate with naphthalene internal standard. Product composition: 75.5 ± 1.5% $R_{cis}H$; 3.0 ± 0.3% $R_{trans}H$; 22 ± 1% $R\alpha H$.

(Table IV). These facts are consistent with a carbonium ion mechanism (see Discussion of Results) as is the result of a control experiment indicating that, although neither the alcohol nor the olefin react appreciably with naphthalene (the analytical internal standard), there is apparently a small amount of a nondiscriminating reaction between the alcohol (or some substance derived from it) and preformed olefin to give high molecular weight products. The extent of this side reaction appears to be so small that it can be ignored in drawing qualitative conclusions from our results.

Experimental[27]

***cis*- and *trans*-2,3-Diphenylacrylic Acids.**—*cis*-2,3-Diphenylacrylic acid (V), m.p. 172–173°, was prepared in 51% yield by the method of Buckles, Bellis, and Coder.[28] The *trans* isomer (IV), m.p. 136.5–137.5°, was isolated in 1.3% yield from the crude reaction product by the procedure of Stoermer and Voht.[29]

***cis*-2,3-Diphenylallyl alcohol (VII)** was prepared by reduction of the *cis* acid (m.p. 172–173°) with lithium aluminum hydride in ether. The product was first crystallized from methanol and water and then from petroleum ether (b.p. 60–70°) to give a 75% yield of crude product, m.p. 70–71°. The analytical sample had m.p. 72–73°, λ_{max}^{EtOH} 257 (ε 12,500) and 222 mμ (15,900). This product is, thus, the same as that of Lutz and Rinker.[26]

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 86.01; H, 7.00.

***trans*-2,3-Diphenylallyl alcohol (VI)** was prepared in low yield from the corresponding acid (m.p. 136.5–137.5°) by the previous method. Better yields were obtained by use of a mixture rich in aluminum hydride. Aluminum chloride (0.60 g., 4.5 mmoles) was dissolved with cooling in 40 ml. of anhydrous ether and 9.4 ml. of ether containing 9 mmoles of lithium aluminum hydride was added. Immediately a solution of 1.0 g. (4.5 mmoles) of *trans*-2,3-diphenylacrylic acid in 10 ml. of ether was added. The mixture was heated at reflux for 1 hr. (magnetic stirring) and hydrolyzed at ice temperature by dropwise addition of 20 ml. of 20% aqueous sodium potassium tartrate. The ether layer was washed with dilute base and concentrated to give a solid which was recrystallized from petroleum ether (b.p. 60–70°) to give 0.67 g. (72%) of almost pure *trans* alcohol, m.p. 76.5–77.5°. A second recrystallization gave 0.57 g., m.p. 77–78°, λ_{max}^{EtOH} 273 mμ (ε 19,800).

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.75; H, 6.96.

α-Bromostyrene was prepared from styrene dibromide,[30] m.p. 71–73° (lit.[31] m.p. 72–73°), by a method essentially that of Ashworth and Burkhardt,[32] except that equimolar amounts of dibromide and potassium hydroxide were used. The product was obtained in 71% yield in several fractions, b.p. 76–78° (10 mm.), $n^{20}D$ 1.5895–1.5920; lit.[33] b.p. 71° (7–8 mm.), $n^{19.5}D$ 1.5881.

α-Styrylphenylcarbinol (VIII).—Lithium wire (0.50 g., 0.072 g.-atom) was cut into very small pieces and placed into 50 ml. of anhydrous ether. The mixture was cooled to −45° and maintained there during the dropwise addition of 5.0 g. (0.028 mole) of α-bromostyrene (about 1 hr.), 1 drop of methyl iodide having been added just prior to the bromide. The mixture was stirred magnetically at −45° for 2.5 hr., and then 2.9 g. (0.028 mole) of benzaldehyde was added dropwise (0.5 hr.). After an additional half hour at −45°, the mixture was allowed to warm to room temperature and was then filtered. The ether solution was extracted with water, aqueous sodium bisulfite, sodium hydroxide, and finally saturated sodium chloride, dried over sodium sulfate, and concentrated under vacuum to give 4 g. of viscous orange-yellow oil. Molecular distillation of 3.0 g. of this crude product gave 1.5 g. of viscous colorless oil in several fractions. The main fraction (1.2 g.) gave a solid, m.p. 44–49°, on seeding. α-Styrylphenylcarbinol (0.45 g.) was obtained in the form of white needles, m.p. 53–54°, after four recrystallizations from petroleum ether (b.p. 60–70°).

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.53; H, 6.75.

***cis*- and *trans*-α-Methylstilbenes.**—Samples of *cis*-α-methylstilbene (m.p. 43–47°, lit.[21] m.p. 48°) and *trans*-α-methylstilbene (m.p. 79–81°, lit.[21] m.p. 81–82°), prepared earlier by Rudesill,[34] had deteriorated slightly on standing but could be purified by gas chromatography; after such purification their melting points agreed with those in the literature. Additional amounts were accumulated by isolation from gas chromatographic analyses.

(27) All melting points are uncorrected. Microanalyses were by Dr. C. S. Yeh, Mrs. I. Groten, and Mrs. V. Keblys; infrared spectra by Mrs. M. Dilling and author H. O. B.

(28) R. E. Buckles, M. P. Bellis, and W. D. Coder, *J. Am. Chem. Soc.*, **73**, 4972 (1951).

(29) R. Stoermer and G. Voht, *Ann.*, **409**, 36 (1915). Our attention has since been called to the improved method by Fieser.[22]

(30) C. Glaser, *ibid.*, **154**, 154 (1870).

(31) R. Fittig and E. Erdmann, *ibid.*, **216**, 194 (1882).

(32) F. Ashworth and G. N. Burkhardt, *J. Chem. Soc.*, 1801 (1928).

(33) C. Dufraisse, *Ann. chim.* (Paris), [9] **17**, 171 (1922).

(34) J. T. Rudesill, Ph.D. thesis, Purdue University, 1957.

α-Benzylstyrene. 2,3-Diphenylpropanoic Acid.—A solution of 22.4 g. (0.10 mole) of *cis*-2,3-diphenylacrylic acid in 150 ml. of ethanol was hydrogenated in a Paar apparatus over 2.5 g. of palladium on charcoal. The catalyst was removed by filtration, the filtrate was concentrated on a steam bath, and water was added. The precipitate was thrice recrystallized from petroleum ether (b.p. 60–70°) to give 15.6 g. (70%) of 2,3-diphenylpropanoic acid, m.p. 87–89° (crystal modifications with m.p. 82°, 88–89°, and 95–96° are reported[35]).

2,3-Diphenylpropyl Acetate.—A solution of aluminum hydride was prepared by adding 3.8 g. (0.10 mole) of lithium aluminum hydride to a solution of 4.4 g. (0.033 mole) of aluminum chloride in 50 ml. of anhydrous ether, using magnetic stirring. Immediately thereafter a solution of 15.6 g. of 2,3-diphenylpropanoic acid in 60 ml. of anhydrous ether was added slowly, the mixture being stirred and maintained at reflux by gentle heating. After 1.5 hr. at reflux the solution was cooled with ice. Excess hydride was destroyed by dropwise addition of 5 ml. of ethyl acetate. Hydrolysis was completed by addition of 100 ml. of a 20% solution of sodium potassium tartrate. The layers were separated, and the aqueous layer was extracted with ether. The ether extract was extracted with base, dried over sodium sulfate, and concentrated under reduced pressure. The crude alcohol was heated to reflux directly with 25 ml. of acetic anhydride. After 12 hr. of reflux, acetic acid and anhydride were removed by distillation, and the residue was distilled through a short Vigreux column to give 15.3 g. (87%) of 2,3-diphenylpropyl acetate, b.p. 123–125° (1 mm.), m.p. 46.2–47.8°, $n^{20}D$ 1.5478.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.41; H, 7.19.

α-Benzylstyrene.—The ester was pyrolyzed by a method similar to that of Bailey and King,[36] 4.7 g. being passed dropwise through a column packed with glass beads which was maintained at 480–485°. There was obtained, after vacuum distillation of the effluent, 2.1 g. of olefin, collected in several fractions, $n^{20}D$ 1.5887–1.5940. Analysis by v.p.c. indicated the presence of small amounts of *cis*- and *trans*-α-methylstilbenes. A small sample, purified by v.p.c. fractionation, had $n^{20}D$ 1.5917 (lit.[37] $n^{20}D$ 1.5903). The infrared spectrum showed no significant bands in the regions 3200–3500 (hydroxy), 1700–1800, 1200–1300 (acetate), 1300–1400 cm.$^{-1}$ (methyl). A strong band at 896 cm.$^{-1}$, with a weak band at 1790 cm.$^{-1}$ (possible overtone) indicates the presence of a disubstituted vinyl group ($R_2C{=}CH_2$). Other bands at 695, 725, 781, 1560, 1590, 1615, 2850, and 3000 cm.$^{-1}$ are consistent with the assigned structure.

Reagent solutions were prepared by dissolving powdered lithium aluminum hydride (Metal Hydrides) in anhydrous ether (Mallinckrodt, dried over sodium hydride) and decanting the solution through glass wool into a previously cooled (0°) solution of granular aluminum chloride (Baker) in anhydrous diethyl ether. The mixture was allowed to stand at 0° for 4 hr., at which time the formation of sediment appeared to be complete, and carefully decanted through a small amount of glass wool into a flask for storage. The solution was assayed for hydride by measurement of the hydrogen evolved when methanol was added to an aliquot. Reagent solutions prepared in liter amounts in this way (usually *ca.* 1 *M* in hydride) were clear and could be stored at −4° for several months without forming further sediment or changing in hydride content. If, however, the solutions were left in contact with the sediment (which possesses some hydride activity), they decomposed slowly with the evolution of hydrogen.

Reductions were carried out in screw-cap vials held in a constant temperature bath for a specified amount of time. In the reactions reported here 10–200-mg. samples of the alcohols were placed in the vials with 3–30-mg. amounts of naphthalene as internal standard (all weighed out on an analytical balance). The required ether solutions of stock reagent (and in some cases, of aluminum chloride) were introduced by means of a calibrated syringe. A little hydrogen was evolved rapidly, from reaction of the alcohol with the reagent, but this reaction was usually complete by the time the screw cap had been tightened. After the desired reaction time a little water was added to decompose unchanged hydride, and the ether solutions were dried over Drierite and analyzed by gas chromatography (following). The reaction conditions used in particular studies are indicated in the footnotes in the tables of results presented in the text.

Analysis by Vapor Phase Chromatography.—All analyses were carried out with an Aerograph Model A-90-C equipped with a manual preheater control. Sharp symmetrical peaks were obtained with a 5-ft. Craig polyadipate column and flow rates of 20–40 ml. of helium per minute. A typical analysis at oven temperature of 220–240° and preheater temperature of 220° required about 15 min. The *cis*- and *trans*-2,3-diphenylallyl alcohols could not be separated under these conditions but gave a single peak. Naphthalene was used as an internal standard and, prior to each sequence of analyses, a determination of the area to weight ratios of the internal standard and each of the olefins was made using standard mixtures, areas being computed by the triangle method (height × base width/2). Thus, in a typical analysis, it was first determined that, for *cis*-α-methylstilbene, the area to weight ratio was

$$R = \frac{\text{area (olefin)}}{\text{g. (olefin)}} \times \frac{\text{g. (standard)}}{\text{area (standard)}} = 0.855$$

In a particular reduction, using 182.6 mg. of the *trans* alcohol and 31.4 mg. of naphthalene, analysis of the product gave areas of 6.72 cm.^{2} for naphthalene and 1.1 cm.^{2} for *cis*-α-methylstilbene. The product thus contained

$$\frac{1.10 \text{ cm.}^2}{6.72 \text{ cm.}^2} \times \frac{31.4 \text{ mg.}}{0.855} = 6.03 \text{ mg. } cis\ \alpha\text{-methylstilbene}$$

Control Experiments. Stability of Internal Standard.—Equal amounts (31.2 mg., 0.15 mmole) of α-styrylphenylcarbinol were placed in two screw-cap vials. In the first was placed 2.0 mg. (0.0156 mmole) of naphthalene, while in the second was placed 19.3 mg. (0.15 mmole). Then 1.5 ml. (0.75 mmole) of standard ethereal dichloroaluminum hydride solution (3:1 reagent) was added with a syringe. The vials were closed and held at 20° for 2 hr. and then worked up and analyzed in the usual way. In the first run the analysis indicated the formation of 66% of the theoretical amount of olefin: 14% I, 57% II, and 29% III; in the second run, the analysis indicated the formation of 70% of the theoretical amount of olefin: 14% I, 58% II, 28% III. We assume that any reaction of olefin or alcohol with naphthalene would occur on a mole-for-mole basis (*e.g.*, alkylation); if so, such reaction would not affect the analysis in the second run, but as little as 1% of such reaction in the first run would consume 10% of the standard and give an apparent yield of 77%. The reproducibility of yield and composition, thus, indicate that the internal standard does not interfere appreciably with the reaction.

Stability of Olefins.—A synthetic mixture containing 39.6 mg. (0.204 mmole, 51.3%) of *trans*-α-methylstilbene, 19.0 mg. (0.098 mmole, 24.6%) of *cis*-α-methylstilbene, and 18.6 mg. (0.096 mmole, 24.1%) of α-benzylstyrene was dissolved in 4 ml. of 0.4 *N* ethereal dichloroaluminum hydride together with 11.2 mg. (0.0875 mmole) of naphthalene. The solution was kept at 34° for 16 hr. and then worked up and analyzed in the usual way; this analysis showed the recovered olefin mixture to contain 51.3% of *trans*-α-methylstilbene, 24.4% of *cis*-α-methylstilbene, and 24.2% of α-benzylstyrene. The recovery of olefin was 100.5%, this meaning simply that there was virtually no change in relative amounts of olefin and naphthalene. Since the solution originally contained a total of 0.396 mmole of olefin and 0.0875 mmole of naphthalene any mole-for-mole reaction of olefin with naphthalene would raise the apparent recovery above 100%. The value obtained corresponds to no more than 1.3% of such reaction. The olefins are not isomerized under these conditions.

Reaction of Olefin Precursors with Olefins.—A solution of 52.5 mg. (0.25 mmole) of *trans*-2,3-diphenylallyl alcohol and 11.1 mg. (0.087 mmole) of naphthalene in 10 ml. of an ether solution of 3:1 reagent containing 1.24 mmoles of active hydride was kept at 20° for 24 hr. and then worked up and analyzed as before. The analysis indicated formation of 0.0608 mmole of *cis*-α-methylstilbene, 0.0268 mmole of *trans*-α-methylstilbene, and 0.0313 mmole of α-benzylstyrene (0.1194 mmole of olefin in all, or 47.8%). An otherwise identical solution, containing in addition 0.0572 mmole of *cis*-α-methylstilbene, 0.1405 mmole of *trans*-α-methylstilbene, and 0.0603 mmole of α-benzylstyrene (0.2580 mmole in all) was simultaneously subjected to the same conditions. Analysis of the product from the second reaction showed the presence of 0.108 mmole of *cis*-α-methylstilbene, 0.152 mmole of *trans*-α-methylstilbene, and 0.0845 mmole of

(35) W. v. Miller and G. Rohde, *Ber.*, **25**, 2017 (1892).
(36) W. J. Bailey and C. King, *J. Am. Chem. Soc.*, **77**, 75 (1955).
(37) J. v. Braun, J. Seemann, and A. Schultheiss, *Ber.*, **56**, 3814 (1922).

α-benzylstyrene (0.3445 mmole in all). The amount of mixed olefin obtained in the second run was thus, 0.033 mmole less than that expected from the results of the first run and the amount of preformed olefin used. We assume that this loss arises from diversion of 0.0165 mmole of preformed olefin (6.4%) and 0.0165 mmole (13.8%) of alcohol into a 1:1 reaction of carbonium ion with olefin, and that this reaction is not discriminating among olefins or possible carbonium ions. On this basis the amount of each olefin to be expected in the second run becomes 0.1059 mmole of *cis*-α-methylstilbene, 0.1547 mmole of *trans*-α-methylstilbene, and 0.0838 mmole of α-benzylstyrene. These values are within 2% of those observed. These results indicate that a side reaction of this nature will occur in all reactions, being presumably most important when about 50% conversion of alcohol to olefin has occurred. Since this side reaction appears not to be discriminating, it should have little effect on *ratios* of olefins obtained.

Hydrogenolyses at 80°.—*trans*-2,3-Diphenylallylalcohol (VI) (0.017 g., 0.080 mmole) and 2 mg. of naphthalene were placed in a 10-mm. i.d. glass tube which was then cooled in a Dry Ice–acetone bath. While a slow stream of dry nitrogen was passed into the tube, 1 ml. of 3:1 reagent (0.4 mmole/ml. in hydride) was added. The tube was quickly sealed and placed in an oil bath set at 80°. The solution turned cloudy and then a clear second liquid layer separated. After a reaction time of 0.5 hr., the tube was cooled and opened. The solution was hydrolyzed and analyzed in the usual way by v.p.c. The hydrocarbon fraction (*ca.* 100% conversion) consisted of 22% *cis*-α-methylstilbene, 39% *trans*-α-methylstilbene, and 39% α-benzylstyrene. In a parallel experiment the *cis* alcohol gave *ca.* 93% of olefin containing 69% *cis*-α-methylstilbene, 2.4% *trans*-α-methylstilbene, and 29% α-benzylstyrene.

Discussion of Results

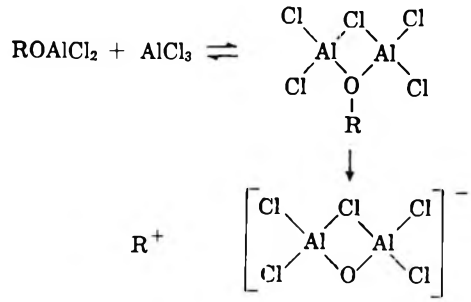
The reaction of an alcohol with an aluminum chloride–lithium aluminum hydride mixture occurs in several distinct steps, the first of which is very rapid, giving one mole of hydrogen per mole of alcohol in a few minutes, presumably according to eq. 1 (following).

$$ROH + HAlCl_2 \longrightarrow ROAlCl_2 + H_2 \qquad (1)$$

An aldehyde or ketone also would react rapidly with one mole of a chloroaluminum hydride to give the same alkoxy compound, without releasing hydrogen (eq. 2).

$$R_2C{=}O + HAlCl_2 \longrightarrow R_2CHOAlCl_2 \qquad (2)$$

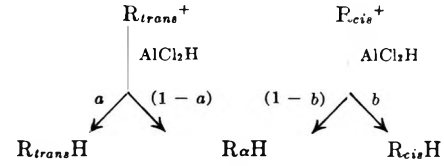
Provided that these steps are much faster than the following ones, the hydrogenolysis reactions of alcohols and of carbonyl compounds should be indistinguishable as to rate and product[38]; it is our experience that this is the case. The rate of *conversion* to hydrocarbons decreases with dilution (Table III) indicating that the slow step in hydrogenolysis is not simple ionization of the chloroaluminum alkoxide but involves additional chloroaluminum hydride. The relative reactivity of variously substituted benzylic alcohols[6-13] (see also part II[19]) and of saturated alcohols (part IV[18]), together with the distribution of products observed in the present work, suggest strongly that the slow step involves the formation of a carbonium ion. Accordingly, we suggest that ionization is preceded by coordination of the oxygen atom with a second molecule of Lewis acid, for example, as in eq. 3.[39] On this basis, the Lewis acidity of the initial reagent (considered either in terms of the amount of aluminum chloride present as such in a re-



(3)

distribution equilibrium or in terms of the Lewis acidity of the individual chloroaluminum hydrides) would be of great importance, as, in fact, it seems to be (Table IV). These results are reminiscent of those of Conover and Tarbell[5] who found that in hydrogenolyses with lithium aluminum hydride alone an excess of the hydride accelerated the reaction.

The distribution of olefins in the products of reduction of the three diphenylallyl alcohols near room temperature falls into a pattern (Fig. 1) which is that to be expected from reactions leading to varying amounts of the two allylic carbonium ions (R_{trans}^+, IX; R_{cis}^+, X) each of which is reduced in characteristic proportions to two olefins. (See eq. 4 following).



(4)

In such a case the amounts of *cis* ($R_{cis}H$, II) and *trans* ($R_{trans}H$, I) olefin will be related to the total amount of olefin formed (RH) as follows. (See eq. 5 and 6).

$$R_{cis}H/b + R_{trans}H/a = RH \qquad (5)$$

whence

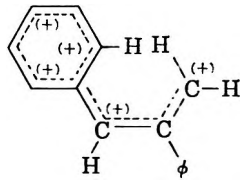
$$a(R_{cis}H/RH) + b(R_{trans}H/RH) = ab \qquad (6)$$

From the data used in preparing Fig. 1, we obtain the values $a = 0.55$ and $b = 0.82$, indicating that, while the *trans* carbonium ion is reduced almost statistically at either end, the *cis* carbonium ion is reduced chiefly to *cis*-α-methylstilbene. The data of Tables I–III indicate that the *trans* carbonium ion (IX) has a strong tendency to isomerize to the *cis* (X); this might most simply occur by reversal of the ionization shown in eq. 3 to form the α-styrylphenylcarbinyl derivative. Any such process, it would appear, is interrupted by reductive attack of a hydride donor before equilibration can occur. It is expected from this analysis that an increase in the concentration of hydride donor (*at this stage of the reaction*) would produce a decrease in the fraction of *cis* olefin (II) in the product of reduction of the *trans* alcohol (VI). This is observed (Tables II and III).

These conclusions indicate that there is an appreciable, but not unsurmountable, barrier to interconversion of geometrically isomeric allylic carbonium ions. It would appear that *in the present system* the *cis* carbonium ion (X) is the more stable and retains its geometric configuration to the extent of about 90%. The *trans* carbonium ion (IX) is less stable, perhaps because of coulombic repulsions or perhaps because of steric hindrance to coplanarity (XI), and so, depending on the

(38) Certain results of Nystrom and Berger[12] which seem to be inconsistent with this conclusion are considered in the following paper.[19]

(39) The structures shown for the complex and the anion are speculative, of course, but are in reasonable analogy to the bridged structures possessed by many aluminum compounds. Analogous structures with hydrogen in place of chlorine can be imagined for cases where the reagent is richer in hydride.



XI

rate at which it is consumed by reduction, is converted in part to the *cis* ion (40–70% conversion in reductions at room temperature). We may, in general, then, expect that one geometrical isomer of an allylic alcohol will be reduced with a high degree of retention of geometric configuration, but that the other isomer will give sizeable amounts of the same products, the nature of these products being determined, first, by the relative stability of the two allylic carbonium ions (*not* to stability of the olefins) and, second, by the extent to which reduction occurs at either end of the allylic systems. The use of this reaction in the assignment of configuration is, thus, not without hazard, and some care should be exercised in its use for this purpose.

Hydrogenolyses with Chloroaluminum Hydrides. II. Benzylic Alcohols

JAMES H. BREWSTER, HORST O. BAYER, AND STANLEY F. OSMAN[1]

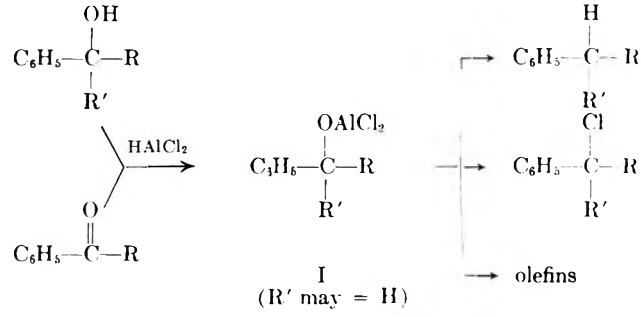
Department of Chemistry, Purdue University, Lafayette, Indiana

Received June 7, 1963

Benzylic alcohols are reduced to hydrocarbons by mixtures of aluminum chloride and lithium aluminum hydride. The ease of reduction is sensitive to the structure of the alcohol and the Lewis acidity of the reagent, the influence of these factors suggesting that the slow step involves formation of a benzylic carbonium ion. Chlorides, which may be formed in a side reaction, appear to be reduced more slowly than alcohols by "dichloroaluminum hydride." Olefins are prominent by-products in the reduction of tertiary benzylic alcohols; in at least one case the elimination reaction follows the Hofmann rule.

Since allylic alcohols undergo hydrogenolysis with mixtures of aluminum chloride and lithium aluminum hydride,[2] it seemed likely that benzylic alcohols would also undergo this reaction. Hydrogenolysis of activated aromatic carbinols has been observed to occur with excess lithium aluminum hydride alone at temperatures of 60–90°.[3] Reductions in which such hydrogenolysis might reasonably be considered to be the final step have been reported to occur when aromatic acids, aldehydes, and ketones are treated with "mixed hydride" reagents.[4,5] The latter papers, however, give the impression that carbinols are not always intermediates and may well be reduced less easily than carbonyl compounds. Thus Nystrom and Berger[5] report that methylphenylcarbinol is not reduced when treated with a large amount of a reagent that reduces acetophenone to ethylbenzene; they also report that benzyl alcohol is not reduced although triphenylcarbinol and benzhydrol are reduced with ease. Brown and White[4] suggest that reduction to the carbinol stage may be a deleterious side reaction leading to the formation of chlorides and olefins. We have, therefore, investigated this matter in more detail and have found that benzylic alcohols in general can be reduced by "mixed hydrides" (Table I). This indicates that the alcohols or, more probably, alkoxyaluminum compounds derived from them (as I) are at least sufficient as intermediates in the reduction of the more highly oxidized compounds. In several cases it was observed that alcohols and ketones are essentially equivalent as starting materials in preparative applications of this reaction.

In accord with an earlier report[5], we found that benzyl alcohol was not detectably reduced by 3:1 reagent[6]



I
(R′ may = H)

after three days in refluxing diethyl ether; it was reduced (in part) to toluene at 70–80°. Under these conditions a higher-boiling product, apparently identical with that formed on benzylation of toluene, also was obtained. In contrast, *p*-methoxybenzyl alcohol was cleanly reduced to *p*-methoxytoluene in half an hour at room temperature, confirming the strong activating effect of methoxy groups observed by Conover and Tarbell[3] and by Brown and White.[4] Methylphenylcarbinol also was more easily reduced than benzyl alcohol. With excess 3:1 reagent the alcohol was almost completely consumed in two hours at room temperature, but virtually no reduction occurred when the ratio of chloride to hydride was low (Table II). We have calculated the chloride-to-hydride ratios obtaining in the reaction mixtures used by Nystrom and Berger[5], assuming rapid formation of I, and find (Table III) that their experimental results are consistent with ours. When the chloride-to-hydride ratio was higher than 2, acetophenone was reduced to ethylbenzene; when it was lower, the ketone was reduced only to the alcohol in the short reaction time allowed. Their failure to obtain hydrogenolysis with the alcohol is now seen to have resulted from the use of *too much* of their 1:1

(1) The authors gratefully acknowledge the financial support of this research by the National Science Foundation (Grant NSF-G 10051).

(2) J. H. Brewster and H. O. Bayer, *J. Org. Chem.*, **29**, 116 (1964). References to earlier examples of this reaction are cited in this paper.

(3) L. H. Conover and D. S. Tarbell, *J. Am. Chem. Soc.*, **72**, 3586 (1950).

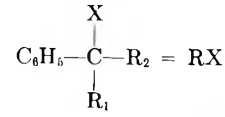
(4) B. R. Brown and A. M. S. White, *J. Chem. Soc.*, 3755 (1957).

(5) R. F. Nystrom and C. R. A. Berger, *J. Am. Chem. Soc.*, **80**, 2896 (1958).

(6) This is the molar ratio of aluminum chloride to lithium aluminum hydride used in preparing stock solutions[2] of "mixed hydride" reagents. The 3:1 reagent has the composition of $AlCl_2H$ and also will be referred to as "dichloroaluminum hydride." In most of this work we have used amounts of this reagent corresponding to 4 moles of this species per mole of alcohol.

TABLE I

HYDROGENOLYSIS OF BENZYLIC ALCOHOLS AND CHLORIDES (3:1 REAGENT)[a]



R_1	R_2	Temp., °C.	Time, hr.	% RX reacted	Reaction product, % composition[b] RH	RCl	Olefin
			X = OH				
H	H	*ca.* 40	72	0			
		ca. 75	24		48 (isolation)		
H[c]	H[c]	*ca.* 25	0.5	*ca.* 100	*ca.* 100		
H	CH_3	*ca.* 25	2	97	74	14	12
CH_3	CH_3	*ca.* 25	4	100	56		44
$-(CH_2)_5-$		*ca.* 25	4	100	56		44
H	$C(CH_3)_3$	*ca.* 25	0.5	2	13	87	
		ca. 25	4	4	38	62	
		ca. 40	24	57	56	44	
		ca. 40	92	100	83	17	Trace
H	*e*-$CH(CH_3)C_6H_5$[d]	*ca.* 25	3	89	61	39	
		ca. 25	24	100	96	4	
H	*t*-$CH(CH_3)C_6H_5$[d]	*ca.* 25	0.2	97	68	32	
		ca. 25	3	100	72	28	
		ca. 25	24	100	96	4	
CH_3	$CH_2C_6H_5$	*ca.* 25	0.05	93	13	+	+
		ca. 25	2	100	39	0	61[e]
		ca. 25	4	100	39	0	61[e]
		0	48	100	39	0	61[e]
			X = Cl				
H	*e*-CHC_6H_5[d]	*ca.* 25	3	7	100		
H	*t*-CHC_6H_5[d]	*ca.* 25	3	18	100		
CH_3	$CH_2C_6H_5$	*ca.* 25	3	100	52		48[f]

[a] See ref. 6. [b] Analysis by gas chromatography unless otherwise noted. [c] *p*-Methoxybenzyl alcohol. [d] *e*-, *erythro*; *t*-, *threo*. [e] 21% *trans*-α-methylstilbene; 79% α-benzylstyrene. [f] 58% *trans*-α-methylstilbene; 42% α-benzylstyrene.

TABLE II

HYDROGENOLYSIS OF METHYLPHENYLCARBINOL

Reactants, mole/mole of alcohol $AlCl_3$[d]	$LiAlH_4$[e]	Ratio, Cl-H[a]	% reaction[b,c]	Product composition,[c] % EB[f]	S[f]	PEC[f]
1	1	1	2	66	15	19
1	1	1	52[g]	76[g]	14[g]	10[g]
2	1	2	75	71	14	15
3	1	3	97	74	12	14
4	1	4	100	74	14	12
4	1	4	100[h]	73[h]	14[h]	13[h]
5	1	5	100	74	14	12
2.67[i]	1.67[i]	1.41[i]	0[i]			

[a] Ratio after assumed formation of alkoxide I. [b] In ether at room temperature; 2 hr. except where noted. [c] Analyses by v.p.c. on Carbowax 20 M at 120° with preheater at 140°. At higher temperatures some of the chloride cracked to form styrene. [d] 1 *M* $AlCl_3$ in ether. [e] 0.25 *M* $LiAlH_4$ in ether. [f] EB, ethylbenzene; S, styrene; PEC, α-phenylethyl chloride. [g] 18 hr. [h] Acetophenone as starting material. [i] Data of Nystrom and Berger[5]; reaction presumably carried out in refluxing ether for 1 hr.

TABLE III

HYDROGENOLYSIS OF ACETOPHENONE[a]

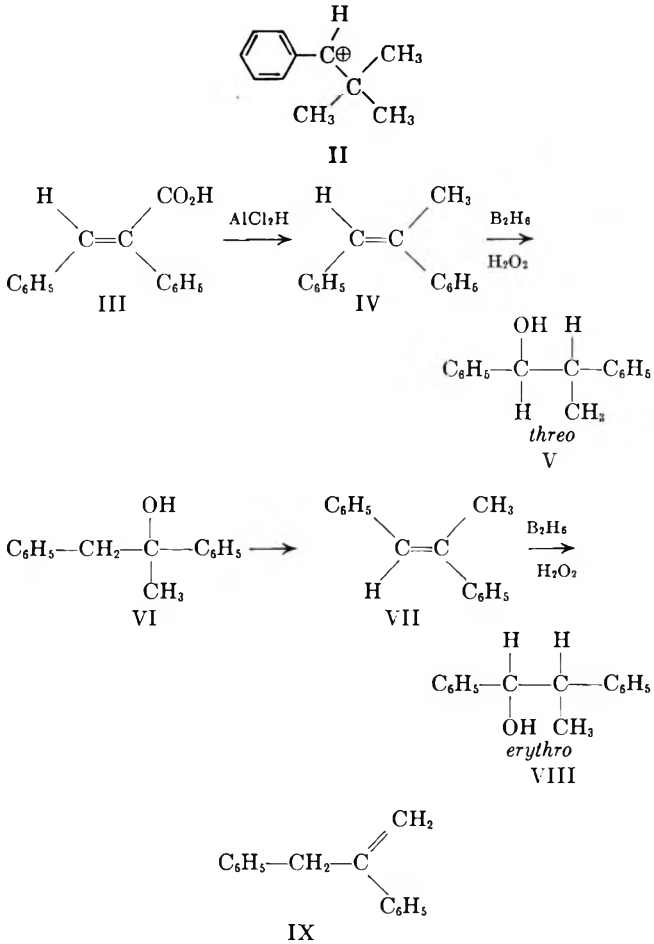
Reactants, mole/mole of ketone $AlCl_3$	$LiAlH_4$	Ratio, Cl-H[b]	Product, %[c] Alcohol	Ethyl benzene
1	1	1.0	91	..
0.77	0.77	1.11	93	..
1.77	0.77	2.6		25
2.75	0.75	4.13		56
4[d]	1[d]	4[d]		74[d]

[a] Calculated from data of Nystrom and Berger.[5] [b] Ratio after assumed reduction and formation of alkoxyaluminum intermediate (I). [c] Isolation after about 1 hr. in refluxing ether. [d] This work; 5 hr. at room temperature; product obtained by isolation.

reagent,[6] which is too rich in hydride to be effective with this alcohol. Their finding that triphenylcarbinol and benzhydrol were reduced with ease by this reagent may then be taken as evidence that additional phenyl groups promote hydrogenolysis even more strongly than does a methyl group. The importance of Lewis acidity (as judged by the chloride–hydride ratio) and of substituents in promoting the reduction of benzylic alcohols indicate that a high degree of carbonium ion character is developed in the transition state for the slow step of this reaction, as does the formation of benzyltoluenes in the reduction of benzyl alcohol.

t-Butylphenylcarbinol was found to be considerably less reactive than methylphenylcarbinol though more reactive than benzyl alcohol (Table I). In this case the product was initially rich in unrearranged chloride, but the amount of chloride in the reaction product decreased as the reaction proceeded, indicating that the chloride was slowly reduced. The final hydrocarbon product was nearly pure (96%) neopentylbenzene. The virtual absence of rearrangement does not exclude

the formation of a carbonium ion; a number of compounds of this series undergo solvolysis reactions (presumably *via* II) without rearrangement.[7,8] An increase in the steric interaction of the phenyl and *t*-butyl groups in the formation of II previously has been invoked to account (in part) for the relatively slow solvolysis of the tosylate and chloride[8]; a similar explanation seems appropriate for the relatively slow reduction of both the alcohol and the chloride observed here.



Chlorides also play a role in the hydrogenolysis of the 1,2-diphenyl-1-propanols (*threo*, V; *erythro*, VIII).[9] Both alcohols gave nearly pure 1,2-diphenylpropane on treatment with excess 3:1 reagent[6] in ether at room temperature for one day. Virtually no olefins were detected in the product, indicating that none were formed at any point in the reaction, the possible olefins being neither reduced nor isomerized by 3:1 reagent.[2] When the reaction was interrupted after three hours, the presence of some 28–35% of olefins was indicated by gas chromatographic analysis. This we attribute to the presence of the chlorides since they (but not the alcohols) were found to give similar olefin mixtures on gas chromatography, apparently cracking quickly and cleanly in the preheater. The conclusion that appreciable amounts of chloride were formed is supported by our observation that the *erythro* chloride[10] can be prepared from the *erythro* alcohol by reaction with 3:1 reagent at ice temperature (seven days). Both of the chlorides were separately prepared and treated with 3:1 reagent; some reduction occurred in each case (Table I), but it is clear that this reduction is so slow that the chlorides cannot be major intermediates in the reduction of the alcohols. Thus, the *threo* alcohol (V) gave 66% of 1,2-diphenylpropane in thirteen minutes while the *threo* chloride gave only 18% in three hours. It is seen that the formation of chlorides is deleterious in the sense that it diverts a portion of the starting material into a pathway that leads to slow formation of hydrogenolysis product; the effects of this side reaction can be overcome by allowing time for reduction of the chlorides to occur. Attack of a hydride donor on a free carbonium ion would provide a more direct and, we suggest, a more rapid route to the reduction product.

Dimethylphenylcarbinol and 1-phenylcyclohexanol, two simple tertiary benzylic alcohols, were rapidly converted to hydrocarbons by 3:1 reagent at room temperature (Table I). In each case a pronounced evolution of hydrogen gas occurred during the first hour of the reaction, and in each case the product contained about 44% of olefin. 1,2-Diphenyl-2-propanol (VI) also reacted rapidly, the product obtained after thirty minutes of reaction being free of alcohol (v.p.c.) and chloride (negative Beilstein test) and identical with that obtained after two or four hours reaction time. This product contained 39% of 1,2-diphenylpropane, 13% of *trans*-α-methylstilbene (VII), and 48% of α-benzylstyrene (IX). The high proportion of IX in the olefinic product indicates that elimination with "dichloroaluminum hydride" is not controlled by the thermodynamic stability of the olefinic product,[11] but by the steric requirements of the leaving group.[12] Eliel[13] has suggested that the oxygen atom of a species such as I, with its inorganic burden, acts as a very bulky group in epimerizations of alcohols. The steric requirement of this group would be increased by attachment of an additional Lewis acid species preliminary to the formation of a carbonium ion.[2] It seems possible, then, that the elimination process involves loss of a proton from an ion pair; we do not, however, have data which exclude other possible explanations for the occurrence of Hofmann elimination.

We conclude that "mixed hydride" reagents are useful in the reduction of phenyl ketones and secondary benzylic alcohols, and that the alkoxides (I) are prob-

(7) P. Skell and C. R. Hauser, *J. Am. Chem. Soc.*, **64**, 2633 (1942).

(8) S. Winstein and B. K. Morse, *ibid.*, **74**, 1133 (1952).

(9) Configurations have been assigned to these alcohols on the assumption that they give *cis* elimination in the formation of *cis*- and *trans*-α-methylstilbene (IV and VII) by the Chugaev reaction [D. J. Cram and F. A. Abd Elhafez, *ibid.*, **74**, 5828 (1952)]. The alcohols can be prepared conveniently from the α-methylstilbenes by hydroboration, the products being those to be expected from *cis* addition to the double bond [H. C. Brown and G. Zweifel, *ibid.*, **81**, 247 (1959); **83**, 2544 (1961)]. *cis*-α-Methylstilbene (IV) can be prepared in one step by reduction of the readily available *cis*-2,3-diphenylacrylic acid (III) with 3:1 reagent.[2]

(10) D. J. Cram and F. A. Abd Elhafez, *ibid.*, **74**, 5851 (1952), have prepared both chlorides and assigned configurations by use of stereospecific elimination reactions.

(11) These olefins are neither reduced nor isomerized by 3:1 reagent.[2] Equilibration of the α-methylstilbenes with acid or with strong base gives nearly pure *trans*-α-methylstilbene [D. J. Cram, F. D. Greene, and C. H. Depuy, *ibid.*, **78**, 790 (1956)] as does treatment of the tertiary chloride with aluminum chloride (see Experimental). Cracking of the chloride during v.p.c. gives 60% VII, 15% IV, and 25% IX, while reduction with excess 3:1 reagent gives 52% 1,2-diphenylpropane, 28% VII, and 20% IX. Hydrolysis with aqueous acetone or reaction with silver nitrate gives 70–80% of tertiary alcohol (VI) and an olefin mixture containing 53% VII, 5% IV, and 42% IX.

(12) See J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 186–206, for a discussion with many references.

(13) E. L. Eliel, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **22**, 129 (1961); E. L. Eliel and M. N. Rerick, *J. Am. Chem. Soc.*, **82**, 1367 (1960).

able intermediates in both cases. Time should be provided for the reduction of chlorides, which are formed in a separate reaction and which appear to be rather slowly reduced by these reagents. The formation of olefins is an important side reaction in the reduction of tertiary benzylic alcohols; this can be minimized by reduction of the chloride with a reagent rich in hydride (see Experimental).

Experimental

Unless otherwise specified reductions were carried out with stock solutions of 3:1 reagent[6] prepared by mixing ether solutions of lithium aluminum hydride and aluminum chloride at 0°, freed of sediment by decantation and stored at −4°. Most of the solutions used were about 1 *N* in hydride as found by measurement of the hydrogen evolved when an aliquot was treated with methanol. At the end of the reactions described subsequently the reaction mixtures (at room temperature or below) were poured onto at least an equal volume of ice. The ether layer was separated and the water layer was extracted with ether; the combined ether extract was washed with aqueous sodium carbonate and with saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate. The solutions were concentrated by distillation of the ether through a Vigreux column or, in the 1,2-diphenylpropane series, by evaporation under vacuum, and then distilled at appropriate pressures and temperatures. Samples of all major products were purified by vapor phase chromatography (Aerograph Model A-90-C) and identified by comparisons of retention time, refractive index,[14] and infrared spectra with published data[15] or available authentic samples. Reaction mixtures and distillation fractions were analyzed by gas chromatography assuming 100% material balance. This assumption should be valid for materials obtained by distillation but would give high results if high molecular weight products were present in undistilled materials. In most cases the analytical results were reasonably consistent with yield data for products isolated by distillation. Chlorides of the 1,2-diphenylpropane series cracked in the v.p.c. preheater and gave clean analyses as mixtures of olefins. Microanalyses were performed by Dr. C. S. Yeh, Mrs. I. Groten, and Mrs. V. Keblys.

Hydrogenolysis of Benzyl Alcohol.—A solution of 5.4 g. (50 mmoles) of benzyl alcohol in 200 ml. (200 mmoles) of "dichloroaluminum hydride" reagent was heated at reflux for 3 days. An insoluble white solid formed, but no toluene could be detected by v.p.c. analysis of aliquots. About 150 ml. of diethyl ether was distilled and saved, the flask temperature rising to about 75°; the mixture was held at this temperature for 24 hr. It was then cooled to room temperature, and the ether distillate was added to the reaction mixture, which was then worked up in the usual way to give 2.2 g. (48%) of toluene, b.p. 109°, n^{20}D 1.4962 (lit.[14a] n^{20}D 1.4962), and 1.1 g. of a higher boiling fraction collected at 85–95° (1 mm.). A sample of this fraction was separated by v.p.c. on Carbowax 20 M at 200° to give about 10% of benzyl alcohol and a hydrocarbon fraction, n^{20}D 1.5721, which, from microanalytical data (following) and comparisons of infrared spectra,[16] appears to be a 40:60 mixture (roughly) of 2-methyldiphenylmethane (lit.[16] n^{20}D 1.5763) and 4-methyldiphenylmethane (lit.[16] n^{20}D 1.5692).

Anal. Calcd. for $C_{14}H_{14}$: C, 92.26; H, 7.74. Found: C, 92.30; H, 8.03.

Alkylation of Toluene with Benzyl Alcohol.—A solution of 50 ml. (50 mmoles) of dichloroaluminum hydride reagent was diluted with 23 g. (250 mmoles) of anhydrous toluene, and then 2.70 g. (25 mmoles) of benzyl alcohol was added dropwise over a 2-min. period. The clear solution was heated to 80°, most of the ether distilling below 70°, and kept at about 80° for 10 hr. A white crusty solid separated and hydrogen evolution ceased after about 2 hr. The mixture was cooled in ice and shaken with 5 ml. of ice water until the solid had dissolved. An ether extract of the aqueous phase was combined with the toluene layer. The organic portion was dried, concentrated, and distilled to give 3.64 g. (80%) of mixed 2- and 4-methyldiphenylmethanes, b.p. 85–87° (1 mm.), n^{20}D 1.5721, infrared spectrum superimposable on the mixture obtained from hydrogenolysis of benzyl alcohol (preceding).

Alkylation of Toluene with Benzyl Chloride.—Addition of 21 g. (230 mmoles) of anhydrous toluene to 24 ml. (24 mmoles) of dichloroaluminum hydride reagent caused precipitation of a granular white precipitate. Benzyl chloride (2.9 g., 23 mmoles) was added, and the solution was heated to 80° and held there for 10 hr. Worked up as before, this reaction mixture gave 2.7 g. (64%) of product, b.p. 85–87° (1 mm.), n^{20}D 1.5721, infrared spectrum superimposable on those obtained previously.

Hydrogenolysis of *p*-Methoxybenzyl Alcohol.—In a small-scale run, 0.5 mmole of *p*-methoxybenzyl alcohol was treated with 2 ml. (2 mmoles) of dichloroaluminum hydride reagent for 0.5 hr. at room temperature. At this time conversion to *p*-methoxytoluene appeared to be complete as judged by v.p.c. analysis. A sample of product obtained by v.p.c. fractionation had n^{20}D 1.5118 (lit.[17] $n^{19.3}$D 1.5124).

Hydrogenolysis of Methylphenylcarbinol. A.—Reagents of varying aluminum chloride content were prepared by mixing appropriate amounts of 1.0 *M* aluminum chloride and 0.25 *M* lithium aluminum hydride in ether. One mole of carbinol was added for every mole of lithium aluminum hydride, and the solutions were let stand 2 hr at room temperature, hydrolyzed, and analyzed by v.p.c. on Carbowax 20 M at 120° for hydrocarbons and chloride, at 150° for carbinol, assuming 100% material balance. The results are shown in Table II.

B.—On a preparative scale 3.7 g. (30 mmoles) of methylphenylcarbinol and 120 ml. (120 mmoles) of dichloroaluminum hydride in ether were allowed to stand at room temperature for 5 hr. The mixture was hydrolyzed and distilled to give 2.7 g. (84%) of a hydrocarbon mixture which v.p.c. analysis showed to contain 12% of styrene and 88% of ethylbenzene. These components were isolated by v.p.c.: styrene, n^{20}D 1.5457 (lit.[14b] n^{20}D 1.5465), and ethylbenzene, n^{20}D 1.4960 (lit.[14c] n^{20}D 1.4960). The infrared spectra were identical with published ones (API No. 170 and 309).[15]

Essentially identical results were obtained when this experiment was repeated using acetophenone as the starting material.

C.—Methylphenylcarbinol (2.0 g., 0.016 mole) was added to a solution of 3:1 reagent made by mixing 20 ml. of an ether solution containing 6.0 g. (0.04€ mole) of aluminum chloride and 12 ml. of 1.35 *M* lithium aluminum hydride (0.016 mole) in ether. The mixture was heated under reflux for 7 hr. and then poured on ice. The product was taken up in ether, and the ether extract was dried and analyzed by gas chromatography on a silicone column. Ethylbenzene was the only product evident, and comparison of retention times indicated the absence of styrene, α-phenylethyl chloride, and the starting alcohol. Under the same conditions acetophenone gave only ethylbenzene, but styrene was not reduced.

Hydrogenolysis of Dimethylphenylcarbinol.—Within minutes of mixing 0.34 g. (2.5 mmoles) of dimethylphenylcarbinol[18] (at least 99% pure by v.p.c.) and 10 ml. (10 mmoles) of 1 *N* ethereal dichloroaluminum hydride an insoluble layer separated. Vigorous evolution of hydrogen continued for about 0.75 hr. after the initial reaction of alcohol and reagent. The mixture was hydrolyzed after 4 hr and analyzed and fractionated by v.p.c. on Carbowax 20 M, showing the formation of cumene (56%), n^{20}D 1.4911 (lit.[14d] n^{20}D 1.4915), and α-methylstyrene (44%), n^{20}D 1.5382 (lit.[14e] n^{20}D 1.5363), infrared spectra identical with published ones (API No. 295 and 329).[15]

Hydrogenolysis of 1-Phenylcyclohexanol.—A mixture of 4.4 g. (25 mmoles) of 1-phenylcyclohexanol[19] and 100 ml. (100 mmoles) of dichloroaluminum hydride solution was let stand 4 hr. at room temperature; after the usual work-up there was obtained 3.5 g. (87%) of hydrocarbon, b.p. 66–73° (1 mm.). Analysis by v.p.c. on Carbowax 20 M at 185°, with identification of fractions *via* isolation, showed this product to contain 56% of phenylcyclohexane, n^{20}D 1.5256 (lit. n^{20}D 1.5249,[14f] 1.5255[20]),

(14) G. Egloff, "Physical Constants of Hydrocarbons," Vol. III, Reinhold Publishing Corp., New York, N. Y., 1940: (a) p. 47; (b) p. 188; (c) p. 60; (d) p. 81; (e) p. 192; (f) p. 265; (g) p. 276.

(15) American Petroleum Institute Research Project 44 (spectrum number indicated in text).

(16) J. H. Lamneck, Jr., H. F. Hipsher, and V. O. Fenn, Natl. Advisory *Comm. Aeronaut. Tech. Note*, **No. 3154**, 9–10 (1954). (Sadtler Standard Spectra, Philadelphia, 1962, no. 8235 and 8237).

(17) K. v. Auwers, *Ann.*, **422**, 178 (1921).

(18) Sample provided by Professor H. C. Brown.

(19) P. Sabatier and A. Mailhe, *Bull. soc. chim. France*, [3] **33**, 74 (1905).

(20) E. L. Eliel, J. W. McCoy, and C. C. Price, *J. Org. Chem.*, **22**, 1533 (1958).

and 44% of 1-phenylcyclohexene, n^{20}D 1.5690 (lit.[14k] n^{20}D 1.5692). The infrared spectra of each compound showed the bands reported by Eliel, McCoy, and Price.[20]

Hydrogenolysis of *t*-Butylphenylcarbinol.—A sample of *t*-butylphenylcarbinol[21] was recrystallized from petroleum ether (b.p. 30–40°) to m.p. 44.5–45.5°; it gave only one peak by v.p.c. A mixture of 4.10 g. (25 mmoles) of carbinol and 100 ml. (100 mmoles) of 1 *N* ethereal dichloroaluminum hydride was prepared at 0°, held at room temperature for 4 hr., and then heated under reflux for 92 hr. The progress of the reaction was followed by v.p.c. analysis of hydrolyzed aliquots on Carbowax 20 M at 175 and 125°; the results of these analyses are presented in Table I. The reaction mixture was hydrolyzed and the ether solution concentrated and distilled to give 3.0 g. (81%) of crude neopentylbenzene, b.p. 57° (7 mm.), and 0.51 g. (11%) of α-chloroneopentylbenzene, b.p. 50° (1 mm.). Samples of the two products were purified by gas chromatography on Carbowax 20 M at 105° to give pure α-chloroneopentylbenzene, n^{20}D 1.5164 (lit.[8] n^{25}D 1.5142), and pure neopentylbenzene, n^{20}D 1.4875 (lit.[22] n^{20}D 1.4885), with infrared spectra identical with those of authentic samples.[23] The hydrocarbon fraction proved to consist of 96% neopentylbenzene with three other components having longer retention times. The slowest moving minor component had the same retention time as authentic 2-methyl-3-phenyl-2-butene.[21] The three minor components, collected together, had an infrared spectrum indicating the presence of a 1,1-disubstituted olefin (bands at 6.03 and 11.18 μ) and other bands suggesting the presence of 2-methyl-3-phenyl-1-butene.

***cis*-α-Methylstilbene.**—Powdered lithium aluminum hydride (4.6 g., 0.12 mole) was added carefully to a solution of 44 g. (0.32 mole) of aluminum chloride in 100 ml. of anhydrous ether, cooled in an ice bath. The solution was stirred for 1 hr. at room temperature and then cooled with an ice bath. *cis*-2,3-Diphenylacrylic acid,[24] m.p. 172–173° (15.6 g., 0.070 mole), was added carefully with ice cooling, over a 20-min. period, and the mixture was kept in the ice bath for an additional half hour. The solution was let stand at room temperature for 1 day and then heated under gentle reflux for 24 hr.

Excess hydride was destroyed by dropwise addition of 4 ml. of water to the cooled, vigorously stirred reaction mixture. The mixture was then poured onto several volumes of shaved ice. The ether layer was separated, and the aqueous layer was extracted twice with 80-ml. portions of ether. The combined ether extract was extracted with saturated sodium chloride solution, dried over sodium sulfate, and finally distilled under vacuum, to give 9.7 g. (71%) of a mixture of olefins, b.p. 108–126° (2 mm.). Analysis by v.p.c. showed the presence of 81% *cis*-α-methylstilbene, 18% α-benzylstyrene, and 1% *trans*-α-methylstilbene. Two recrystallizations from petroleum ether gave 4.2 g. of pure *cis*-α-methylstilbene (as analyzed by v.p.c.), m.p. 47–48.5° (lit.[25] m.p. 48°). An additional 0.94 g. was recovered from filtrates for a total of 5.1 g. (38%). This material was identical in retention time and infrared spectrum with a sample prepared by Dr. J. T. Rudesill using published methods[9] and repurified by v.p.c. after storage.

***threo*-1,2-Diphenyl-1-propanol.**—Diborane, generated externally from 14.8 g. (94 mmoles) of boron trifluoride etherate and 2.7 g. (70 mmoles) of sodium borohydride,[26] was passed at room temperature into a solution of 18.1 g. (94 mmoles) of *cis*-α-methylstilbene in 70 ml. of diglyme. After 2 hr. at room temperature the solution was cooled to 0° and treated dropwise with 5 ml. of water. After 10 ml. of 3 *M* sodium hydroxide had been added, 10 ml. of 30% hydrogen peroxide was added dropwise, the temperature being kept near 0° by ice cooling. The cooling bath was removed 1 hr. after the addition of peroxide was complete; occasional cooling was necessary to keep the temperature from rising above 45° while the reaction proceeded. When the reaction had subsided the mixture was warmed to 60°. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic solution was washed twice with water and thrice with saturated sodium chloride, dried over sodium sulfate, and concentrated, finally, at about 2 mm. The colorless viscous oil was crystallized three times from pentane to give 12.3 g. of *threo*-1,2-diphenyl-1-propanol, m.p. 33.5–35°; an additional 1.6 g., m.p. 33–35°, was obtained from the filtrates to give a total yield of 70%. The acid phthalate had m.p. 127.5–128.5° (lit.[27] m.p. 128–129°).

The alcohol was identical with material obtained *via* reaction of phenylmagnesium bromide with hydratropaldehyde.[9]

***trans*-α-Methylstilbene** was prepared by dehydration of 1,2-diphenyl-2-propanol (from acetophenone and benzylmagnesium chloride)[28] with acetyl chloride and acetic anhydride[29]; it had m.p. 80–80.5° (lit.[29] m.p. 82°).

***erythro*-1,2-Diphenyl-1-propanol.**—Diborane generated as before was passed into a solution of 23.5 g. (121 mmoles) of *trans*-α-methylstilbene in 120 ml. of dry tetrahydrofuran. The boron intermediate was oxidized as before except that the temperature was maintained at 10–15° for 1 hr. and then at room temperature for 1 hr. The product was isolated as before to give 13.0 g. (50%) of *erythro* alcohol, m.p. 50.5–51.5° (lit.[9] m.p. 50–51°), some loss having occurred due to boiling over of the ether solution during concentration. The acid phthalate had m.p. 151–152° (lit.[27] m.p. 151–152°).

Reduction of *threo* and *erythro* Alcohols.—In the following runs, 21.2 mg. (0.1 mmole) of the alcohol to be reduced was added to 0.4 ml. (0.4 mmole) of 1 *N* ethereal dichloroaluminum hydride. The solutions were let stand at room temperature for the specified times, hydrolyzed on ice, and extracted with ether. The dried extracts were analyzed by v.p.c. on Carbowax 20 M at 225° as mixtures of alcohol, 1,2-diphenylpropane, and chloride, the last being estimated by summing the olefin peaks, which were in about the same ratios as observed by v.p.c. of solutions of the chlorides (following).

The *erythro* **alcohol** in 3 hr. gave 11% alcohol, 25% chloride, and 54% 1,2-diphenylpropane; in 24 hr. the analysis showed 4% chloride and 96% 1,2-diphenylpropane. In the latter run 1,2-diphenylpropane was isolated by preparative v.p.c.; n^{22}D 1.5583 (lit.[30] n^{20}D 1.5585).

The *threo* **alcohol** in 13 min. gave 3% alcohol, 31% chloride, 66% 1,2-diphenylpropane; in 3 hr. the analysis showed 28% chloride, 73% 1,2-diphenylpropane; in 24 hr. the yield was 4% chloride, 96% 1,2-diphenylpropane. In the last run 1,2-diphenylpropane was isolated by preparative v.p.c.; n^{22}D 1.5580.

1,2-Diphenylpropane.—To a solution prepared by adding 3.7 g. (28 mmoles) of anhydrous aluminum chloride to 10 ml. (10 mmoles) of 1 *M* ethereal lithium aluminum hydride was added 2.12 g. (10 mmoles) of *threo*-1,2-diphenyl-1-propanol. The mixture was let stand 3 days at room temperature, poured on ice, and worked up in the usual way to give 1.71 g. (87%) of 1,2-diphenylpropane, b.p. 87–88° (1 mm.), n^{21}D 1.5583 (lit.[30] n^{20}D 1.5585). The infrared spectrum was identical with a published one[31]; v.p.c. analysis indicated no other component present.

***erythro*-1,2-Diphenyl-1-chloropropane.**—*erythro*-1,2-Diphenyl-1-propanol (1.06 g., 5 mmoles) was added to 20 ml. (20 mmoles) of ethereal dichloroaluminum hydride, and the reaction mixture was let stand 7 days at 0° and then poured on ice. The product was worked up in the usual way to the point where ether had been removed (under vacuum at room temperature). The crude product was dissolved in 8 ml. of absolute ethanol and the solution was cooled to −4°. The solid which crystallized was washed twice with cold ethanol to give 275 mg. (23%) of impure *erythro*-1,2-diphenyl-1-chloropropane, m.p. 125–132° dec.; this material was recrystallized twice from hexane to give material with m.p. 138–140° (lit.[10] m.p. 139.5–140.5°). A benzene solution, behaved, on v.p.c. analysis on Carbowax 20 M at 215°, as a mixture containing 44% *trans*-α-methylstilbene, 28% *cis*-α-methylstilbene, and 28% α-benzylstyrene, due presumably to cracking in the preheater.

Anal. Calcd. for $C_{15}H_{15}Cl$: C, 78.08; H, 6.55; mol. wt., 231. Found: C, 78.51, 78.53; H, 6.61, 6.44; mol. wt. (Rast), 220.

The previous crude reduction product before crystallization from ethanol gave, on v.p.c. analysis, 72% of 1,2-diphenylpropane and 28% of a mixture of the three olefins in the ratios given previously.

(21) J. H. Brewster, J. Patterson, and D. A. Fidler, *J. Am. Chem. Soc.*, **76**, 6368 (1954).

(22) V. N. Ipatieff and L. Schmerling, *ibid.*, **60**, 1476 (1938).

(23) D. A. Fidler, M.S. thesis, Purdue University, 1953.

(24) R. E. Buckles, M. P. Bellis, and W. D. Coder, *J. Am. Chem. Soc.*, **73**, 4972 (1951).

(25) E. Ellingboe and R. C. Fuson, *ibid.*, **55**, 2964 (1933).

(26) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1136 (1957).

(27) F. A. Abd Elhafez and D. J. Cram, *J. Am. Chem. Soc.*, **74**, 5846 (1952).

(28) C. Hell, *Ber.*, **37**, 453 (1904).

(29) H. Ley *ibid.*, **50**, 243 (1917).

(30) K. T. Serijan and P. H. Wise, *J. Am. Chem. Soc.*, **73**, 4766 (1951).

(31) K. Serijan, I. A. Goodman, and W. J. Yankauskas, *Natl. Advisory Comm. Aeronaut. Tech. Note*, **No. 2557**, 10 (1951).

threo-1,2-Diphenyl-1-chloropropane was prepared from the *threo* alcohol by reaction with purified thionyl chloride[32]; m.p. 52–53.5° (lit.[10] m.p. 54–55°). An ether solution of the chloride behaved like a mixture of 53% *trans*-α-methylstilbene, 24% *cis*-α-methylstilbene, and 23% α-benzylstyrene by v.p.c. on Carbowax 20 M at 215°.

Reduction of *erythro*- and *threo*-1,2-Diphenyl-1-chloropropanes.—The chloride (23 mg., 0.1 mmole) was added to 0.1 ml. of anhydrous ether and 0.3 ml. of 1 *N* ethereal dichloroaluminum hydride to give solutions comparable in substrate and hydride concentration to those used in the reductions of the alcohols (assuming loss of one equivalent of hydride in the initial fast reaction of alcohol with the reagent). In all other respects these runs were carried out in the same way as those in which alcohols were used as substrates.

The *erythro* **chloride** in 3 hr. gave 93% chloride and 7% 1,2-diphenylpropane. The recovered chloride (unrecrystallized) had m.p. 133–136°.

The *threo* **chloride** in 3 hr. gave 82% chloride and 18% 1,2-diphenylpropane. The recovered chloride (unrecrystallized) had m.p. 48–50°.

The *erythro* **chloride** (23 mg., 0.1 mmole) was added to 1.0 ml. (1.0 mmole) of 1 *N* ethereal dichloroaluminum hydride, and the mixture was let stand 36 hr. at room temperature and then worked up and analyzed as before showing 29% chloride and 71% 1,2-diphenylpropane.

Reduction of 1,2-Diphenyl-2-propanol.—In the first of the following runs 270 mg. (1.25 mmoles) of the prior alcohol[28] was added to 5 ml. (5 mmoles) of dichloroaluminum hydride in ether; the other runs were on a four-fifths scale. The mixtures were let stand at room temperature for the specified amount of time, hydrolyzed, worked up, and analyzed by v.p.c. on Carbowax 20 M at 225°.

A reaction time of 3 min. gave 7% alcohol, 93% hydrocarbon (29% *trans*-α-methylstilbene, 57% α-benzylstyrene, 2% *cis*-α-methylstilbene, 13% 1,2-diphenylpropane).

A reaction time of 2 hr. gave 100% hydrocarbon (13% *trans*-α-methylstilbene, 48% α-benzylstyrene, 39% 1,2-diphenylpropane). Essentially identical results were obtained after 4-hr. reaction at room temperature and also after 48-hr. reaction at 0°. In these three cases the crude product was chloride-free, as indicated by a negative Beilstein test.

1,2-Diphenyl-2-chloropropane.—A solution of 5.3 g. (25 mmoles) of 1,2-diphenyl-2-propanol[28] in 50 ml. of distilled methylene chloride was held at 0° while dry hydrogen chloride, generated from ammonium chloride and concentrated sulfuric acid, was passed through for 1 hr. The solution was dried over sodium sulfate and concentrated at the water pump and finally under 1-mm. pressure (1.5 hr.), the materials being kept at ice-bath temperature throughout. The product was clear and colorless and did not crystallize; it was stored at −4° until use. Like the secondary chlorides of this series, this material was cracked to olefins on attempted v.p.c. analysis on Carbowax 20 M at 225°: 60% *trans*-α-methylstilbene, 15% *cis*-α-methylstilbene, and 25% α-benzylstyrene.

Solutions containing 180–250 mg. of the chloride were heated to boiling in a solvent composed of 10 ml. of water and 20 ml. of acetone, cooled and titrated with standard sodium hydroxide. This analysis showed the formation of 97% of the theoretical amount of hydrogen chloride. V.p.c. analysis of the hydrolysis product showed the presence of 72% 1,2-diphenyl-2-propanol and 28% of an olefin mixture having the composition 53% *trans*-α-methylstilbene, 5% *cis*-α-methylstilbene, and 42% α-benzylstyrene. The chloride reacted at once with silver nitrate in acetone (15 ml.)–water (5 ml.) solution; the reaction product after 1 hr. at room temperature consisted of 79% 1,2-diphenyl-2-propanol and 21% of olefins in essentially the same proportions. Reaction of equimolar amounts of chloride and aluminum chloride in ether at room temperature (3 hr.) gave a hydrocarbon mixture, m.p. 76–80.5°, analyzed by v.p.c. as 94% *trans*-α-methylstilbene, 3.6% *cis*-α-methylstilbene, and 2.4% α-benzylstyrene.

Reductions of 1,2-Diphenyl-2-chloropropane.—In each of the following runs 110 mg. (0.50 mmole) of the chloride was added to the indicated ethereal reducing agent and the mixture let stand at room temperature (*ca.* 25°) for the indicated length of time. The mixtures were worked up in the usual way and analyzed by v.p.c. on Carbowax 20 M at 215°.

A. **Lithium aluminum hydride** (0.52 ml. of 0.96 *M* reagent, 2.0 mequiv. of hydride; 3 hr.) reduction gave 19% *trans*-α-methylstilbene 19% α-benzylstyrene, and 62% 1,2-diphenylpropane. Essentially identical results were obtained with 12-hr. reaction time. A slow evolution of gas was observed during the reaction.

B. **Aluminum hydride** (0.39 ml. of 0.96 *M* lithium aluminum hydride plus 17 mg. of aluminum chloride in 1 ml. of ether, 1.5 mequiv. of hydride; 12 hr.) reduction gave 11% *trans*-α-methylstilbene, 12% α-benzylstyrene, and 78% 1,2-diphenylpropane. Evolution of gas was observed during the 1st hr. of reaction.

C. **Monochloroaluminum hydride** reagent was prepared by diluting 10.4 ml. of 0.96 *M* lithium aluminum hydride with a solution of 1.35 g. (10 mmoles) of aluminum chloride in 30 ml. of ether. A white precipitate formed and the reagent solution was obtained by decantation. With 1.0 ml. of reagent (1.0 mequiv. of hydride) and 3-hr. reaction time the yield was 11% *trans*-α-methylstilbene, 10% α-benzylstyrene, and 78% 1,2-diphenylpropane. Vigorous gas evolution occurred.

D. **Dichloroaluminum hydride** [0.5 ml. of 1 *N* dichloroaluminum hydride reagent (0.5 mequiv. of hydride); 3 hr.] reduction gave 74% *trans*-α-methylstilbene, 2% *cis*-α-methylstilbene, and 24% 1,3-diphenylpropane; with 1.0 ml. of 1 *N* reagent (3 hr.) the yield was 32% *trans*-α-methylstilbene, 23% α-benzylstyrene, and 44% 1,2-diphenylpropane; with 1.5 ml. of 1 *N* reagent (3 hr.) the yield was 28% *trans*-α-methylstilbene, 20% α-benzylstyrene, and 52% 1,2-diphenylpropane.

(32) F. A. Abd Elhafez and D. J. Cram, *J. Am. Chem. Soc.*, **75**, 345 (1953).

Hydrogenolyses with Chloroaluminum Hydrides. III. Allylic Alcohols

JAMES H. BREWSTER AND HORST O. BAYER[1]

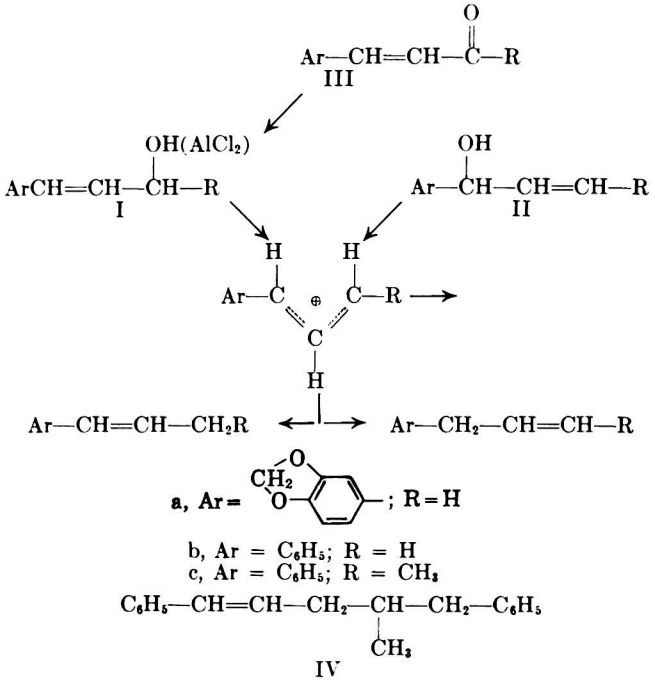
Department of Chemistry, Purdue University, Lafayette, Indiana

Received June 7, 1963

Hydrogenolysis of an allylic alcohol with a 3:1 mixture of aluminum chloride and lithium aluminum hydride gives the products to be expected from reduction of the allylic carbonium ion, often accompanied by dehydration products. In several cases the corresponding α,β-unsaturated carbonyl compounds were found to give the same mixtures of products, indicating that they are hydrogenolyzed *via* the alcohols. Several allylic isomers were shown to give identical distributions of *reduction* products, but tertiary alcohols gave larger amounts of dehydration products. The products of hydrogenolysis of cinnamyl alcohol, 1-phenylallyl alcohol, benzalacetone, carvone, 1,5-dimethylcyclohexen-3-one (and 3-ol), 1-vinylcyclohexanol, cyclohexylideneethanol, 1-acetylcyclohexene, pulegone, linalool, nerol (and neral), and geraniol were determined. The products derived from nerol were largely cyclic, those from geraniol largely acyclic.

Our studies of the hydrogenolysis of the diphenylallyl alcohols[2] and of benzylic alcohols[3] with mixtures of aluminum chloride and lithium aluminum hydride indicated that this reaction was potentially of value in synthesis since in some cases single products were formed in such large amounts that isolation and purification was easy. In other cases more complex mixtures were obtained but these were often rich in the less stable products and so could serve as sources from which small amounts of these substances might be isolated by v.p.c. A preference for retention of the geometry of the original allylic double bond was observed, suggesting that this reaction also might be useful in stereochemical correlations. It seemed desirable, therefore, to establish the characteristics of this method of hydrogenolysis by determining the products formed from a variety of allylic alcohols.

Birch and Slaytor[4] found that 3,4-methylenedioxycinnamyl alcohol (Ia) was reduced to a mixture of the 1- and 3-arylpropenes by a 2:1 mixture of aluminum chloride and lithium aluminum hydride in ether, but stated that cinnamyl alcohol (Ib) was not reduced under their conditions. These observations are consistent with the carbonium ion mechanism[4] shown subsequently. On the other hand, it has been reported that benzalacetone (IIIc), which should be reduced easily to the alcohol (Ic), gave a mixture of 1-phenyl-1-butene (isolated) and *n*-butylbenzene (detected by v.p.c. analysis)[5] when reduced with a similar reagent system. We have found that cinnamyl alcohol (Ib) can be reduced in a few hours at room temperature with excess 3:1 reagent[6] ("dichloroaluminum hydride") to a hydrocarbon mixture, the monomer fraction of which consisted of 71% *trans*-1-phenylpropene, 29% of allylbenzene, and *ca.* 0.5% of *n*-propylbenzene. Each of these products was isolated by preparative v.p.c. and identified by refractive index and infrared spectrum; the identification and v.p.c. analysis were checked by use of authentic samples. The same mixture (63% yield) was obtained from a reaction run at reflux temperature for one day, indicating again[2] that simple olefins are neither reduced nor isomerized by the reagent. As expected from the carbonium ion mechanism for cleavage of the carbon–oxygen bond,[4] the same monomer mixture also was received (64%) from 1-phenylallyl alcohol (IIb) under these conditions. In this case the still-pot residue was examined; from this residue was obtained about 16% of a product which appears, from its boiling point, composition, infrared, ultraviolet and n.m.r. spectra to be *trans*-1,5-diphenyl-4-methyl-1-pentene (IV). This by-product is that to be expected from alkylation of 1-phenylpropene by the carbonium ion, followed by reduction. Benzalacetone (IIIc) was similarly reduced with excess 3:1 reagent, giving 69% of a monomer fraction consisting of 76% of *trans*-1-phenyl-1-butene and 33% of *trans*-1-phenyl-2-butene (both isolated by v.p.c.). No *n*-butylbenzene was found; even trace amounts could have been detected in our v.p.c. analyses.



The reduction of (+)-carvone (V, v.p.c. purified, 96% optically pure) with excess 3:1 reagent gave nearly *racemic* dipentene (2% excess (−) isomer, v.p.c. purified) suggesting that most of the product was formed from the symmetrical carbonium ion. Assuming that the slight optical activity is not due to trace impurities, this result indicates that another pathway of reaction,

(1) The authors gratefully acknowledge the financial support of this research by the National Science Foundation (NSF-G 10051).

(2) J. H. Brewster and H. O. Bayer, *J. Org. Chem.*, **29**, 105 (1964).

(3) J. H. Brewster, H. O. Bayer, and S. F. Osman, *ibid.*, **29**, 110 (1964).

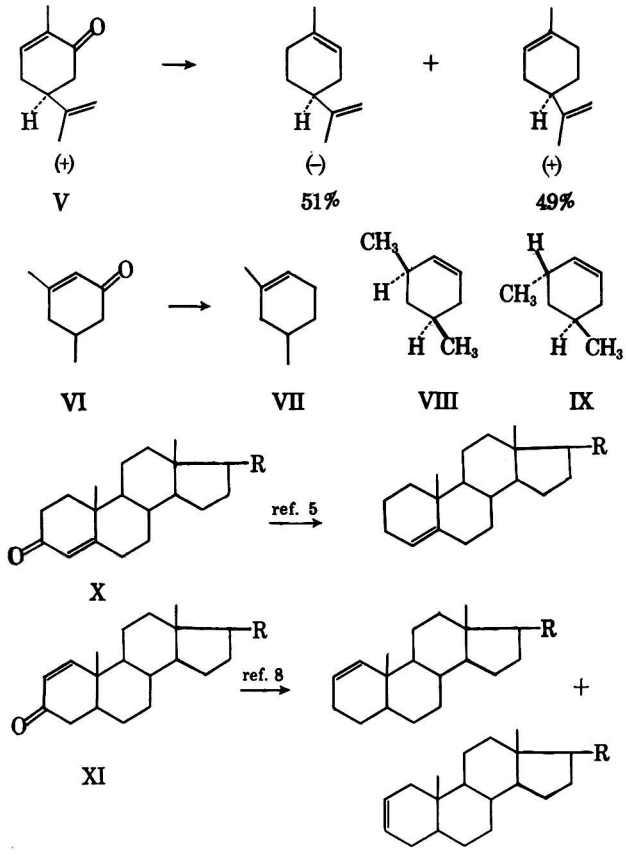
(4) A. J. Birch and M. Slaytor, *Chem. Ind.* (London), 1524 (1956).

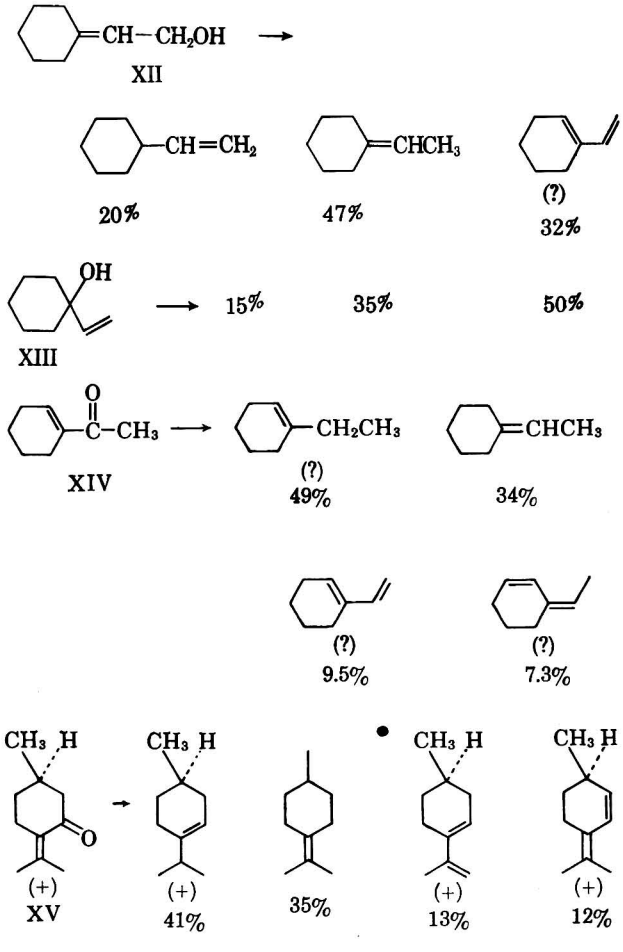
(5) J. Broome, B. R. Brown, A. Roberts, and A. M. S. White, *J. Chem. Soc.*, 1406 (1960).

(6) This reagent is prepared by mixing 3 moles of aluminum chloride with one of lithium aluminum hydride in ether to give solutions about 1 *M* in active hydride. This reagent can be stored for several months at −4° if it is freed of the sediment which forms within an hour of mixing. In most of our work we have used amounts of reagent solution containing 4 moles of active hydride per mole of alcohol or ketone.

possibly involving reduction of the olefinic double bond followed by dehydration, may be available[7]; this pathway does not seem to be of great importance with 3:1 reagent. Hydrogenolysis of 1,5-dimethylcyclohexen-3-one (VI) gave, after two hours at room temperature, 65% of a hydrocarbon containing (v.p.c. analysis) six components. One of these, forming 70% of the mixture, was isolated by v.p.c.; its n.m.r. spectrum was that to be expected of 1,5-dimethylcyclohexene (VII). Two other components (15% and 3%) had retention times on oxyadiponitrile suggesting that they also were monoolefins. They were collected and hydrogenated to give a mixture of two saturated hydrocarbons; the principal component of this mixture (80%) was isolated (v.p.c.) and identified (infrared spectrum) as *cis*-1,3-dimethylcyclohexane, indicating the second most abundant monoolefin product to be *cis*-3,5-dimethylcyclohexene (VIII). The third monoolefin might, thus, be the *trans* isomer (IX), these being the three expected reduction products. The retention times of the remaining components (totaling 12%) suggest that they are dienes, formed by dehydration of the allylic alcohol. A sample of the alcohol formed as major product on reduction of the ketone with aluminum isopropoxide gave the same mixture of mono- and diolefins as the ketone. These results, taken with those obtained in the steroid series, where cholest-4-en-3-one (X) gave cholest-4-ene[5] and where cholest-1-en-3-one (XI) gave (in low yield) a 2:1 mixture of cholest-1-ene and cholest-2-ene (among other products),[8] suggest that a cyclohexenyl carbonium ion will tend to add hydride at its less sterically hindered end. This often will give the more stable olefin but the stability of the olefins cannot be crucial since cholest-1-ene is less stable than cholest-2-ene,[9] yet is formed in greater amounts.[8]

Cyclohexylideneethanol (XII) and 1-vinylcyclohexanol (XIII) can give the same carbonium ion and gave the same mixture of monoolefins (30% vinylcyclohexane and 70% ethylidenecyclohexane). Major amounts of a diene, believed to be 1-vinylcyclohexene, also were formed, XIII giving the larger amount, indicating that at least a part of the diene derived from the tertiary alcohol was formed by a pathway not involving the common carbonium ion. The hydrocarbon from 1-acetylcyclohexene (XIV, 71%) contained two major components (49% and 34%), the less abundant of which had the same retention time as ethylidenecyclohexane. These components could be separated from the others but not from one another on a preparative Carbowax column; the mixture showed all the infrared bands of ethylidenecyclohexane and of 1-ethylcyclohexene but no other bands; thus it is thought to be a mixture of the two. One of the minor components had the same retention time as the diene formed from XII and XIII, suggesting that it is 1-vinylcyclohexene. (+)-Pulegone (XV) gave four products, each of which was isolated. The two principal products were identified as (+)-3-menthene (41%) and 4-menthene (35%); the minor products (12% and 13%) were the dextrorotatory dienes, 2,4(8)-menthadiene and 3,8-menthadiene.





(7) The reduction of chalcones (III, R also aromatic) with 2:1 reagent systems is reported to occur with specific shifting of the double bond to the original carbonyl carbon atom: M. M. Bokadia, B. R. Brown, D. Cobern, A. Roberts, and G. A. Somerfield, *J. Chem. Soc.*, 1658 (1962).

(8) R. Albrecht and C. Tamm, *Helv. Chim. Acta*, **40**, 2216 (1957).

(9) R. B. Turner, W. R. Meador, and R. E. Winkler, *J. Am. Chem. Soc.*, **79**, 4122 (1957).

TABLE I

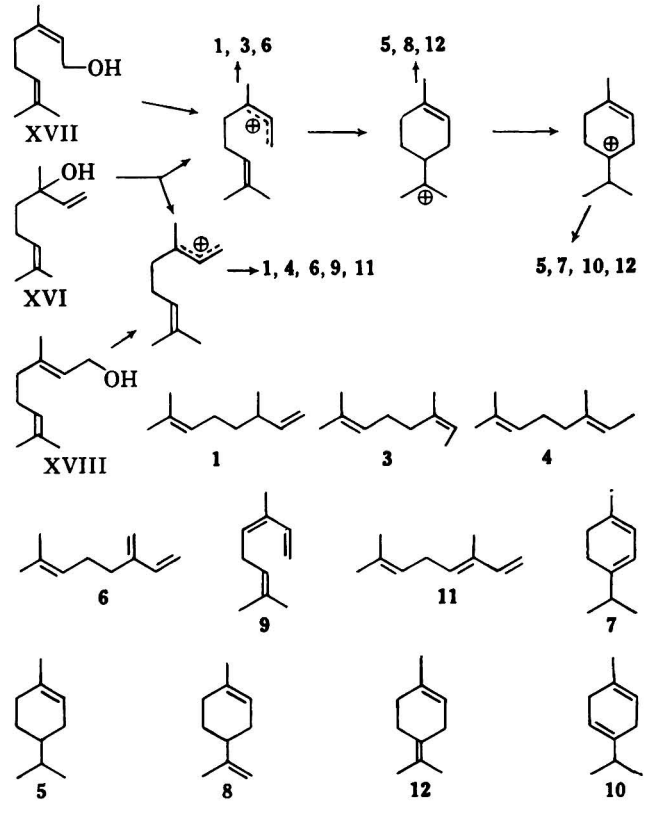
MIXED HYDRIDE REDUCTION OF ACYCLIC TERPENE ALCOHOLS

Product	Peak[a]	Relative retention time[b]	$n^{20}D$[c]	% in hydrocarbon from Nerol	Geraniol	Linalool
3,7-Dimethyl-1,6-octadiene	1	0.33[d]	1.4376 (1.4370)[e,f]	1.7	14.0	13.0
Unknown	2	0.44	Not isolated	2.9	0.7	0.8
2,6-Dimethyl-*cis*-2,6-octadiene	3	0.48	1.4476	6.0	1.6	7.7
2,6-Dimethyl-*trans*-2,6-octadiene	4	0.53	1.4502 ($n^{17}D$ 1.4517)[g]	1.8	60.0	29.0
1-*p*-Menthene	5	0.68[d]	Not isolated	13.0	2.4	2.8
Myrcene	6	0.75[d]	1.4689 (1.4697)[e,h]	2.0	6.3	22.0
α-Terpinene	7	0.88[d]	Not isolated	3.8		1.0
Dipentene	8	1.00[d]	1.4728 (1.4720)[e,h]	51.0	3.9	7.0
Ocimene-A	9	1.18	1.4859 (1.4873)[h]		3.3	4.6
γ-Terpinene	10	1.30[d]	Not isolated	5.8		0.8
Ocimene B	11	1.35	1.4890 (1.4862)[i]		6.8	8.8
Terpinolene	12	1.60[d]	1.4888 (1.4888)[e,h]	13.0	1.5	1.7

[a] These numbers are used to identify the structures shown in the text. [b] On Carbowax 20 M at 70–85°, relative to dipentene as measured from an air peak. Ocimene B and γ-terpinene were not completely resolved on this column but were on oxyadiponitrile–silver nitrate. [c] Products from hydrogenolysis of linalool, trapped on emergence from v.p.c. on repetitive analyses. Reinjection showed each isolated substance to be at least 98% pure (sharp, smooth symmetrical v.p.c. peaks). Values in parentheses are literature values for samples from which published infrared spectra were obtained. [d] Retention time identical with that of an authentic sample (alone and in admixture). [e] Infrared spectrum identical with that of authentic sample (direct comparison). Authentic samples: **1**, International Flavors and Fragrances; **5**, Dr. K. Murray; **6**, Hercules Powder Co.; **8**, Eastman Kodak Co.; **7, 10, 12**, The Glidden Co. [f] See ref. 11. [g] See ref. 10. [h] See ref. 12. [i] See ref. 14.

The terpene alcohol, linalool (XVI), gave twelve products on reaction with four equivalents of 3:1 reagent for five hours at room temperature (Table I). Eight of these could be isolated by v.p.c. and were identified by their infrared spectra; three more were tentatively identified by comparisons of retention times with authentic samples. Most of the same products also were formed from the stereoisomeric primary alcohols, nerol (XVII) and geraniol (XVIII). About 87% of the product from nerol, but only 8% of that from geraniol, was cyclic. This result indicates that the stereoisomeric allylic carbonium ions are not interconverted to any great extent before further reactions intervene. The cyclized carbonium ion suffered loss of a proton to a greater extent than reduction while the reverse was true of the acyclic intermediate. Here again the tertiary alcohol of series XVI gave more direct dehydration (33%) than did the others.

Several of these products are of interest. The major product from geraniol (60%) and linalool (29%) has an infrared spectrum identical with that of the 2,6-dimethyl-2,6-octadiene formed on reduction of geraniol with sodium and alcohol[10]; it is, therefore, presumed to have the geranyl configuration about the double bond (**4**). A second substance, with a similar retention time and a very similar infrared spectrum, is the major *noncyclic* compound from nerol and is, therefore, probably the geometric isomer (**3**). All three of the terpene alcohols gave as the fastest moving product a substance having the same infrared spectrum as 3,7-dimethyl-1,6-octadiene (**1**), which has been prepared by pyrolysis of pinane at 450°[11]; this is the other product to be expected from reduction of either of the acyclic carbonium ions. Two ocimenes were obtained, as products of dehydration along with myrcene, from geraniol and linalool. The infrared spectrum of one ("Ocimene-A," **9**) is identical with that of a hydrocarbon prepared by cracking α-pinene[12,13] while the spectrum of the other ("Ocimene-B," **11**), though very similar, differs in just those respects in which that of the ocimene from oil of lavender differs from the first.[14] In this case the configurations cannot be deduced from those of the allylic alcohols; the formation of "Ocimene-A" from α-pinene[13] and the sensitivity of this isomer to thermal rearrangement[15] indicate that their configurations[15] are as shown.



(10) N. Sheppard and G. B. B. M. Sutherland, *J. Chem. Soc.*, 1541 (1947); R. F. Naylor, *ibid.*, 1532 (1947).

(11) H. Pines, N. E. Hoffman, and V. N. Ipatieff, *J. Am. Chem. Soc.*, **76**, 4412 (1954).

(12) R. T. O'Connor and L. A. Goldblatt, *Anal. Chem.*, **26**, 1726 (1954).

(13) J. E. Hawkins and W. A. Burris, *J. Org. Chem.*, **24**, 1507 (1959).

(14) Y.-R. Naves and P. Tullen, *Helv. Chim. Acta*, **43**, 1619 (1960); **44**, 316 (1961).

(15) J. Wolinsky, B. Chollar, and M. D. Baird, *J. Am. Chem. Soc.*, **84**, 2775 (1962). These workers used samples of the two ocimenes isolated by v.p.c. from our product of reduction of linalool.

We conclude that this reaction cannot be counted on to give high yields of individual products; on the other hand, it does give mixtures from which small amounts of particular products can be isolated by v.p.c.[15] Even with purely aliphatic primary allylic alcohols where a direct displacement mechanism for cleavage of the carbon–oxygen bond would seem most likely, the products are those to be expected from an essentially free allylic carbonium ion. None of our results with 3:1 reagent require a significant amount of reaction *via* reduction of the double bond followed by elimination[7]; indeed the results reported in the following paper[16] indicate that the saturated alcohols which might be formed in such a process would not react further under the conditions used here. Dehydration of the allylic alcohol is, however, often a significant side reaction; our data suggest that this process cannot occur exclusively by way of a free allylic carbonium ion since it occurs to different extents with compounds which should give the same ion. Here, as before,[2] the geometric configuration of the original double bond is retained to a high degree, suggesting that this reaction may be useful in stereochemical correlations.

Experimental[17]

Hydrogenolysis of Cinnamyl Alcohol.—Cinnamyl alcohol (5.0 g., 37 mmoles) was added dropwise to a cooled solution prepared from 30 ml. of an ether solution containing 37 mmoles of lithium aluminum hydride and a solution of 13 g. (97 mmoles) of aluminum chloride in 60 ml. of ether. The solution was heated at reflux for 1 day and then cooled and treated cautiously with 33 ml. of water followed by 30 ml. of a 20% sodium potassium tartrate solution. The ether extract was extracted with brine, dried over magnesium sulfate, concentrated, and distilled to give 2.74 g. (63%) of hydrocarbons, $n^{22}D$ 1.5379, collected at 88–92° (52 mm.). Analysis by v.p.c. (Carbowax 20 M, 110°) using authentic samples of allyl benzene (Columbia Organic Chemicals) and 1-phenylpropene (Sapon Laboratories) alone and in admixture for comparison indicated the presence of 70% of 1-phenylpropene and 30% of allylbenzene. Fractionation on a Carbowax preparative column gave 1-phenylpropene, $n^{22}D$ 1.5489 (lit.[18] $n^{20}D$ 1.5492), and allylbenzene, $n^{22}D$ 1.5098 (lit.[19a] $n^{20}D$ 1.5126, lit.[19b] $n^{25}D$ 1.5042); the infrared spectra were identical with those of the authentic samples.

In a small scale run, 0.27 g. (2 mmoles) of cinnamyl alcohol was treated with 8 ml. (8 mmoles) of 1 *N* 3:1 reagent for 4 hr. at room temperature. Analysis of the hydrolyzed mixture by v.p.c. showed 71% 1-phenylpropene, 29% allylbenzene, and *ca.* 0.5% of *n*-propylbenzene.

1-Phenylallyl Alcohol.—The procedure of Goering and Dilgren,[20] involving addition of benzaldehyde to vinylmagnesium bromide, was followed to give 83% of crude product, b.p. 74–75° (2 mm.). V.p.c. on Carbowax 20 M at 155° showed the presence of two components; the major component (64%, longer retention time) was readily isolated by use of a preparative Carbowax column and was identified as 1-phenylallyl alcohol, $n^{23}D$ 1.5392 (lit.[21] $n^{25}D$ 1.5390). The other component had $n^{23}D$ 1.5227 and an infrared spectrum indicating the presence of a phenyl group and a hydroxy group but it was not further identified.

Hydrogenolysis of 1-phenylallyl alcohol (purified by v.p.c., 2.69 g., 20 mmoles) with 80 ml. (80 mmoles) of 1 *N* ethereal "dichloroaluminum hydride" for 4 hr. at room temperature gave, after the usual work-up, 1.52 g. (64%) of hydrocarbon collected at 55–60°(1–10 mm.). This mixture was analyzed by v.p.c. and the three components were isolated by preparative v.p.c. and identified by comparisons of their infrared spectra with those of authentic samples: 0.2% *n*-propylbenzene, 30% allylbenzene, and 70% 1-phenylpropene.

Distillation of the still-pot residue gave 0.39 g. of a hydrocarbon, b.p. 140–150°(2 mm.), $n^{20}D$ 1.5756, apparently homogeneous by v.p.c. on Carbowax 20 M at 220°. Its composition and boiling point are consistent with its being dimeric. The ultraviolet spectrum was styrene-like, λ_{max}^{EtOH} 252 mμ (ε 14,300), while the infrared spectrum indicated the presence of phenyl-, methyl-, and *trans*-olefin groups. The n.m.r. spectrum (p.p.m., relative to tetramethylsilane, in carbon tetrachloride) showed a doublet at 0.90 (CH_3–C(H)–), a complex set of bands in the region 1.59–2.22 (–C(H)– and –C(H)–C=C), a set in the region 2.28–2.71 (Ar–C(H)–), a set of three at 6.0–6.22, almost identical in shape to those shown in this region by *trans*-1-phenylpropene (Ar–C(H)=C(H)–), and one very strong band at 7.10 (phenyl). These peaks and regions indicated protons of the types shown above in the ratio 3:3:2:2:10, whence it seems probable that this substance is *trans*-1,2-diphenyl-4-methyl-1-pentene.

Anal. Calcd. for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.46; H, 8.76.

Hydrogenolysis of Benzalacetone.—Fresh 3:1 mixed hydride reagent was prepared from 13 g. (100 mmoles) of anhydrous aluminum chloride in 40 ml. of ether and 27 ml. of a 1.27 *M* solution of lithium aluminum hydride in ether (34 mmoles). A solution of 5.0 g. (34 mmoles) of benzalacetone[22] in 15 ml. of ether was added dropwise and the mixture was then let stand 12 hr. at room temperature. Unchanged hydride was decomposed by dropwise addition of 5 ml. of ethyl acetate and then of 25 ml. of water to the cooled solution. The layers were separated and the aqueous layer was extracted with ether. The combined ether layer was dried over sodium sulfate, concentrated, and distilled to give, at 85–88° (22–25 mm.), 3.12 g. (69%) of hydrocarbon, $n^{21.5}D$ 1.5310. V.p.c. on a Craig polyester product column gave *trans*-1-phenyl-1-butene, $n^{22}D$ 1.5408 (lit.[23] $n^{16}D$ 1.5414, lit.[24] $n^{20}D$ 1.5387), dibromide m.p. 71–72° (lit.[25] m.p. 70–71°), and *trans*-1-phenyl-2-butene, $n^{22}D$ 1.5104 (lit.[24] $n^{20}D$ 1.5101). The infrared spectrum and retention time of the latter were the same as those of an authentic sample (Phillips Petroleum Co., $n^{22}D$ 1.5110). Analysis of the product mixture by v.p.c. (polyadipate, 150°) indicated it to contain 67% of 1-phenyl-1-butene and 33% of 1-phenyl-2-butene, consistent with the refractive index of the mixture. Virtually the same mixture (66% 1-phenyl-1-butene and 34% 1-phenyl-2-butene) was obtained by reducing 1.0 g. (6.9 mmoles) of benzalacetone with 2:1 reagent from 10.3 mmoles of aluminum chloride and 5.2 mmoles of lithium aluminum hydride. It has been reported that this reduction gives some *n*-butylbenzene[5]; an authentic sample (National Bureau of Standards standard, $n^{22}D$ 1.4886) showed a shorter retention time on polyadipate than did any of the components of our reduction product mixtures. Less than 1% of this material could have been detected.

Hydrogenolysis of (+)-Carvone.—A sample of (+)-carvone (Matheson Coleman and Bell) was purified by v.p.c. on a preparative polyester column at 175° and had $\alpha^{20}D$ +58.20° (1-dcm. capillary tube). The ketone (2.0 g., 13.3 mmoles) was added dropwise to 60 ml. (60 mmoles) of "dichloroaluminum hydride"

(16) J. H. Brewster, S. F. Osman, H. O. Bayer, and H. B. Hopps, *J. Org. Chem.*, **29**, 121 (1964).

(17) Unless otherwise specified, reductions were carried out with stock solutions of 3:1 mixed hydride reagent ("dichloroaluminum hydride").[2,3] Products were analyzed and, where possible, isolated and purified by vapor phase chromatography (v.p.c.) using an Aerograph Model A-90-C. Microanalyses were performed by Dr. C. S. Yeh, Mrs. I. Groten, and Mrs. V. Keblys. Infrared spectra were obtained by Mrs. M. Dilling and author H. O. B. Proton nuclear magnetic resonance (n.m.r.) spectra were obtained by Mr. W. Baitinger, using a Varian A-60 instrument (60 Mc.); δ-values in parts per million from tetramethylsilane.

(18) A. Klages, *Ber.*, **36**, 2574 (1903).

(19) (a) R. C. Huston and K. Goodemoot, *J. Am. Chem. Soc.*, **56**, 2432 (1934); (b) J. F. McKenna and F. J. Sowa, *ibid.*, **59**, 470 (1937).

(20) H. L. Goering and R. E. Dilgren, *ibid.*, **82**, 5744 (1960).

(21) H. L. Goering and R. E. Dilgren, *ibid.*, **81**, 2556 (1959).

(22) N. L. Drake and P. Allen, Jr., "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 77.

(23) A. Klages, *Ber.*, **37**, 2311 (1904).

(24) C. N. Riiber, *ibid.*, **44**, 2393 (1911).

(25) B. Radziszewski, *ibid.*, **9**, 261 (1876).

solution initially at 0° and the solution warmed almost to reflux as the ketone was added. The solution was let stand 2 hr. at room temperature, poured on ice, and worked up in the usual way to give, after distillation at 10–12 mm., 1.26 g. (70%) of crude limonene, $n^{20}D$ 1.4722, $\alpha^{20}D$ −2.26° (1 dcm.). This product was purified on a polyester preparative v.p.c. column at 85° and then had $n^{20}D$ 1.4728 (lit.[26] $n^{18}D$ 1.4727, lit.[12] $n^{20}D$ 1.4720), $\alpha^{20}D$ −1.56° (1 dcm.), infrared spectrum identical with a published one.[12] The carvone was about 96% optically pure[27] while the limonene was about 1.5% optically pure.[28]

Hydrogenolysis of 1,5-Dimethylcyclohexen-3-one.—A sample of the ketone, prepared by Dr. G. Asato, had $n^{20}D$ 1.4843 after purification by v.p.c. on a preparative column. Purified ketone (2.48 g., 20 mmoles) was added to 80 ml. (80 mmoles) of ice-cold "dichloroaluminum hydride" in ether. The solution was let stand at room temperature for 2 hr. and worked up as usual to give 1.42 g. (65%) of hydrocarbon distillate. Analysis by v.p.c. on oxyadiponitrile–silver nitrate at 30° indicated the presence of three monoolefins (A, 15%; B, 3%; C, 70%) as well as three dienes which, together, constituted about 12% of the product. The monoolefins were separated into two fractions by preparative v.p.c., the two lesser components being collected together ($n^{20}D$ 1.4383) and the major (slower-running) component being isolated pure, $n^{20}D$ 1.4465.[29]

The n.m.r. spectrum (Varian A-60 instrument, carbon tetrachloride with tetramethylsilane as internal reference) showed three well resolved peaks (p.p.m.): a doublet centered at 0.85 (H—C—CH_3), a sharp singlet at 1.65 (=C—CH_3), and a peak at 5.35 (=$\overset{H}{\overset{|}{C}}$—), with integrated areas in the ratio 3:3:1. Signals for seven more protons formed a broad "hill" in the region 0.60–2.15 p.p.m. This spectrum indicates that this product is 1,5-dimethylcyclohexene. The mixture of minor products was hydrogenated over platinum oxide to give a mixture of two components which could be separated by preparative v.p.c. The fast-moving major component (*ca.* 80%) was identified as *cis*-1,3-dimethylcyclohexane, $n^{20}D$ 1.4228 (lit.[30] $n^{20}D$ 1.4229) by comparison of its infrared spectrum with a published one (API-1570).

Vinylcyclohexanol.—A solution of vinylmagnesium bromide in tetrahydrofuran was prepared from 32 g. (0.30 mole) of vinyl bromide and 7.3 g. (0.30 g.-atom) of magnesium according to the procedure of Goering and Dilgren.[20] To this was added dropwise 24.5 g. (0.25 mole) of cyclohexanone. The reaction mixture was stirred overnight and then decomposed with 50 ml. of a cold solution containing 33 g. of ammonium chloride. The organic layer was decanted and the viscous aqueous layer was extracted with four portions of ether. The combined organic solution was dried over sodium sulfate and then over magnesium sulfate, concentrated at the water pump and distilled to give 18.1 g. boiling at 55–56° (7 mm.). This product, as analyzed by v.p.c. on Carbowax 20 M, contained about 70% of one alcohol and 30% of another. Fractionation on a Carbowax preparative column at 155° gave a sample of the main component, vinylcyclohexanol, $n^{23}D$ 1.4761 (lit.[31] $n^{20}D$ 1.4777, lit.[32] 1.4755). The other component had $n^{24}D$ 1.4729 and was not further investigated.

Ethyl Cyclohexylideneacetate.—The procedure of Wittig and Haag[33] for the condensation of carbethoxymethyl–triphenylphosphonium bromide with benzaldehyde was adapted for this preparation. A solution of 43 g. (0.10 mole) of carbethoxymethyl–triphenylphosphonium bromide in 100 ml. of absolute ethanol was added to a solution of 0.10 mole of sodium ethoxide (prepared from 2.3 g. of sodium) in about 100 ml. of ethanol. After 9.8 g. (0.10 mole) of freshly distilled cyclohexanone had been added the mixture was stored at room temperature for 3 days. The solution was filtered and concentrated in a Rinco evaporator and the residue was taken up in pentane. Distillation gave 2.0 g. of unchanged cyclohexanone and 4.4 g. (55%) of a mixture of esters, collected at 62–64° (1 mm.). Analysis and fractionation by v.p.c. on Carbowax 20 M at 150° gave ethyl cyclohexenylacetate (64%), $n^{20}D$ 1.4623 (lit.[34] $n^{18}D$ 1.4639), ethyl cyclohexylideneacetate (28%), $n^{20}D$ 1.4790 (lit.[34] $n^{18}D$ 1.4799), and about 8% of an unknown substance, $n^{21}D$ 1.4511.

Cyclohexylideneethanol.—A mixture (1.10 g., 6.6 mmoles) containing 90% of ethyl cyclohexylideneacetate and 10% of ethyl cyclohexenylacetate was obtained from the above mixture by preparative gas chromatography. This was dissolved in 15 ml. of anhydrous ether and the solution was cooled in ice while 10 ml. of 1 *M* lithium aluminum hydride in ether was added dropwise (2 hr.). The solution was then let stand 8 hr. at room temperature and hydrolyzed by dropwise addition of water. Aluminum hydroxide was removed by filtration; the solid was washed several times with ether. The ether solution was dried over sodium sulfate and concentrated. Analysis of the crude product by v.p.c. indicated the presence of two compounds in the ratio of the constituents of the starting material. The major product was isolated and purified by v.p.c. on a preparative Carbowax 20 M column to give 0.52 g. of cyclohexylideneethanol, $n^{20}D$ 1.4955 (lit.[32] $n^{20}D$ 1.4910).

Anal. Calcd. for $C_8H_{14}O$: C, 76.17; H, 11.18. Found: C, 76.27; H, 11.50.

Hydrogenolysis of Vinylcyclohexanol and Cyclohexylideneethanol.—"Dichloroaluminum hydride" solution (3.2 ml., 3.2 mmoles) was cooled in ice and 0.10 g. (0.8 mmole) of vinylcyclohexanol was added. The solution was let stand 4 hr. at room temperature, treated with water, dried over anhydrous potassium carbonate, and analyzed by v.p.c. on oxyadiponitrile–silver nitrate at 62°. As analyzed in this way, the product contained, in addition to *ca.* 1% of a fast moving component, two substances, A (15%) and B (35%), with relative retention times of 0.68 and 1.00 and a third substance, C (50%), with a relative (to B) retention time of 2.20; neither vinylcyclohexanol nor cyclohexylideneethanol were present. Identical results were obtained with a reaction time of 15 min. at 45°. The same products were obtained in parallel and concurrent reductions of cyclohexylideneethanol: A, 20%; B, 47%; C, 32%. The individual products from vinylcyclohexanol were isolated in 64% combined yield by v.p.c. on a preparative Carbowax column. Component A was identified as vinylcyclohexane, $n^{20}D$ 1.4456 (lit.[35] $n^{20}D$ 1.4462), infrared spectrum identical with a published one (API 1830). Component B was identified as ethylidenecyclohexane, $n^{20}D$ 1.4620 (lit.[36] $n^{20}D$ 1.4626, lit.[35] 1.4623), infrared spectrum identical with a published one (API 1962). The third component is believed to be the expected dehydration product, 1-vinylcyclohexene, since its infrared spectrum shows bands at 6.05, 6.2, 10.1, 10.9, and 11.2 μ consistent with this structure. Its refractive index, $n^{19}D$ 1.5112, is, however, considerably higher than that reported for products obtained by dehydration of vinylcyclohexanol, lit.[37] $n^{20}D$ 1.4915 (lit.[31] $n^{20}D$ 1.4952). The isolated components also were used in v.p.c. identification of the products obtained on hydrogenolysis of acetylcyclohexene, where compounds with retention times identical with those of B and C were formed.

1-Acetylcyclohexene.—Ethynylcyclohexanol was converted to acetylcyclohexene by the method of Chanley.[38] From 13 g. (0.10 mole) of starting material there was obtained 8.2 g. of nearly pure (by v.p.c. analysis) acetylcyclohexene, b.p. 63–65° (5 mm.), $n^{20}D$ 1.4917. A pure sample, $n^{20}D$ 1.4913 (lit.[38] $n^{20}D$ 1.4900), was obtained by v.p.c. on a preparative Carbowax column.

Hydrogenolysis of 1-Acetylcyclohexene.—In the usual manner, 3.10 g. (25 mmoles) of 1-acetylcyclohexene was hydrogenolysed with 100 ml. of 1 *M* "dichloroaluminum hydride" in ether for 3 hr. at room temperature to give 1.96 g. (71%) of hydrocarbon distillate. V.p.c. analysis on oxyadiponitrile–silver nitrate at 45° indicated the presence of four constituents. The two principal

(26) F. Richter and W. Wolff, *Ber.*, **63**, 1725 (1930).

(27) Based on the values $[\alpha]^{20}D$ 62.93° [H. Rupe, *Ann.*, **409**, 354 (1915)] and d^{20}_4 0.9608 [J. W. Brühl, *Ber.*, **32**, 1224 (1899)].

(28) Based on the value $\alpha^{20}D$ 55° (5 dcm.): J. von Braun and G. Lemke, *ibid.*, **56B**, 1563 (1923).

(29) O. Wallach [*Ann.*, **396**, 271 (1913)] gives $n^{21}D$ 1.4466 for a product described as 1,5-dimethylcyclohexene, prepared by dehydration of 1,3-dimethylcyclohexanol.

(30) "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds," A. P. I. Research Project 44, Carnegie Press, Pittsburgh, Pa., 1953, p. 51 (*trans* isomer has $n^{20}D$ 1.4309).

(31) S. F. Birch, R. A. Dean, N. J. Hunter, and E. V. Whitehead, *J. Org. Chem.*, **20**, 1187 (1955).

(32) I. N. Nazarov, I. N. Azerbaev, and V. N. Rakcheeva, *Bull. acad. sci. URSS, classe sci. chim.*, 419 (1946); *Chem. Abstr.*, **42**, 7730 (1948).

(33) G. Wittig and W. Haag, *Ber.*, **88**, 1664 (1955).

(34) G. A. R. Kon and R. P. Linstead, *J. Chem. Soc.*, 1278 (1929).

(35) J. R. van der Bij and E. C. Kooyman, *Rec. trav. chim.*, **71**, 840 (1952).

(36) O. Wallach and E. Evans, *Ann.*, **360**, 45 (1908).

(37) I. N. Nazarov and T. D. Nagibina, *J. Gen. Chem. USSR* (Eng. Transl.), **23**, 599 (1953).

(38) J. D. Chanley, *J. Am. Chem. Soc.*, **70**, 244 (1948).

ones, A (49%) and B (34%), had similar short retention times while the minor constituents, C (9.5%) and D (7.3%), had longer but similar retention times. Comparisons with samples obtained in the reduction of vinylcyclohexanol indicated that B was ethylidenecyclohexane and C was vinylcyclohexene. The two major components were not resolved on a preparative Carbowax column, but a sample of a mixture of the two, $n^{20}D$ 1.4588, could be obtained. The infrared spectrum contained the bands shown by ethylcyclohexene (API No. 1958) (lit.[39] $n^{20}D$ 1.4576) and by ethylidenecyclohexane (API No. 1962), $n^{20}D$ 1.4260.

Hydrogenolysis of Pulegone.—Pulegone, as purified on a Carbowax 20 M preparative column at 150°, had $n^{19}D$ 1.4878 (lit.[40] $n^{19}D$ 1.4880) and $\alpha^{20}D$ +20.87° (neat, 1 dcm.) (lit.[41] $[\alpha]^{15}D$ +23.60°). Reduction of 2.0 g. (13 mmoles) with 50 ml. (50 mmoles) of 3:1 reagent for 4 hr. at room temperature gave a crude product, containing (by v.p.c.) 83% of hydrocarbon, 7% of menthone and isomenthone, and four components of higher retention time which may be alcohols. The hydrocarbon distillate (1.20 g., 71%) was analyzed and fractionated on a Carbowax 20 M column to give four products which were identified by their refractive indices, optical rotations, and infrared spectra[42,43]: 3-menthene (41%), $n^{20}D$ 1.4522, $[\alpha]^{20}D$ +112° (*c* 1.00, chloroform) (lit.[42] $n^{20}D$ 1.4519, lit.[44] 1.4523, lit.[44] $[\alpha]^{20}D$ 114.5°, homogeneous); 4(8)-menthene (35%), $n^{20}D$ 1.4682, optically inactive (lit.[42] $n^{20}D$ 1.4689); 3,8-menthadiene (13%), $n^{20}D$ 1.4930, $[\alpha]^{20}D$ +159° (*c* 0.898 chloroform) (lit.[43] $n^{20}D$ 1.4936, lit.[12] 1.4893, lit.[41] $[\alpha]^{14}D$ +140.6°); 2,4(8)-menthadiene (12%), $n^{20}D$ 1.5037, $[\alpha]^{20}D$ +63°, (c 0.312, chloroform) (lit.[43] $n^{20}D$ 1.5050, lit.[12] 1.5030).

Hydrogenolyses of Linalool, Nerol, and Geraniol.—Commercial linalool (Eastman Kodak, white label) was found to be about 98% pure by v.p.c. on Carbowax 20 M at 130° and was used directly. The alcohol (3.08 g., 20 mmoles) was added dropwise over a 10-min. period to 80 ml. (80 mmoles) of "dichloroaluminum hydride" cooled in an ice bath. The solution was let stand 5 hr. at room temperature and then poured on ice and worked up in the usual way. Flash distillation under vacuum gave 2.26 g. (*ca.* 81%) of hydrocarbon mixture; this mixture was analyzed by v.p.c. on Carbowax 20 M and oxyadiponitrile–silver nitrate (see Table I). Commercial nerol (Fluka), found to contain 39% of geraniol by v.p.c., gave 2.15 g. (77%) of hydrocarbon mixture in a fully parallel experiment.

A sample of pure nerol, $n^{20}D$ 1.4748 (lit.[45] n_D 1.4754), was obtained by repetitive gas chromatography at 160° on a Carbowax 20 M analytical column; this product gave a single peak on v.p.c. analysis. Practical grade geraniol (Eastman Kodak) was partially purified by conversion to the crystalline calcium chloride complex[46] and then further purified by v.p.c. on Carbowax 20 M at 180° to give a product with $n^{20}D$ 1.4777 (lit.[47] $n^{20}D$ 1.4766). These two alcohols were separately reduced in parallel runs; 30 mg. (0.2 mmole) of alcohol was added to 0.80 ml. (0.8 mmole) of "dichloroaluminum hydride" in ice-chilled screwcap vials. The vials were closed and held at room temperature for 5 hr. Then several drops of water were added and the ether solutions were transferred to separate vials and dried over potassium carbonate and then sodium sulfate. These mixtures were analyzed by v.p.c. without concentration (see Table I). Assuming 100% material balance in the analysis, it was found that about 10% of alcohol had not reacted in each case; the residual alcohol was, in each case, apparently pure starting material. Infrared spectra were obtained for all substances for which refractive indices are reported; they were identical with those of authentic samples or comparable to published ones.

Commercial citral was fractionated by v.p.c. on Carbowax 20 M at 125°[48] to give a sample of neral, $n^{22}D$ 1.4852 (lit.[49] $n^{20}D$ 1.4869). This substance gave a mixture virtually identical with that obtained from nerol on hydrogenolysis with 3:1 reagent.

(39) O. Wallach and P. Mendelsohn-Bartholdy, *Ann.*, **360**, 50 (1908).
(40) J. Doeuvre and H. Perret, *Bull. soc. chim. France*, [5] **2**, 301 (1935).
(41) W. J. Grubb and J. Read, *J. Chem. Soc.*, 242 (1934).
(42) R. L. Frank and R. E. Berry, *J. Am. Chem. Soc.*, **72**, 2985 (1950).
(43) H. Pines and H. E. Eschinazi, *ibid.*, **77**, 6314 (1955).
(44) A. J. van Pelt and J. P. Wibaut, *Rec. trav. chim.*, **60**, 62 (1941).
(45) A. Béhal, *Bull. soc. chim. France*, [4] **26**, 452 (1919).
(46) J. Bertram and E. Gildemeister, *J. prakt. Chem.*, [2] **53**, 225 (1896); **56**, 506 (1897).
(47) F. Tiemann and F. W. Semmler, *Ber.*, **26**, 2711 (1893).
(48) G. Ohloff [*Tetrahedron Letters*, **11**, 10 (1960)] reports that citral is isomerized at temperatures above 130°; v.p.c. of citral at higher temperatures gave products which were always found to be mixtures on reanalysis.
(49) Y.-R. Naves, *Bull. soc. chim. France*, [5] **19**, 521 (1952).

Hydrogenolyses with Chloroaluminum Hydrides. IV. Saturated and Homobenzylic Alcohols[1]

JAMES H. BREWSTER, STANLEY F. OSMAN, HORST O. BAYER, AND HARVEY B. HOPPS

Department of Chemistry, Purdue University, Lafayette, Indiana

Received June 7, 1963

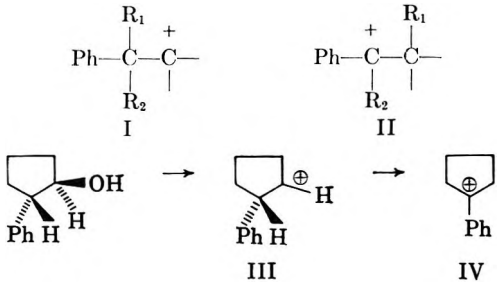
Saturated alcohols react with "dichloroaluminum hydride" at 60–80° in higher-boiling ethers to give hydrocarbons. Wholly aliphatic secondary and tertiary alcohols give some reduction but large amounts of olefins are formed. β-Phenyl alcohols give predominating reduction of the hydroxy group. Rearrangements suggestive of carbonium ion processes are observed in several instances.

Evidence indicating that hydrogenolyses with mixtures of aluminum chloride and lithium aluminum hydride occur with the formation of carbonium ions[2-5] suggested the possibility that conditions might be found for the hydrogenolysis of saturated alcohols. Orientation experiments (in which the products were analyzed by gas chromatography, but in which individual products were not actually isolated) indicated that saturated secondary and tertiary alcohols do indeed react with "dichloroaluminum hydride"[3-5] in di-*n*-butyl ether or in diphenyl ether at 60–80° to give small amounts of paraffins together with large amounts of olefins. Phenyl-2-propanone gave nearly pure *n*-propylbenzene while benzyldimethylcarbinol gave nearly equal amounts of isobutylbenzene and a mixture of olefins. No hydrocarbons were, however, obtained from 1-hexanol, which was recovered on hydrolysis of the reaction mixture.

In experiments in which pure products were isolated and identified by comparisons of infrared spectra with authentic samples, several other homobenzylic alcohols gave principally products of reduction rather than of elimination. Thus, *trans*-2-phenylcyclopentanol gave phenylcyclopentane containing about 11% of 1-phenylcyclopentene, while 2-phenylcyclohexanol (mixed isomers) gave a 1:2:1 mixture of benzylcyclopentane, phenylcyclohexane, and 1-phenylcyclohexene. Reduction of 1,1-diphenyl-2-propanone, or of the corresponding alcohol, gave 1,2-diphenylpropane.

(1) The authors are grateful for financial support from the National Science Foundation (Grant NSF-G 10051).
(2) E. L. Eliel, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **22**, 129 (1961).
(3) J. H. Brewster and H. O. Bayer, *J. Org. Chem.*, **29**, 105 (1964).
(4) J. H. Brewster, H. O. Bayer, and S. F. Osman, *ibid.*, **29**, 110 (1964).
(5) J. H. Brewster and H. O. Bayer, *ibid.*, **29**, 116 (1964).

The failure of 1-hexanol to undergo reduction, elimination, or conversion to chloride suggests strongly that the transition state for each of these reactions has a high degree of carbonium ion character. The formation of olefins[4,5] as by-products (or even major products as above) and of chloride,[4] the occurrence of alkylation of olefins[3,5] and aromatics,[4] and the isomerizations mentioned earlier are all accounted for most easily by the postulate that a carbonium ion intermediate is formed. The rearrangements observed here in the homobenzylic systems can all be interpreted as involving rearrangement of the initial carbonium ion (I) to a benzylic carbonium ion (II) by 1,2-migration of a hydrogen atom, an alkyl group, or an aromatic group. On this basis, we suggest that the formation of 1-phenylcyclopentene from *trans*-2-phenylcyclopentanol occurs by way of loss of a proton from the rearranged tertiary phenylcyclopentyl carbonium ion (IV) rather than by *cis* elimination.



Experimental

Vapor phase chromatographic (v.p.c.) analyses and separations were performed with an Aerograph Model A-90-C using silicone or Carbowax analytical columns or a Craig polyadipate preparative column. Identifications by retention time were based on successive alternating runs of mixtures and authentic samples of pure hydrocarbons, many of which were provided by Prof. H. C. Brown. Identification by infrared spectra was based on comparisons with published data or with spectra of authentic samples of hydrocarbons prepared by literature methods and purified by preparative gas chromatography.

Orientation Experiments.—The following compounds, 1-hexanol, 2-octanol, cyclohexanol, cyclopentanone, 1-methylcyclohexanol, triethylcarbinol, phenyl-2-propanone, and benzyldimethylcarbinol, were subjected to reaction conditions described subsequently, the major variation being one of scale of operations. Hydrocarbons were obtained in amounts corresponding to 60–90% yields, except from 1-hexanol, which gave no hydrocarbon. In these experiments the products were analyzed by v.p.c. without isolation of individual components.

In an apparatus that could be set for distillation or reflux was placed a mixture of 20.8 g. (0.16 mole) of aluminum chloride, 50 ml. of 1 *M* lithium aluminum hydride (0.05 mole) in diethyl ether, and 60 ml. of diphenyl ether or di-*n*-butyl ether. About 0.05 mole of the alcohol or ketone was added and diethyl ether was distilled (Dry Ice cooled receiver) until the internal temperature was at about the boiling point of the expected hydrocarbon or 80°, whichever was lower. The mixture was heated at reflux for 3 hr., and the products were obtained either by further distillation or by decomposition of the mixture on ice and extraction with ether. Ethereal distillates and extracts were combined and distilled to remove most of the ether before v.p.c. analysis. Each of the saturated secondary alcohols gave products containing 10% of paraffin and 90% of olefin; the hydrocarbon from 2-octanol contained about 10% of 1-octene and 80% of a mixture of the 2-octenes. The hydrocarbon from methylcyclohexanol appeared to be about 50% methylcyclohexane and 50% 1-methylcyclohexene, while that from triethylcarbinol appeared to be pure 3-ethyl-2-pentane. The hydrocarbon from phenyl-2-propanone appeared to be essentially pure *n*-propylbenzene, while that from benzyldimethylcarbinol appeared to be 50% isobutylbenzene and 50% of a mixture of phenyl-2-methylpropenes.

Hydrogenolysis of 2-Phenylcyclohexanol.—Commercial 2-phenylcyclohexanol (both isomers) (10 g., 0.059 mole) was added to a solution of 3 g. (0.081 mole) of lithium aluminum hydride and 21 g. (0.16 mole) of aluminum chloride in 75 ml. of di-*n*-butyl ether, and the mixture was heated at 80° for 8 hr. The mixture was cooled and decomposed on ice, and the organic layer was separated, dried, and distilled at 102–118° (2 mm.) to give 6 g. of mixed hydrocarbons. Repeated gas chromatography on a preparative Craig polyadipate column gave four fractions. The first fraction was small and could not be identified. The second (about 25% of the hydrocarbon) had n^{20}D 1.5180 and gave an infrared spectrum corresponding to that of benzylcyclopentane[6] (lit.[6] n^{20}D 1.5178). The third fraction (about 50%) had n^{20}D 1.5259 and gave an infrared spectrum corresponding to that of phenylcyclohexane[6] (lit.[6] n^{20}D 1.5255). The fourth fraction (about 25%) had n^{20}D 1.5675 and gave an infrared spectrum corresponding to that of 1-phenylcyclohexene[6] (lit.[6] n^{20}D 1.5692).

1,1-Diphenyl-2-propanone, m.p. 45.5–47° (lit.[7] m.p. 46°), was prepared by dehydration of 1,2-dihydroxy-1,1-diphenylpropane with dilute sulfuric acid,[8] the diol having been prepared by the reaction of phenylmagnesium bromide with ethyl lactate.[8]

1,1-Diphenylpropane was prepared by the Huang-Minlon modification of the Wolff–Kishner reduction[9] of 1,1-diphenyl-2-propanone. The product was fractionated on a polyester product column to give a 57% yield of 1,1-diphenylpropane, n^{21}D 1.5634 (lit.[10] n^{20}D 1.5643), infrared spectrum identical with one reported earlier,[11] and also 27% of diphenylmethane, n^{21}D 1.5766 (lit.[12] n^{20}D 1.5768), m.p. 25–27° (lit.[12] m.p. 26–27°), infrared spectrum identical with that of an authentic sample.

Hydrogenolysis of 1,1-Diphenyl-2-propanone and 1,1-Diphenyl-2-propanol.—A mixture, prepared by adding 2.10 g. (10 mmoles) of 1,1-diphenyl-2-propanone to mixed hydride reagent from 3.7 g. (28 mmoles) of anhydrous aluminum chloride and 10 ml. of 1 *M* ethereal lithium aluminum hydride, was heated at 75° until no further ether distilled. Heating was continued at 68° for 4.5 days and worked up in the usual way to give 1.73 g. (88%) of 1,2-diphenylpropane, b.p. 87–88° (2 mm.), n^{21}D 1.5585 (lit.[10] n^{20}D 1.5585). The infrared spectrum was superimposable on that of an authentic sample (part I, this series[3]) and different from that of 1,1-diphenylpropane. The presence of small amounts of the latter hydrocarbon is not excluded, however, since no v.p.c. separation of the isomeric hydrocarbons could be achieved on the columns available to us.

In a separate run the same amounts of materials were not heated but held at room temperature for 1 hr. Work-up in the usual manner gave almost pure 1,1-diphenyl-2-propanol, m.p. 63.5–64.5° (lit.[13] m.p. 63–64°). Hydrogenolysis of this carbinol under conditions used for the ketone gave, after fractionation of the product on a preparative v.p.c. column, 61% of 1,2-diphenylpropane, n^{21}D 1.5582, indistinguishable by v.p.c. or infrared spectroscopy from that obtained from the ketone.

Under the reaction conditions described above, 1,1,1-triphenyl-2-propanol[14] gave an insoluble white substance, from which, on hydrolysis, 71% of the starting material was recovered.

***trans*-2-Phenylcyclopentanol**, b.p. 112–117° (1 mm.), n^{21}D 1.5478, phenylurethane, m.p. 81–82.5° [lit.[15] b.p. 110–113° (2 mm.), n^{25}D 1.5478, phenylurethane, m.p. 82–83°] was prepared[16] by hydroboration[17] of 1-phenylcyclopentene.[18]

***trans*-2-Phenylcyclopentyl tosylate** was prepared by the general method of Brown and Ham[19]; on a 0.185 *M* scale yields of 80% of the tosylate, m.p. 66–67° (hexane), were obtained. The analytical sample had m.p. 68–69°.

(6) E. L. Eliel, J. W. McCoy, and C. C. Price, *J. Org. Chem.*, **22**, 1533 (1957).
(7) R. Stoermer and P. Riebel, *Ber.*, **39**, 2302 (1906).
(8) A. McKenzie and R. Roger, *J. Chem. Soc.*, **125**, 844 (1924).
(9) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).
(10) K. T. Serijan and P. Wise, *ibid.*, **73**, 4766 (1951).
(11) K. Serijan, I. A. Goodman, and W. J. Yankauskas, *Natl. Advisory Comm. Aeronaut. Tech. Note*, **No. 2557** (1951).
(12) K. von Auwers and A. Frühling, *Ann.*, **422**, 224 (1921).
(13) F. A. Abd Elhafez and D. J. Cram, *J. Am. Chem. Soc.*, **75**, 339 (1953).
(14) Sample provided by Professor H. C. Brown.
(15) W. H. Tallent, *J. Org. Chem.*, **21**, 862 (1956).
(16) J. H. Brewster and H. B. Hopps, to be published elsewhere.
(17) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1136 (1957); *J. Am. Chem. Soc.*, **81**, 6423 (1959).
(18) Y. Amiel, A. Löffler, and D. Ginsburg, *ibid.*, **76**, 3625 (1954).
(19) H. C. Brown and G. Ham, *ibid.*, **78**, 2735 (1956).

Anal. Calcd. for $C_{18}H_{20}SO_3$: C, 68.32; H, 6.37. Found: C, 68.20; H, 6.42.

3-Phenylcyclopentene.—A solution of sodium ethoxide prepared from 7 g. (0.3 g.-atom) of sodium and 500 ml. of absolute ethanol was heated to 80° under nitrogen. A solution of 31.2 g. (0.099 mole) of *trans*-2-phenylcyclopentyl tosylate in 500 ml. of absolute ethanol was added dropwise over 46 hr. The mixture was heated for 7 hr., cooled to room temperature, diluted with water, and extracted three times with petroleum ether (b.p. 35–37°). The extract was dried, concentrated, and distilled through a 12-in. spiral-packed rectifying column to give 5.5 g. (38.5%) of 3-phenylcyclopentene, b.p. 51.5–54° (1 mm.), $n^{20.6}$D 1.5415 [lit.[20] b.p. 92–93° (13 mm.), n^{19}D 1.5396]. This olefin is readily separated from the higher boiling 1-phenylcyclopentene by vacuum distillation or, for analytical purposes, by gas chromatography.

Phenylcyclopentane was prepared by catalytic hydrogenation of 1-phenylcyclopentene over platinum in methanol; b.p. 49–53° (1 mm.), n^{20}D 1.5283 (lit.[21] b.p. 213–215°, nD 1.5320). This substance had the same retention time as 3-phenylcyclopentene on silicone or Carbowax gas chromatography columns; its infrared spectrum lacked a number of moderately strong peaks shown by that of the 3-olefin.

Hydrogenolysis of *trans*-2-Phenylcyclopentanol.—In a flask fitted with an addition funnel, a magnetic stirrer, and a distilling head was placed 3.6 g. (0.0224 mole) of *trans*-2-phenylcyclopentanol. The system was flushed with nitrogen and 75 ml. of a 1.22 *N* hydride solution, prepared from 8.5 g. (0.224 mole) of lithium aluminum hydride and 180 g. (0.6 mole) of crystalline aluminum chloride in 800 ml. of ether, was added dropwise with stirring. The flask was then heated, distilling ether until the internal temperature reached 70°, which temperature was maintained for 24 hr. The mixture was cooled, diluted with ether, treated cautiously with water, and extracted with ether. Concentration gave 3.2 g. of a yellow oil which was distilled under vacuum. The distillate, b.p. 55–64° (1 mm.), amounted to 1.58 g., $n^{19.5}$D 1.5364, and gave an infrared spectrum indicating it to be slightly impure phenylcyclopentane. Analysis by v.p.c. showed two peaks, the first (89% of the total area) corresponding to phenylcyclopentane and the second (11% of the total area) to 1-phenylcyclopentene. The refractive index of the product is that to be expected of a mixture of 88% phenylcyclopentane and 12% 1-phenylcyclopentene, indicating that little or none of the 3-olefin is present.

(20) J. von Braun and M. Kühn, *Ber.*, **60**, 2551 (1927).
(21) W. Borsche and W. Menz, *ibid.*, **41**, 205 (1908).

Dehydration of Alcohols, Diols, and Related Compounds in Dimethyl Sulfoxide[1]

VINCENT J. TRAYNELIS, WILLIAM L. HERGENROTHER,[2] AND IN PART WITH HARRY T. HANSON AND JOHN A. VALICENTI

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana

Received July 26, 1963

This report lists additional examples of the dehydration of alcohols (particularly 1-alkylcycloalkanols) to olefins, the dehydration of alcohols to ethers and certain diols to cyclic ethers, the pinacol rearrangement *vs.* diene formation from 1,2-diols, the dehydration and in part oxidation of two 1,3-diols, the conversion of ethers to olefins, and the preparation of furans from 1,4-diketones. Additional observations on the mechanism are discussed.

The initial report of the dehydration of alcohols in dimethyl sulfoxide described the scope of the reaction as limited to secondary and tertiary benzylic alcohols and tertiary aliphatic alcohols.[3] In view of the stereochemistry of the elimination in *erythro*- and *threo*-1,2-diphenyl-1-propanol and other data, the mechanism of this dehydration appeared to involve carbonium ions.[3] In this paper we wish to extend the scope of this reaction and offer additional comments about the mechanism.

The previous paper in this series noted several examples of primary and secondary alcohols which failed to dehydrate[3]; among these was 1-phenyl-2-propanol. However, when this alcohol was heated in dimethyl sulfoxide at 190° for 48 hr. under nitrogen, 41% of 1-phenylpropene, 49% of unchanged alcohol, and less than 1% of phenylacetone were found. Performing the reaction in air caused the formation of appreciable amounts of phenylacetone (25%). This example represents the first successful dehydration of a simple secondary alcohol in dimethyl sulfoxide. Additional cases of dehydration of primary and secondary alcohols in polyfunctional compounds will appear later.

The newest group of tertiary alcohols capable of dehydration in dimethyl sulfoxide are the 1-alkylcycloalkanols, and data concerning these examples are listed in Table I. Analysis of the olefin composition was by v.p.c. while identification of these products employed various combinations of physical constants, infrared spectra, and/or n.m.r. spectra. The major product in each of these reactions was the endocyclic olefin, 1-alkylcycloalkene. In the case of 1-methylcyclohexanol, dehydration in dimethyl sulfoxide produced an olefin mixture (1-methylcyclohexene and methylenecyclohexane) similar with that obtained from an iodine- or *p*-toluenesulfonic acid[4]-catalyzed dehydration. The result remains consistent with a carbonium ion intermediate in the dimethyl sulfoxide dehydration. The appearance of 2-cyclohexylpropene from 1-isopropylcyclohexanol requires double bond migration which can be accommodated by intermediate carbonium ions.

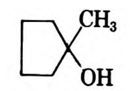
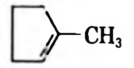
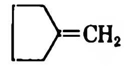
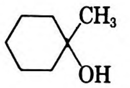
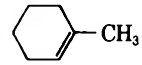
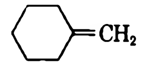
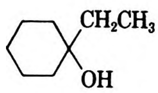
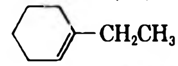
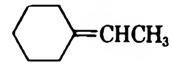
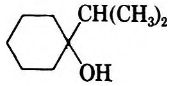
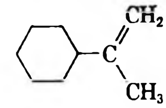
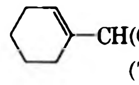
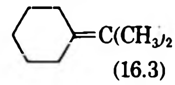
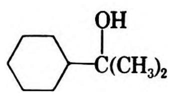
The dehydration of 1,2-diphenylethanol in dimethyl sulfoxide produced *trans*-stilbene (93%) and unchanged alcohol (5%).

When a series of experiments was performed on the dehydration of 1-phenyl-1-propanol in varying amounts of dimethylsulfoxide, a new mode of dehydration was observed, namely, ether formation. These data are summarized in Table II and show that, in the presence of small amounts of dimethyl sulfoxide, ether production is favored. Control experiments ruled out a thermal

(1) Acknowledgment is made to the donors of the Petroleum Research Fund administered by the American Chemical Society for support of this research.
(2) Abstracted from part of the Ph.D. dissertation of W. L. H., submitted in July, 1963.
(3) V. J. Traynelis, W. L. Hergenrother, J. R. Livingston, and J. A. Valicenti, *J. Org. Chem.*, **27**, 2377 (1962).
(4) A. C. Cope, C. L. Bumgardner, and E. E. Schweizer, *J. Am. Chem. Soc.*, **79**, 4732 (1957). These workers reported the dehydration of 1-methylcyclohexanol and other 1-methylcycloalkanols by treatment with *p*-toluenesulfonic acid and found 2–5% of the exocyclic olefin in their product mixture.

TABLE I

THE DEHYDRATION OF 1-ALKYLCYCLOALKANOLS

Alcohol	Olefin yield, %	Olefin composition[a]					
	88		(100)		(0)		
	74.5		(95)		(5)		
	60[b]		(95)		(5)		
	37[c]		(97)		(3)		
	55.5		(94)		(6)		
	62		(5.4)		(78.3)		(16.3)
	57		(72.8)		(0)		(27.2)

[a] The olefin composition was determined by v.p.c. [b] Iodine-catalyzed dehydration. [c] Dehydration by a trace of p-toluenesulfonic acid

TABLE II

THE DEHYDRATION OF 1-PHENYL-1-PROPANOL IN VARYING AMOUNTS OF DIMETHYL SULFOXIDE[a]

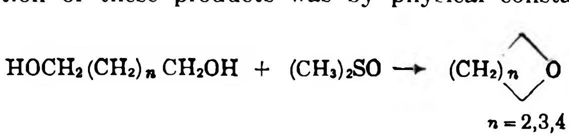
Alc:dimethyl sulfoxide mole ratio	Product composition[b] $C_6H_5CH{=}CHCH_3$	$C_6H_5C(=O)CH_2CH_3$	$C_6H_5CH(OH)CH_2CH_3$	$C_6H_5CH(C_2H_5)OCH(C_2H_5)C_6H_5$
1:8	89	6	6	0
1:3	80	5.5	7	7
1:1	56	8	4	34
3:1	30	3	14	53

[a] These reactions were run at 175° for 9 hr. [b] The product composition was determined by v.p.c., for the product residue isolated in essentially quantitative yield. The starting alcohol was stable to the conditions used for v.p.c.

dehydration leading to either the olefin or ether. Identification of 1-phenylpropyl ether was accomplished by physical constants, the infrared spectrum, and the n.m.r. spectrum, which also revealed that the ether was a mixture of two components, most likely the *meso* and *dl* isomers. Table III lists the n.m.r. data for benzyl ether, α-phenethyl ether, and 1-phenylpropyl ether.

The previous report[3] described the thermal dehydration and dimethyl sulfoxide dehydration of *threo*-1,2-diphenyl-1-propanol and cited the isolation of an unidentified solid and oil. These materials have now been identified as a mixture of isomers of 1,2-diphenyl-1-propyl ether on the basis of their infrared spectra and n.m.r. spectra (see Table III).

These observations of ether formation suggested the possibility of preparing cyclic ethers by the dehydration of certain diols. This reaction recently has been applied by Gillis and Beck[5] toward the synthesis of a variety of substituted tetrahydrofurans in yields of 50–98%. By way of addition to these examples, we wish to report the conversion of 1,4-butanediol, 1,5-pentanediol, and 1,6-hexanediol, using 2 moles of alcohol per mole of dimethyl sulfoxide, to the corresponding heterocycles, tetrahydrofuran (70%), tetrahydropyran (47%), and oxepane (24%). Characterization of these products was by physical constants

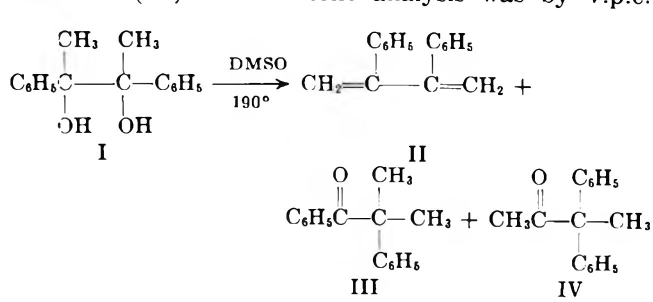


(5) B. T. Gillis and P. E. Beck, *J. Org. Chem.*, **28**, 1388 (1963).

and comparison of retention times in v.p.c. and infrared spectra with authentic samples.

A second series of diols investigated were the pinacols and other 1,2-diols which provided information on the pinacol rearrangement *vs.* diene formation. In these reactions the operating temperature was 160°–190° with a time variation of 7–48 hr. When 1-phenyl-1,2-ethanediol was heated at 190° for 48 hr., the major product was phenylacetaldehyde (64%) isolated as the 2,4-dinitrophenylhydrazone derivative. A solution of 2-methyl-2,3-butanediol in dimethyl sulfoxide, after 36 hr. at 190°, produced 3-methyl-2-butanone (66%) isolated by distillation. In these two cases only pinacol rearrangement products were observed; of course, in the first example, diene formation was not possible.

With the pinacols, both diene and rearranged ketones were found and in some cases the diene was the major product. The reaction of 2,3-diphenyl-2,3-butanediol (a mixture of *meso* and *dl*) and dimethyl sulfoxide for 14 hr. at 190° gave 2,3-diphenylbutadiene (II, 17%) and a 65% yield of ketones composed of 11% 1,2-diphenyl-2-methyl-1-propanone (III) and 89% 3,3-diphenyl-2-butanone (IV). The ketone analysis was by v.p.c.



I, II, III, IV

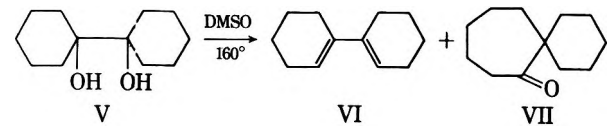
TABLE III

NUCLEAR MAGNETIC RESONANCE SPECTRA OF SOME BENZYL ETHERS[a]

Compound	Peak description	τ-Values	Weight	Proton assignment
$C_6H_5CH_2OCH_2C_6H_5$	Singlet	2.80	10	Benzene
	Singlet	5.58	4	Methylene
		A[a] B[b]		
$C_6H_5CH(CH_3)CH(CH_3)C_6H_5$ (*meso* and *dl*)	Singlet	2.82 2.76	10	Benzene
	Quartet center	5.56[c] 5.85[c]	2	Methine
	Doublet center	8.57[c] 8.67[c]	6	Methyl
		C[d] D[d]		
$C_6H_5CH(CH_3)CH(CH_2)C_6H_5$ (*meso* and *dl*)	Singlet	2.95 2.85	10	Benzene
	Triplet center	5.86[e] 6.08[e]	2	Methine
	Multiplet center	8.21 8.50	4	Methylene
	Triplet center	9.17[f] 9.25[f]	6	Methyl
$C_6H_5CH(CH_3)CH(CH_3)C_6H_5$ / $C_6H_5CHOCHC_6H_5$ (solid product)[j]	Multiplet center	3.03	10	Benzene
	Doublet center	5.88[g]	2	O-Methine
	Multiplet center	6.94	2	C-Methine
	Doublet center	8.66[h]	3	Methyl
		E[i] F[i]		
$C_6H_5CH(CH_3)CH(CH_3)C_6H_5$ / $C_6H_5CHOCHC_6H_5$ (liquid product)	Multiplet center	3.03	10	Benzene
	Doublet center	6.05[g] 5.82[g]	2	O-Methine
	Multiplet center	7.00	2	C-Methine
	Doublet center	9.11[h] 8.68[h]	6	Methyl

[a] These spectra were determined in carbon tetrachloride solution with tetramethylsilane as an internal standard. [b] Analysis of components A and B was by comparison of the relative peak areas for the methine proton. This was found to be 37% A and 63% B. [c] J = 6.8 c.p.s. [d] Analysis of components C and D was by comparison of the relative peak areas for the methine proton. This was found to be 46% C and 54% D. [e] J = 6.1 c.p.s. [f] J = 7.3 c.p.s. [g] J = c.p.s. [h] J = 7 c.p.s. [i] Analysis of components E and F was by comparison of the relative peak areas for the O-methine proton. This was found to be 25% E and 75% F. [j] The unknown solid from the dehydration of *threo*-1,2-diphenyl-1-propanol was recrystallized several times from petroleum ether (b.p. 60–90°) and had m.p. 151–154.5°. *Anal.* Calcd. for $C_{30}H_{30}O$: C, 88.63; H, 7.44. Found: C, 88.60, 88.68; H, 7.40, 7.55.

and the product identification involved physical constants, infrared spectra, and solid derivatives. When a second reaction was processed after 7 hr. at 190°, 15% diene II, 33% ketones (19% III and 81% IV), 33% pure *dl* diol I, and 14% diol I (mixture of *meso* and *dl*) were found. This procedure provides a convenient method for preparing the pure *dl* diol I. When the dehydrations were performed with *dl* diol I for 14 hr. and pure *meso* diol I for 7 hr., similar results were obtained, 12% and 15% diene II, 65% ketones (2% III and 98% IV), and 68% ketones (2.4% III and 97.6% IV), respectively. These data point out the greater reactivity of the *meso* compound toward rearrangement. Although the rearrangement of pure *dl* diol I and *meso* diol I in sulfuric acid has been described,[6] no mention was made of the relative ease of rearrangement of the two diastereomers and the only product reported was ketone IV. The dehydration of pinacol itself was performed at several temperatures with little effect on the ratio of products. When pinacol and dimethyl sulfoxide were heated at 160°, 175°, and 185°, the products which distilled from the reaction vessel were 2,3-dimethylbutadiene, 52%, 56%, and 55%; and pinacolone, 20%, 27%, and 30%, respectively. Bicyclohexyl-1,1′-diol (V) was heated in dimethyl sulfoxide at 160° for 16 hr. and gave bicyclohexyl-1,1′-diene (VI, 85%), spiro[5.6]dodecan-7-one (VII, 4%), and an unidentified component. The mixture composition was analyzed by v.p.c. and the diene



V VI VII

was conveniently purified by column chromatography on alumina.

The dehydration of two 1,3-diols also has been observed. In the case of 2-methyl-2,4-pentanediol, the products isolated were 49% of a mixture of 2-methylpentadienes and 29% of 2-methyl-1-penten-4-ol. This diol contains both a tertiary and secondary hydroxyl group and, if the tertiary alcohol dehydrates first, this could lead to 2-methyl-1-penten-4-ol or 2-methyl-2-penten-4-ol. The latter compound now has an allylic hydroxyl which may dehydrate to a diene. Subsequent isomerization of the diene could explain the mixture observed. The suggestion of a facile dehydration of allylic alcohols is based on the present scope of this reaction: tertiary and benzylic alcohols dehydrate under conditions where primary and secondary alcohols fail. However, 2-methyl-1-penten-4-ol was subjected to the same reaction conditions as for the parent diol and produced a mixture of 2-methylpentadienes in 55% yield. Whether this alcohol dehydrated directly or was first isomerized to 2-methyl-2-penten-4-ol is not known. When 1,3-butanediol (containing a secondary and primary hydroxyl) was heated at 190° for 48 hr., the products isolated were crotonaldehyde (26%) and 2-buten-1-ol (54%). This example provided an interesting case where both an oxidation and

(6) M. Ramart-Lucas and M. E. Salmon-Legagneur, *Bull. soc. chim. France*, [4] **45**, 718 (1929); M. Ramart-Lucas and M. Biguard, *Compt. rend.*, **194**, 189 (1932).

TABLE IV

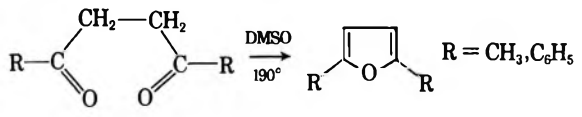
DIMETHYL SULFOXIDE DEHYDRATION OF ALCOHOLS IN THE PRESENCE OF BASE

Alcohol (moles)	Dimethyl sulfoxide, moles	Base (moles)	Yield, %	
5-Butyl-5-nonanol (0.053)	0.371	$C_6H_5NH_2$ (0.005)	5-Butyl-4-nonene (94)	Recovered alcohol (0)
(0.0158)	0.110	(0.0158)	(91)	(1)
(0.0158)	0.110	(0.110)	(79)	(8)
(0.158)	0.110	n-$C_8H_{17}ONa$ (0.0158)	(98)	(0)
2-Methyl-2-hexanol (0.0258)	0.181	(0.0026)	45% 2-Methyl-1-hexene, 55% 2-Methyl-2-hexene	(84)
(0.0058)	(0.40)	$C_6H_5NH_2$ (0.0058)	45.5% 2-Methyl-1-hexene, 54.5% 2-Methyl-2-hexene	(85)

$$CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CH_2OH \xrightarrow[190^\circ]{DMSO} CH_3CH{=}CHCH_2OH + CH_3CH{=}CHCHO$$

dehydration occurred with the dehydration involving a secondary alcohol. To account for the origin of crotonaldehyde two alternatives were available, dehydration followed by oxidation or oxidation followed by dehydration. In order to decide between these possibilities, the two intermediates were subjected to the reaction conditions. 2-Buten-1-ol distilled from the reaction mixture with no crotonaldehyde while aldol was converted to crotonaldehyde (64%) in only 6 hr. Another example of a facile dehydration of a β-hydroxycarbonyl system is the conversion of diacetone alcohol in dimethyl sulfoxide at 190° for 8 hr. to mesityl oxide (81%).

Some miscellaneous examples which bear on the scope of this reaction involve the conversion of ethers to olefins and the synthesis of furans. 4-Methoxy-4-methyl-2-pentanone readily lost methanol upon heating in dimethyl sulfoxide to afford mesityl oxide (90%). When α-methylbenzyl ether was heated in dimethyl sulfoxide at 175° for 9 hr., polystyrene was isolated in 38% yield. In the previous paper[3] it was shown that when styrene was formed by dehydration of α-phenethyl alcohol in dimethyl sulfoxide, it polymerized. The conversion of acetonylacetone and 1,4-diphenyl-1,4-butanedione to 2,5-dimethylfuran and 2,5-diphenyl-



furan in 66% and 60% yield, respectively, suggests this procedure as a potential method of furan synthesis.[7] This approach enjoys the advantage that nonacidic conditions are employed and thus possible side reactions of alkylfurans are reduced.

In considering the various mechanisms for the dehydration of alcohols in dimethyl sulfoxide, a simple thermal elimination of water was excluded in previous work.[3] An acid-catalyzed elimination was considered as a possibility. Although precautions were taken to exclude acidic and other contaminants in dimethyl sulfoxide, this substance undergoes some decomposition upon prolonged heating at the reaction temperatures.[8] A study of the direction of elimination in *t*-pentyl alcohol and 2-methyl-2-hexanol[3] did not permit one to discard an acid-catalyzed mechanism. We now wish to report the reaction of 5-*n*-butyl-5-nonanol and 2-methyl-2-hexanol in dimethyl sulfoxide with aniline or sodium *n*-octoxide added. The results reported in Table IV reveal that neither base has any appreciable effect on the yield of olefins or the direction of elimination. This removes the possibility of an acid-catalyzed dehydration. In the previous paper[3] the stereochemistry of *erythro*- and *threo*-1,2-diphenyl-1-propanol favored a carbonium ion intermediate, and support for this path is now available from the several pinacol rearrangements reported in this work. Also consistent with this mechanism are the structural requirements of the alcohols which undergo dehydration, namely, benzylic or tertiary alcohols. Therefore, dimethyl sulfoxide appears to serve as a solvent for promoting ionization of alcohols.

In order to determine whether such solvent properties as dielectric constant and dipole moment are mainly responsible for the dehydration of alcohols in dimethyl sulfoxide, a series of high boiling solvents was investigated. When 1-phenyl-1-propanol was heated in these materials at 160° for 14 hr., only starting alcohol was recovered in yields of 82% or better. Table V

TABLE V

EFFECTS OF VARIOUS SOLVENTS ON 1-PHENYL-1-PROPANOL AT 160°

Solvent	Dielectric constant,[a] E	Dipole moment,[b] μ	Recovered alcohol, %
Dimethyl sulfone		4.4	90
Acetamide	59	3.7	100
Dimethyl sulfoxide	48.9[c]	3.95	3
Nitrobenzene	36	3.98	82
Benzonitrile	25	3.94	85
Quinoline	9	2.25	93
Diphenylmethane	2.7	2.95	91

[a] A. A. Maryott and E. R. Smith, National Bureau of Standards Circular, No. 514, 1951. [b] L. G. Wesson, "Table of Electric Dipole Moments," The Technology Press, Cambridge, Mass., 1948. [c] H. L. Schlafer and W. Schaffernicht, *Angew. Chem.*, **72**, 618 (1960).

summarizes these data and clearly shows that, of the examples studied, dimethyl sulfoxide is unique in promoting dehydration. A sample of 2-methyl-2-hexanol was heated in pyridine N-oxide (μ = 4.9[9]) and gave 12% olefin and 65% unchanged alcohol. This amount of olefin could be attributed to a thermal dehydration.[3] Thus the dehydration of alcohols in dimethyl sulfoxide is not a result of the high dielectric strength of this solvent. One must consider other solvating properties.

(7) See A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, for synthesis of furans.

(8) V. J. Traynelis and W. L. Hergenrother, *J. Org. Chem.*, **29**, 221 (1964).

(9) E. P. Linton, *J. Am. Chem. Soc.*, **62**, 1945 (1940).

Experimental[10]

Dimethyl Sulfoxide.—Dimethyl sulfoxide,[11] b.p. 83° (17 mm.), $n^{20}D$ 1.4795, was purified as previously described.[3]

Starting Materials.—The following available liquids were distilled prior to use and had boiling points corresponding to literature values: 1-phenyl-1-propanol,[3] 5-butyl-5-nonanol, 1,3-butanediol, 2-methyl-2,4-pentanediol, aldol, diacetone alcohol, α-phenethyl ether, and acetonylacetone. The following available solids were recrystallized to literature melting points when necessary: 1,2-diphenylethanol, 1,6-hexanediol, 1-phenyl-1,2-ethanediol, pinacol, and bicyclohexyl-1,1′-diol.[12]

1-Phenyl-2-propanol.—Phenylacetone (50.0 g., 0.372 mole) in 95% ethanol (100 ml.) was added dropwise and with stirring to a solution of sodium borohydride (4.7 g., 0.13 mole) in 95% ethanol (200 ml.) kept at 0.5°. The mixture was refluxed 1 hr., cooled, treated with 10% hydrochloric acid, and extracted with petroleum ether (b.p. 30–60°). The extract was dried and distillation gave 27.0 g. (53%) of pure 1-phenyl-2-propanol, b.p. 103–104° (14 mm.), $n^{20}D$ 1.5200 [lit.[13] b.p. 101–102° (11 mm.), $n^{14.5}D$ 1.5243].

2-Methyl-2-hexanol, b.p. 137–139°, $n^{20}D$ 1.4183 (lit.[14] b.p. 143°, lit.[15] $n^{20}D$ 1.4186), was prepared in 72% yield by the procedure of Church, Whitmore, and McGraw.[15]

1-Methylcyclopentanol, b.p. 54–56° (25 mm.), m.p. 35–36° [lit.[16] b.p. 135.6 (760 mm.), m.p. 36°], was prepared in 22% yield according to the procedure of Chavanne and Vogel.[16]

1-Alkylcyclohexanols and 2-Cyclohexyl-2-propanol.—1-Methylcyclohexanol, b.p. 55–56° (10 mm.), m.p. 24–25°, $n^{20}D$ 1.4605 [lit.[17] b.p. 55–56° (10 mm.), m.p. 24–25°, $n^{20}D$ 1.4587]; 1-ethylcyclohexanol, b.p. 79° (22 mm.), m.p. 29–30°, $n^{20}D$ 1.4633 [lit.[17] b.p. 78° (20 mm.), m.p. 33°, $n^{20}D$ 1.4642]; 1-isopropylcyclohexanol, b.p. 81.0–81.5° (20 mm.), $n^{20}D$ 1.4682 [lit.[17] b.p. 76–78° (18 mm.), $n^{20}D$ 1.4683]; and 2-cyclohexyl-2-propanol, b.p. 97° (18 mm.), $n^{20}D$ 1.4690 [lit.[17] b.p. 96° (20 mm.), $n^{20}D$ 1.4700], were prepared by reaction of methyl, ethyl, isopropyl, and cyclohexyl Grignard reagents upon the appropriate ketone according to the procedure of Mosher[17] in 76, 55, 38, and 42% yield, respectively.

2,3-Diphenyl-2,3-butanediol.—A mixture of the *meso*- and *dl*-2,3-diphenyl-2,3-butanediol, m.p. 82–112° (lit.[18] m.p. 82–112°), was prepared in 56% yield from acetophenone (47.7 g., 0.397 mole) according to the procedure of Newman.[18]

***dl*-2,3-Diphenyl-2,3-butanediol.**—Pure *dl*-2,3-diphenyl-2,3-butanediol, m.p. 121–122° (lit.[6] m.p. 122°), was obtained from a mixture of the *meso* and *dl* diol by incomplete dehydration in dimethyl sulfoxide. The procedure is described in the section on dehydration of alcohols.

***meso*-2,3-Diphenyl-2,3-butanediol.**—Chromatography of 2.00 g. (0.0082 mole) of 2,3-diphenyl-2,3-butanediol (*meso* and *dl*) on 200 g. of Alcoa F-20 activated alumina gave, upon elution with 1000 ml. of 60% ether in petroleum ether (b.p. 30–60°), 0.30 g. (15%) of pure *meso*-2,3-diphenyl-2,3-butanediol, m.p. 118–118.5° (lit.[6] m.p. 117–118°), and 1.65 g. of a mixture of *meso* and *dl* diol, m.p. 92–114°. A mixture melting point of pure *dl* and pure *meso* was 92–110°.

An alternate method utilized the procedure of Tiffeneau and Levy[19] which involved the addition of phenylmagnesium bromide to biacetyl. A reaction employing 0.10 mole of biacetyl produced pure *meso* diol, m.p. 115.5–117°, in 15% yield and a mixture of *meso* and *dl* diol, m.p. 82–112°, in 30% yield.

1,4-Diphenyl-1,4-butanedione.—Employing the procedure of Conant and Cutter,[20] a solution of sodium hydrosulfite (19.2 g., 0.110 mole) in 100 ml. of water was added to a hot solution of 1,4-diphenyl-2-butene-1,4-dione (23.6 g., 0.100 mole) in 300 ml. of 95% ethanol. After addition was complete, the solution was cooled, poured into water, and the resulting solid collected. Recrystallization from 95% ethanol gave 15.2 g. (64%) of 1,4-diphenyl-1,4-butanedione, m.p. 143–144° (lit.[21] m.p. 144–145°).

Dehydration of Alcohols. General Procedure.[3] Method A.—A solution of alcohol and dimethyl sulfoxide was heated in an oil bath at 160–190° (reflux) under a reflux condenser for the specified periods of time, cooled, and diluted with water. The mixture was extracted with petroleum ether (b.p. 30–60°) and after the extract was dried, the products were isolated and purified by distillation, crystallization, or column chromatography.

Method B.[3]—This varies from the procedure A in that the reflux condenser was replaced by a Claisen head and the product (having b.p.<100°), which distilled during the reaction, was collected in an appropriate receiver cooled in an ice bath or an acetone–Dry Ice bath.

1-Phenyl-2-propanol.—Dry nitrogen was passed through a solution of 1-phenyl-2-propanol (1.3 g., 0.010 mole) and dimethyl sulfoxide (5.5 g., 0.070 mole) for 8 hr. at room temperature and the resulting oxygen-free solution was heated under nitrogen at 190° for 48 hr. The reaction was processed according to method A and analysis of the product by v.p.c. (10-ft. column of Tide detergent on firebrick, at 160°, and a helium flow rate of 60 cc./min.) showed 41% 1-phenylpropene, 48% 1-phenyl-1-propanol, and less than 1% phenylacetone.

1-Methylcyclopentanol.—A solution of 1-methylcyclopentanol (4.00 g., 0.040 mole) and dimethyl sulfoxide (22.0 g., 0.280 mole) was heated at 160° for 6 hr. and processed according to method B. V.p.c. (10-ft. column, Ucon polar on firebrick (30–60 mesh), at 22°, and a helium flow rate of 60 cc./min.) showed only one peak.[22] Distillation of this material gave 2.90 g. (88%) of pure 1-methylcyclopentene, b.p. 74°, $n^{20}D$ 1.4321 (lit.[23] b.p. 75.5–76°, $n^{15}D$ 1.4347).

1-Methylcyclohexanol.—After a solution of 1-methylcyclohexanol (12.50 g., 0.110 mole) and dimethyl sulfoxide (60.0 g., 0.768 mole) was heated at 180° for 9 hr., the reaction mixture was dried over anhydrous sodium sulfate. Distillation gave 8.03 g. (74.5%) of 1-methylcyclohexene, b.p. 52° (110 mm.), $n^{20}D$ 1.4502 [lit.[17] b.p. 110° (760 mm.), $n^{20}D$ 1.4508]. Analysis of this material by v.p.c. (same column as the preceding experiment at 80° and a helium flow rate of 18 cc./min.) showed the presence of 5% of methylene cyclohexane.

A sample of 1-methylcyclohexanol also was dehydrated by distillation from iodine according to the procedure of Mosher.[17] The yield of olefins was 60% with a composition of 95% 1-methylcyclohexene and 5% methylene cyclohexane.

Dehydration of 1-methylcyclohexanol by *p*-toluenesulfonic acid was accomplished by heating these materials in tetralin and distillating out the olefin as formed. Redistillation of this material gave a 37% yield of olefins composed of 97% 1-methylcyclohexene and 3% methylenecyclohexane.

When pure 1-methylcyclohexanol was heated at 180° for 9 hr., no olefins were obtained.

1-Ethylcyclohexanol.—According to method A, 1-ethylcyclohexanol (8.60 g., 0.0651 mole) and dimethyl sulfoxide (35.6 g., 0.456 mole) at 180° for 9 hr. gave 4.0 g. (56%) of 1-ethylcyclohexene, b.p. 61° (79 mm.), $n^{20}D$ 1.4581 [lit.[17] b.p. 134° (760 mm.), $n^{20}D$ 1.4577], and the product was shown by v.p.c. to contain 94% 1-ethylcyclohexene and 6% ethylidenecyclohexane.

When pure 1-ethylcyclohexanol was heated at 180° for 9 hr., an 18% yield of olefin, b.p. 61° (80 mm.), was isolated.

1-Isopropylcyclohexanol.—A solution of 1-isopropylcyclohexanol (2.40 g., 0.019 mole) and dimethyl sulfoxide (10.0 g., 0.128 mole) was heated for 14 hr. at 185° and processed according to method A, giving 1.3 g. (62%) of olefins. V.p.c. (Ucon polar column at 95° and a helium flow rate of 60 cc./min.) showed the presence of 78.3% 1-isopropylcyclohexene, 5.4% 2-cyclohexylpropene, and 16.3% isopropylidenecyclohexane. The first and last compounds listed were separated by v.p.c. and were identi-

(10) All melting points and boiling points are uncorrected. V.p.c. was performed on Wilkens Aerograph instruments, Model A-90 and A-90P, and the relative peak areas were determined with a Keuffel and Esser Co. No. 4242 compensating planimeter. Infrared spectra were recorded on a Perkin-Elmer Infracord, while the n.m.r. spectra were measured by Mr. B. Nowak and Mr. R. Daignault on a Varian Associates 60-Mc. high resolution n.m.r. spectrometer, Model V-4300B.

(11) The authors wish to thank the Chemical Products Division of the Crown Zellerbach Co. for making generous samples of this material available for this work.

(12) This compound was provided by Professor B. T. Gillis of Duquesne University for which the authors express grateful acknowledgment.

(13) P. M. Tiffeneau, *Ann. chim.* (Paris), [8] **10**, 356 (1907).

(14) P. M. Ginnings and M. Hauser, *J. Am. Chem. Soc.*, **60**, 2581 (1938).

(15) J. M. Church, F. C. Whitmore and R. V. McGraw, *ibid.*, **56**, 176 (1934).

(16) G. Chavanne and L. de Vogel, *Bull. soc. chim. Belges*, **37**, 141 (1928).

(17) W. A. Mosher, *J. Am. Chem. Soc.*, **62**, 552 (1940).

(18) M. S. Newman, *J. Org. Chem.*, **26**, 582 (1961).

(19) M. Tiffeneau and M. J. Levy, *Bull. soc. chim. France*, [4] **41**, 1362 (1927).

(20) J. B. Conant and H. B. Cutter, *J. Am. Chem. Soc.*, **44**, 2654 (1922).

(21) S. Kapf. and C. Paal, *Ber.*, **21**, 3056 (1888).

(22) Although this column was successful in separating the exo- and endocyclic olefins in the cyclohexane system, it may not have been successful in the cyclopentane system and the product may contain some methylenecyclopentane.

(23) G. Chavanne and P. Becker, *Bull. soc. chim. Belges*, **36**, 591 (1927).

fied by their infrared and n.m.r. spectra.[24] In the n.m.r. spectrum, 1-isopropylcyclohexene had a doublet at 9.04 with a weight of 6 protons, a multiplet at 8.20 with a weight of 9 protons, and a singlet at 4.60 τ with a weight of 1 proton, while isopropylidene cyclohexane had two singlet absorptions at 8.53 with a weight of 6 protons and 8.38 τ with a weight of 10 protons. 2-Cyclohexylpropene had the same retention time as the material identified in the following experiment.

2-Cyclohexyl-2-propanol (3.25 g., 0.0227 mole) and dimethyl sulfoxide (12.5 g., 0.160 mole) were heated at 175° for 15 hr., and processed according to method A to give 1.60 g. (57%) of olefins. When this mixture was analyzed by v.p.c., the composition was 72.8% 2-cyclohexylpropene and 27.2% isopropylidene cyclohexane. The 2-cyclohexylpropene was collected from v.p.c. (conditions as before), n^{20}D 1.4575 (lit.[17] n^{20}D 1.4586), and was characterized by its infrared spectrum.

1,2-Diphenylethanol.—A solution of 1,2-diphenylethanol (1.00 g., 0.0050 mole) and dimethyl sulfoxide (3.12 g., 0.040 mole) was heated at 160° for 9 hr. and processed by method A to give 0.90 g. of solid material. Chromatography of this mixture on 80.0 g. of Alcoa F-20 activated alumina and elution with petroleum ether (b.p. 30–60°) gave 0.85 g. (93%) of *trans*-stilbene, m.p. 122–124° (lit.[25] m.p. 125°). Elution with ether gave 0.05 g. (5%) of starting alcohol, melting point and mixture melting point with an authentic sample 64–66°.

1-Phenyl-1-propanol.—Four experiments were performed using 1-phenyl-1-propanol (5.0 g., 0.037 mole) and varying amounts of dimethyl sulfoxide at 175° for 9 hr. The reactions were processed according to method A and gave 4.44, 4.52, 4.80, and 4.75 g. of residue, respectively. The residue composition was determined by v.p.c. (conditions same as described under 1-phenyl-2-propanol). The results of this study appear in Table II.

1,4-Butanediol.—A solution of 1,4-butanediol (36.0 g., 0.400 mole) and dimethyl sulfoxide (15.6 g., 0.200 mole) was heated for 14 hr. at 190° and processed according to method B to give 20.2 g. (70%) of tetrahydrofuran, b.p. 64–65°, n^{20}D 1.4038 (lit.[26] b.p. 64–66°, n^{25}D 1.4040).

1,5-Pentanediol (31.2 g., 0.300 mole) and dimethyl sulfoxide (23.4 g., 0.300 mole) were heated for 24 hr. at 190° and processed according to method B. Fractional distillation of the condensate (24.7 g.) which contained tetrahydropyran, dimethyl sulfide, dimethyl disulfide, and bismethylthiomethane gave 12 g. (47%) of tetrahydropyran, b.p. 87–89°, n^{20}D 1.4255 (lit.,[27] b.p. 88°, n^{20}D 1.4205). This was contaminated with a small amount of by-products containing sulfur and when a pure sample, n^{20}D 1.4208, was collected from v.p.c. its infrared spectrum was identical with that of an authentic sample.

Employing the procedure of Franke, *et al.*,[28] 1,5-pentanediol (10.4 g., 0.10 mole) and 50% sulfuric acid (100 ml.) were heated until tetrahydropyran ceased to distil. Redistillation gave 6.5 g. (76%) of tetrahydropyran, b.p. 86–88°, n^{20}D 1.4190.

1,6-Hexanediol—When a solution of 1,6-hexanediol (23.6 g. 0.200 mole) and dimethyl sulfoxide (7.8 g., 0.100 mole) was heated at 190° for 24 hr. according to method B, 9.5 g. of liquid was collected. Distillation of this condensate gave 4.7 g. (24%) of oxepane, b.p. 116°, n^{20}D 1.4547 (lit.[27] b.p. 116°, n^{20}D 1.4355). A pure sample, n^{20}D 1.4393, was collected by v.p.c. and had an infrared spectrum identical with that of an authentic sample.

Dehydration of 1,6-hexanediol (6.4 g., 0.050 mole) also was accomplished by the method of Franke, *et al.*,[28] and gave 3.0 g. of distillate from which a sample of oxepane, n^{20}D 1.4387, was isolated by v.p.c.

1-Phenyl-1,2-ethanediol.—From 1-phenyl-1,2-ethanediol (13.8 g., 0.100 mole) and dimethyl sulfoxide (54.6 g., 0.700 mole) at 190° for 48 hr., 9.0 g. of a black liquid was obtained by procedure A. A sample (1.00 g.) of this substance was treated with 2,4-dinitrophenylhydrazine and gave 2.0 g. of phenylacetaldehyde 2,4-dinitrophenylhydrazone, m.p. 119–120.5° (lit.[29] m.p. 121°). Based on this analysis the yield of phenylacetaldehyde in the dehydration reaction was 67%.

2-Methyl-2,3-butanediol.—A solution of 2-methyl-2,3-butanediol (15.6 g., 0.150 mole) and dimethyl sulfoxide (93.4 g., 1.20 mole) was heated for 36 hr. at 190° and processed according to method B. Distillation of the condensate gave 8.5 g. (66%) of 3-methyl-2-butanone, b.p. 92–96°, n^{20}D 1.3968, 2,4-dinitrophenylhydrazone derivative m.p. 118–119°, and semicarbazone derivative m.p. 110–112° (lit.[30] b.p. 93°, n^{20}D 1.3879, 2,4-dinitrophenylhydrazone derivative m.p. 117°, semicarbazone derivative m.p. 113°).

2,3-Diphenyl-2,3-butanediol.—Using method A, 2,3-diphenyl-2,3-butanediol (2.0 g., 0.0082 mole) and dimethyl sulfoxide (9.0 g., 0.116 mole) after 14 hr. at 190° gave 1.8 g. of a yellow oil which upon chromatography on 100 g. of Alcoa F-20 activated alumina was separated into 0.30 g. (17%) of 2,3-diphenylbutadiene, m.p. 44–46° (lit.[31] m.p. 49°), which exhibited strong absorption at 11.05 μ in the infrared spectrum, and 1.20 g. (65%) of a mixture of ketones. The ketone mixture was analyzed by v.p.c. (silicone QF-1 column at 220° and a helium flow rate of 40 cc./min.) and contained 11% 1,2-diphenyl-2-methyl-1-propanone and 89% 3,3-diphenyl-2-butanone.

A second experiment was performed using twice the quantities of reactants at 190° for 7 hr. and gave, upon chromatography, 0.50 g. (15%) of 2,3-diphenylbutadiene, 1.20 g. (33%) of a ketone mixture (composition, 19% 1,2-diphenyl-2-methyl-1-propanone and 81% 3,3-diphenyl-2-butanone), and 1.90 g. (48%) of unreacted diol from which 1.3 g. (33%) of pure *dl*-2,3-diphenyl-2,3-butanediol, m.p. 121–122°, was obtained by recrystallization from petroleum ether (b.p. 30–60°).

A sample of the previous ketone mixture (0.50 g.) was treated with sodium hypoiodite in dioxane and gave 0.10 g. (20%) of a brown oil with one carbonyl absorption in the infrared spectrum at 5.95 μ. This was converted to the oxime of 1,2-diphenyl-2-methyl-1-propanone, m.p. 190–192° (lit.[6] m.p. 192–193°).

When pure *dl*-2,3-diphenyl-2,3-butanediol (1.0 g., 0.0041 mole) and dimethyl sulfoxide (4.5 g., 0.058 mole) were heated for 14 hr. at 190° and similarly processed, 0.10 g. (12%) of 2,3-diphenylbutadiene and 0.60 g. (65%) of a ketone mixture were isolated. The ketone mixture was composed of 2% 1,2-diphenyl-2-methyl-1-propanone and 98% 3,3-diphenyl-2-butanone. The oxime of 3,3-diphenyl-2-butanone, m.p. 149–150° (lit.[19] m.p. 151°), was prepared in the usual manner.

A second reaction identical with the preceding experiment except using the *meso* diol and reaction time of 7 hr. gave a 15% yield of 2,3-diphenylbutadiene and a 68% yield of ketones (2.4% 1,2-diphenyl-2-methyl-1-propanone and 97.6% 3,3-diphenyl-2-butanone).

Pinacol.—Anhydrous pinacol, m.p. 35–37° (11.8 g., 0.10 mole) and dimethyl sulfoxide (54.6 g., 0.70 mole) were heated at 160°, 175°, and 185° for 16 hr. and processed according to method B. The condensates were analyzed by v.p.c. (mineral oil column at 75° and a helium flow rate of 40 cc./min.) and contained 52%, 56%, and 55% 2,3-dimethylbutadiene and 20%, 27%, and 30% of pinacolone, respectively. Distillation gave pure 2,3-dimethylbutadiene, b.p. 68–69°, $n^{21.4}$D 1.4370; 4,5-dimethyl-1,2,3,6-tetrahydrophthalic anhydride, m.p. 76–78°, lit.[32] b.p. 69–70°, n^{20}D 1.4377 (lit.[33] m.p. 78°); and pinacolone, b.p. 104–105°, n^{20}D 1.3970, 2,4-dinitrophenylhydrazone derivative m.p. 124–125° (lit.[33] b.p. 105°, n^{20}D 1.3956, 2,4-dinitrophenylhydrazone derivative m.p. 126–127°).

When pinacol was heated without dimethyl sulfoxide for 16 hr. at 185°, no product collected in the cold trap and pinacol was recovered quantitatively.

Bicyclohexyl-1,1′-diol.—A solution of bicyclohexyl-1,1′-diol (5.0 g., 0.025 mole) and dimethyl sulfoxide (16.4 g., 0.210 mole) was heated at 160° for 16 hr. and processed according to method A. The resulting yellow oil (4.0 g.) was chromatographed on 150 g. of Alcoa F-20 activated alumina and gave 3.4 g. (85%) of bicyclohexyl-1,1′-diene, n^{20}D 1.5282 (lit.[34] n^{20}D 1.5287) (eluted with petroleum ether), and 0.60 g. of a mixture (eluted with ether) from which was prepared spiro[5.6]dodecan-7-one semicarbazone, m.p. 206–208°, and 2,4-dinitrophenylhydrazone, m.p. 111–113° (lit.[35] semicarbazone m.p. 208–209°, lit.[36] 2,4-dinitrophenylhydrazone m.p. 114°). The diene was characterized by its infrared spectrum and by a Diels–Alder reaction with maleic an-

(24) The n.m.r. spectra were measured in a carbon tetrachloride solution with tetramethylsilane as an internal standard.

(25) W. Schlenk and E. Bergmann, *Ann.*, **463**, 116 (1928).

(26) R. Paul, *Bull. soc. chim. France*, **2**, 2220 (1935).

(27) A. Kirrmann and N. Hamaide, *ibid.*, 789 (1957).

(28) A. Franke, *et al.*, *Monatsh.*, **69**, 167 (1936).

(29) G. D. Johnson, *J. Am. Chem. Soc.*, **75**, 2720 (1953).

(30) S. Daniloff and E. Venus-Danilova, *Ber.*, **59**, 382 (1926).

(31) J. M. Joblin, *J. Am. Chem. Soc.*, **39**, 293 (1917).

(32) E. H. Farmer and F. L. Warren, *J. Chem. Soc.*, 897 (1929).

(33) F. C. Whitmore, C. I. Noll, and V. C. Meunier, *J. Am. Chem. Soc.*, **61**, 684 (1939).

(34) O. Wallach, *Ann.*, **381**, 112 (1911).

(35) C. R. Walter, Jr., *J. Am Chem. Soc.*, **74**, 5185 (1952).

(36) R. Jacquier and H. Christol, *Comp. rend.*, **239**, 1805 (1954).

hydride which gave $\Delta^{12,13}$-dodecahydrophenanthrene-9,10-dicarboxylic acid, m.p. 241–242° (lit.[37] m.p. 242°).

An authentic sample of bicyclohexyl-1,1′-diene was prepared by the procedure of Greidinger and Ginsburg[38] which required the dehydration of bicyclohexyl-1,1′-diol with phosphorus oxychloride in pyridine.

The reaction of bicyclohexyl-1,1′-diol with 50% sulfuric acid by the procedure of Walter[35] gave 79% yield of bicyclohexyl-1,1′-diene and 17% spiro[5.6]dodecan-7-one.

2-Methyl-2,4-pentanediol.—The distillate (16.5 g.), which was collected from 2-methyl-2,4-pentanediol (23.6 g., 0.20 mole) and dimethyl sulfoxide (110 g., 1.40 moles) at 190° for 24 hr. using method B, upon fractional distillation gave 8.0 g. (49%) of a mixture of 2-methyl-1,3-pentadiene and 2-methyl-2,4-pentadiene, b.p. 74–76°, n^{20}D 1.4480 (lit.[39] 2-methyl-1,3-pentadiene b.p. 75.6–76.0°, n^{20}D 1.4466; 2-methyl-2,4-pentadiene b.p. 76–76.5°, n^{20}D 1.45317), and 5.0 g. (25%) of 2-methyl-1-penten-4-ol, b.p. 129–131°, n^{20}D 1.4334 (lit.[40] b.p. 130.3°, lit.[41] n^{20}D 1.4330).

2-Methyl-1-penten-4-ol.—After a solution of 2-methyl-1-penten-4-ol (4.5 g., 0.045 mole) and dimethyl sulfoxide (24.6 g., 0.318 mole) was heated at 190° for 24 hr. under a reflux condenser, distillation of the reaction mixture gave 2.0 g. (55%) of a mixture of 2-methyl-1,3-pentadiene and 2-methyl-2,4-pentadiene, b.p. 74–76°, n^{20}D 1.4472.

1,3-Butanediol.—When 1,3-butanediol (18.1 g., 0.20 mole) and dimethyl sulfoxide (124.8 g., 1.60 mole) were heated for 48 hr. at 190°, 28.7 g. of an organic liquid was collected from the reaction. Distillation of this material gave 4.15 g. (26%) of crotonaldehyde, b.p. 103–110°, n^{20}D 1.4403, 2,4-dinitrophenylhydrazone derivative melting point and mixture melting point with an authentic sample 187–189° (lit.[42] b.p. 104–105°, n^{20}D 1.4384, lit.[29] 2,4-dinitrophenylhydrazone derivative m.p. 189°), and 8.6 g. (54%) of 2-buten-1-ol, b.p. 112–115°, n^{20}D 1.4223 (lit.[43] b.p. 118°, n^{20}D 1.4240).

Aldol.—When a solution of aldol (17.6 g., 0.20 mole) and dimethyl sulfoxide (109 g., 1.40 mole) was heated at 190° for 6 hr. and processed according to method B, 10 g. of an organic liquid was obtained. Distillation gave 8.9 g. (64%) of crotonaldehyde, b.p. 103–105°, n^{20}D 1.4372, 2,4-dinitrophenylhydrazone m.p. 187–188°.

Diacetone Alcohol.—A solution of diacetone alcohol (12.2 g., 0.10 mole) and dimethyl sulfoxide (54.6 g., 0.700 mole) was heated at 190° for 8 hr. The solution was distilled collecting all material boiling below 150°. Redistillation gave 8.2 g. (81%) of mesityl oxide, b.p. 130–135°, n^{20}D 1.4458, 2,4-dinitrophenylhydrazone derivative melting point and mixture melting point with an authentic sample 198–200° (lit.[44] b.p. 131°, n^{13}D 1.4484, lit.[29] 2,4-dinitrophenylhydrazone derivative m.p. 203°).

4-Methoxy-4-methyl-2-pentanone.—The reaction of 4-methoxy-4-methyl-2-pentanone (26.0 g., 0.20 mole) and dimethyl sulfoxide (125 g., 1.60 mole) at 190° for 48 hr., gave 10.4 g. of condensate. Distillation of this material gave 5.2 g. (81%) of methanol, b.p. 66–70°, n^{20}D 1.3343 (lit.[45] b.p. 64–65°, n^{20}D 1.3312), α-naphthylurethane m.p 118–121° (lit.[46] m.p. 124°). The residue (5.2 g.) from this distillation was combined with 18.4 g. of material, b.p. 140–160°, obtained from distillation of the dimethyl sulfoxide solution. Redistillation of this material gave 17.7 g. (90%) of mesityl oxide, b.p. 128–145°, n^{20}D 1.4455, 2,4-dinitrophenylhydrazone derivative m.p. 198–200°.

α-Phenethyl Ether.—After α-phenethyl ether (10.0 g., 0.0442 mole) and dimethyl sulfoxide (24.2 g., 0.31 mole) were heated for 9 hr. at 175°, the reaction was processed according to method A using benzene as the extracting solvent. When the benzene extract was poured into methanol, 3.1 g. (35%) of polystyrene was isolated. An additional 0.4 g. (3%) was isolated upon concentration of the mother liquors.

2,5-Hexanedione.—A solution of 2,5-hexanedione (11.4 g., 0.100 mole) and dimethyl sulfoxide (54.5 g., 0.700 mole) was heated for 60 hr. at 190° and gave 16.1 g. of distillate isolated by method B. Redistillation of this material gave 6.3 g. (66%) of 2,5-dimethylfuran contaminated with dimethyl disulfide, b.p. 94–97°, n^{20}D 1.4568 (lit.[47] b.p. 94°, $n^{17.7}$D 1.4427). A pure sample of 2,5-dimethylfuran, n^{20}D 1.4403, was collected by v.p.c.

1,4-Diphenyl-1,4-butanedione.—After a solution of 1,4-diphenyl-1,4-butanedione (8.0 g., 0.034 mole) and dimethyl sulfoxide (19 g., 0.24 mole) was heated for 48 hr. at 190° and processed by method A, chromatography of the product on 150 g. of Alcoa F-20 activated alumina gave upon elution with 20% benzene in petroleum ether (b.p. 30–60°), 4.5 g. (60%) of 2,5-diphenylfuran, m.p. 88–89° (lit.[48] m.p. 89.5–90°).

Effect of Base on the Dehydration of Alcohols in Dimethyl Sulfoxide.—Solutions of 5-butyl-5-nonanol, dimethyl sulfoxide, and aniline or sodium *n*-octoxide were heated for 16 hr. at 185° and processed according to method A. Table IV contains a listing of the quantity of reactants and the yield of products. Analysis was accomplished by v.p.c. (Ucon polar column, at 180°, and a helium flow rate of 50 cc./min.).

Similar experiments were performed with 2-methyl-2-hexanol and processed by method A.

In both series the olefins were freed of starting materials and other contaminants by chromatography on alumina.

Attempted Dehydrations of 1-Phenyl-1-propanol in Various Solvents.—A solution of 1-phenyl-1-propanol (0.005 mole) and 0.035 mole of dimethyl sulfone, acetamide, nitrobenzene, benzonitrile, quinoline or diphenylmethane was heated at 160° for 14 hr. and processed according to method A. The resulting residues from this work-up were examined by v.p.c. and infrared spectra. In some cases the residues were distilled or chromatographed on alumina. No evidence for olefins was found and the recovery of 1-phenyl-1-propanol ranged from 82–100%, see Table V.

Dehydration of 2-Methyl-2-hexanol in Pyridine N-Oxide.—A solution of 2-methyl-2-hexanol (7.20 g., 0.062 mole) and pyridine N-oxide (23.8 g., 0.250 mole) was heated at 185° for 24 hr. and gave 0.60 g. (12%) of the 2-ethyl-1- and 2-hexenes. From the reaction vessel 4.7 g. (65%) of 2-methyl-2-hexanol, n^{20}D 1.4170 (starting alcohol, n^{20}D 1.4183), was isolated and had an infrared spectrum identical with the starting alcohol.

(37) C. Buchanan and C. C. Ritchie, *J. Chem. Soc.*, 4523 (1954).
(38) D. S. Greidinger and D. Ginsburg, *J. Org. Chem.*, **22**, 1406 (1957).
(39) N. U. Keersbilck, *Bull. soc. chim. Belges*, **38**, 205 (1929).
(40) R. M. Keefer, L. J. Andrews, and R. E. Kepner, *J. Am. Chem. Soc.*, **71**, 3907 (1949).
(41) C. E. Rehberg and C. H. Fischer, *J. Org. Chem.*, **12**, 228 (1947).
(42) J. Timmermans, *Bull. soc. chim. Belges*, **31**, 391 (1922).
(43) K. Hess and W. Wustrow, *Ann.*, **437**, 263 (1924).
(44) K. V. Auwers and F. Eisenlohr, *J. prakt. Chem.*, [2] **82**, 124 (1910).
(45) J. F. Norris and A. A. Ashdown, *J. Am. Chem. Soc.*, **47**, 837 (1925).
(46) V. T. Bickel and H. E. French, *ibid.*, **48**, 747 (1926).
(47) R. Nasini and G. Carrara, *Gazz. chim. ital.*, **241**, 271 (1894).
(48) R. A. Lutz and R. J. Rowlett, Jr., *J. Am. Chem. Soc.*, **70**, 1360 (1948).

Anhydridization of Carbohydrate C-Nitroheptitols[1]

JOHN C. SOWDEN,[2] CAROLINE H. BOWERS, AND KENNETH O. LLOYD

Department of Chemistry, Washington University, St. Louis, Missouri

Received July 22, 1963

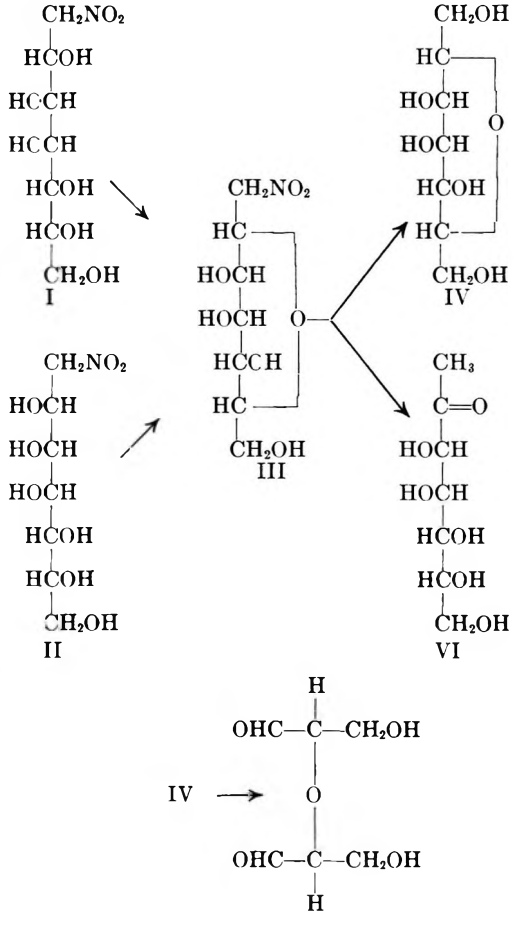
Heating aqueous solutions of 1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol or 1-deoxy-1-nitro-D-*glycero*-D-*talo*-heptitol results in the formation of 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol (III). The structure of III was established by periodate oxidation studies and conversion, by reduction to the amine followed by treatment with nitrous acid, to 2,6-anhydro-D-*glycero*-D-*galacto*-heptitol. The nitrosation reaction also gave 1-deoxy-D-*manno*-heptulose. Periodate oxidation of III gives a method for the determination of the structure of any 2,6-anhydro-1-deoxy-1-nitroheptitol. The method was applied to 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol obtained by the anhydridization of 1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol or 1-deoxy-1-nitro-D-*glycero*-L-*gluco*-heptitol.

The anhydridization of 1-deoxy-1-nitrohexitols has been studied by Sowden and Oftedahl.[3] They showed that epimeric pairs of nitrohexitols give the same 2,6-anhydro-1-deoxy-1-nitrohexitol and postulated a common intermediate, probably a nitroolefin, to account for this.

We have now extended the scope of the anhydridization reaction to include the 1-deoxy-1-nitroheptitols. Studies on the anhydridization of 1-deoxy-1-nitro-D-*glycero*-L-*manno*-hepitol recently have been reported by Hough and Shute.[4] They have shown that a 2,6-anhydro compound again is formed as the main product and have proven the configuration of the compound by application of Hudsons' isorotation rules. We have studied the anhydridization of the four 1-deoxy-1-nitroheptitols obtained by the application of the nitromethane synthesis[5] to D-mannose and D-galactose. The structure of the products was determined by periodate cleavage and, in one case, by deamination of the corresponding amine.

Following the procedure of Sowden and Oftedahl,[3] 1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol (I) and 1-deoxy-1-nitro-D-*glycero*-D-*talo*-heptitol (II), prepared from D-*mannose*, were refluxed in aqueous solution for 48 hr. In each case 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol (III) was obtained as the main product. A minor product of each reaction was D-mannose. It was identified by chromatography and the preparation of D-mannose phenylhydrazone from the anhydridization reaction of I. The formation of aldose is not unexpected and is explained by re-equilibration of the nitroalditol with nitromethane and aldose.[3]

The ring structure of the 2,6-anhydro product was proven by the observation that it rapidly consumed two moles of periodate with the concomitant formation of one mole of formic acid. The configuration of III was established by periodate oxidation studies on the 2,6-anhydroheptitol obtained from III by a procedure used by Sowden and Oftedahl to prove the configurations of the anhydronitrohexitols. Reduction of the 2,6-anhydronitroheptitol (III) to the amine (not isolated) and nitrosation of the latter gave a 2,6-anhydroheptitol which had to be either 2,6-anhydro-D-*glycero*-D-*galacto*-heptitol (IV) or 2,6-anhydro-D-*glycero*-D-*talo*-heptitol



(V). Another crystalline product, which will be discussed later, also was isolated from this reaction.

Periodate oxidation of the 2,6-anhydroheptitol gave an optically inactive dialdehyde. Of the two possible structures only IV will give a *meso* dialdehyde on oxidation. The dialdehyde from V is the same as the dialdehyde obtained by the periodate oxidation of 2,5-anhydro-D-mannitol and is known to have a $[\alpha]_D$ of $+33.5°$.[6] This positive value shows that the optically inactive solution formed by the oxidation of IV is not due to racemization of the product. Hence this reaction sequence unequivocally establishes the configuration about C-2 and shows that III is 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol.

Once the structure of this anhydro compound is known a simple method is available for the proof of the configuration about C-2 of any 2,6-anhydro-1-deoxy-1-nitro-D-heptitol. Periodate cleavage of III will result in a nitrodialdehyde which will have the structure VII.

(1) A preliminary report of some of this work has been published: J. C. Sowden, C. H. Bowers, L. Hough, and S. H. Shute, *Chem. Ind.* (London), 1827 (1962).

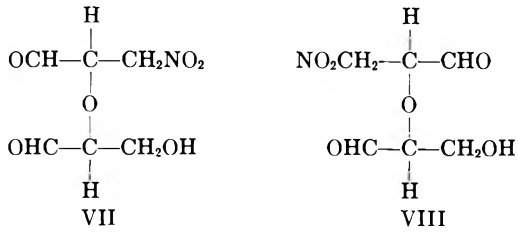
(2) Deceased April 14, 1963.

(3) J. C. Sowden and M. L. Oftedahl, *J. Org. Chem.*, **26**, 1974 (1961).

(4) L. Hough and S. H. Shute, *J. Chem. Soc.*, 4633 (1962).

(5) J. C. Sowden, *Advan. Carbohydrate Chem.*, **6**, 291 (1951).

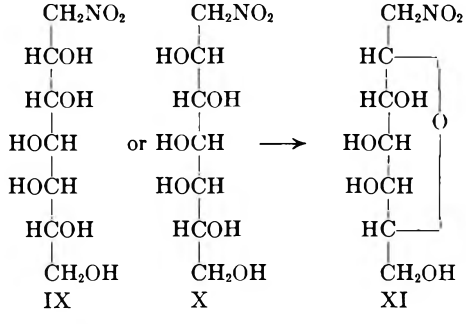
(6) J. C. Sowden and K. O. Lloyd, unpublished experiments.



VII VIII

The observed specific rotation of the dialdehyde formed from III (but not isolated) was −17°. After anhydridization of a nitro-D-heptitol only VII or VIII can be formed by periodate oxidation. Thus if the resulting dialdehyde has a rotation of −17° then the configuration about C-2 is the same as in 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol. If it is not −17° then the opposite configuration is indicated. The same argument can be applied to the nitro-L-heptitols except that the rotation will be +17° in one case and in the other case will be opposite in sign to the rotation of VIII but, more importantly, it will not be +17°. Thus, knowing the structure of the original nitroheptitol the configuration of the 2,6-anhydro compound resulting from its anhydridization can be determined by a simple periodate cleavage.

The method was demonstrated by its application to the determination of the structure of the product obtained by the anhydridization of the two nitroheptitols formed by the condensation of nitromethane with D-galactose. Both 1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol (IX) and 1-deoxy-1-nitro-D-*glycero*-L-*gluco*-heptitol (X) gave the same 2,6-anhydronitroheptitol as the main product.



IX X XI

The ring size was demonstrated by periodate oxidation. The dialdehyde formed by periodate cleavage had a specific rotation of −17.5°. This demonstrates that the anhydro compound has the same configuration about C-2 as III and is, therefore, 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol (XI). Chromatography indicated that, in addition to XI, three minor products are formed during the anhydridization reaction. One of these has the same R_f as galactose and the other two are probably other anhydro products.[4] Apparently the products formed are in equilibrium with each other. This was demonstrated by refluxing an aqueous solution of XI for 20 hr. Chromatography of the reaction mixture showed four products. The chromatograms were identical with those of the anhydridzation reaction mixtures of 1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol (IX). The existence of this equilibrium means that the anhydro ring is labile.

It is interesting to note that the major product formed by the anhydridization of each pair of isomers is the one having the chair conformation with the smaller number of nonbonded interactions. Thus, 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol can assume a chair configuration with only one bulky group (hydroxyl) in an axial position whereas the epimeric D-*glycero*-D-*talo* isomer has at least two bulky axial groups in the chair conformation. Similarly, 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol which can exist in a chair configuration with only one hydroxyl group axial is formed in great excess over the D-*glycero*-L-*gluco* product. The formation of the same product from both isomers supports the theory, postulated by Sowden and Oftedahl, of a common intermediate in the anhydridization reaction.

The side product formed during the nitrosation of the amine from III was isolated as a white crystalline solid. Analysis of the compound indicated a molecular formula of $C_7H_{14}O_6$. It was identified as 1-deoxy-D-*manno*-heptulose (VI). The compound reduces Fehling's reagent very readily and forms a crystalline osazone also. A positive iodoform test confirmed the presence of a CH_3–CO group. The possibility of a 2-deoxy sugar was eliminated because the compound gave only a pale green color in the Dische deoxy sugar test.[7] 2-Deoxy-D-*erythro*-pentose gave a purple color and fructose a pale green color. The compound gave a positive Seliwanoff ketose test.[8] The identity of VI was confirmed by reduction with sodium borohydride to crystalline 1-deoxy-D-*glycero*-D-*galacto*-heptitol. This heptitol has been synthesized by the reductive desulfurization of D-*glycero*-D-*galacto*-heptose diethyl mercaptal.[9] A second product of the borohydride reduction could not be crystallized and was probably the other isomer, 1-deoxy-D-*glycero*-D-*talo*-heptitol. The formation of VI during the deamination reaction resembles the nitrosation of 2-aminoglycerol to give acetol[10] and the formation of deoxyinoses by nitrosation of inosamines.[11] The mechanism is probably similar to the one proposed by Foster[12] for the deamination of 1,2-amino alcohols, although in our case the anhydro ring must open either before or during the migration of the hydrogen atom from C-2.

Only one other 1-deoxyketose is reported in the literature. Wolfrom, *et al.*,[13] synthesized 1-deoxy-D-*arabino*-hexulose tetraacetate by condensing diazomethane with aldehydo-D-arabinose tetraacetate. On the other hand a simple method is available for the preparation of 1-deoxy-2-keto sugars in the addition of nitroethane to aldose sugars.[5]

Experimental

All melting points are uncorrected. Paper chromatography was carried out on Whatman No. 1 paper with the upper phase of 1-butanol–ethanol–water (4:1:5 v/v).[14] Compounds were detected with periodate–benzidine spray.[15]

(7) Z. Dische, *Mikrochemie*, **8**, 4 (1930).

(8) Z. Dische, "Methods of Biochemical Analysis," Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1955, p. 330.

(9) E. Zissis, N. K. Richtmyer, and C. S. Hudson, *J. Am. Chem. Soc.*, **72**, 3882 (1950).

(10) Y. Matsushima, *Sci. Papers Osaka Univ.*, **35**, 13 (1951); *Chem. Abstr.*, **46**, 7053 (1952).

(11) T. Pasternak, *Helv. Chim. Acta*, **33**, 1597 (1950).

(12) A. B. Foster, *Chem. Ind.* (London), 627 (1955).

(13) M. L. Wolfrom, D. I. Weisblat, W. H. Zoply, and S. W. Waisbrot, *J. Am. Chem. Soc.*, **63**, 201 (1941).

(14) B. Lindberg, A. Misiorny, and C. A. Wachtmeister, *Acta Chem. Scand.*, **7**, 591 (1953).

(15) M. Viscontini, D. Hoch, and P. Karrer, *Helv. Chim. Acta*, **38**, 642 (1955).

2,6-Anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol (III).—A solution of 50 g. of 1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol (I)[16] in 500 ml. of water was refluxed for 48 hr. Chromatography of the reaction mixture showed the presence of III (R_f 0.38) and mannose (R_f 0.20). The solution was evaporated to about 60 ml. and cooled. Filtration gave 18.9 g. (41%) of III, m.p. 146–152°. Several recrystallizations from 95% 1-butanol yielded 12.9 g. (27%) of pure product, m.p. 151–152° and $[\alpha]^{25}D$ −26.1° (*c* 2.5, water). From the combined mother liquors another 9.6 g. of III, m.p. 151–152°, was isolated to give a total yield of 49%.

Anal. Calcd. for $C_7H_{13}O_7N$: C, 37.65; H, 5.87; N, 6.28. Found: C, 37.79; H, 5.91; N, 6.28.

From 0.50 g. of sirupy mother liquors a crystalline phenylhydrazone was prepared,[17] m.p. 187.5° dec. The decomposition point of D-mannose phenylhydrazone is 186–187°.[18]

When 1-deoxy-1-nitro-D-*glycero*-D-*talo*-heptitol[16] was heated in water as before, the major product (42%) was again 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol, m.p. 151–152° and $[\alpha]^{25}D$ −26.1° (*c* 3.2, water).

Oxidation of 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol in aqueous solution with sodium periodate[19] showed the consumption of two molecular equivalents of oxidant after 4 hr. with the production of one molecular equivalent of formic acid and no formaldehyde. At this stage the specific rotation based on the dialdehyde was −17° (*c* 2.0). After 26 hr. the values were unchanged.

2,6-Anhydro-D-*glycero*-D-*galacto*-heptitol (IV).—A solution of 5.0 g. of 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol in 110 ml. of water was treated with 200 mg. of Adams' platinum catalyst and 3 ml. of glacial acetic acid. The mixture was reduced with hydrogen at 1 atm. for 3.5 hr. The catalyst then was removed by filtration and 5.0 ml. of glacial acetic acid was added to the filtrate. The solution was stirred and 4.63 g. of sodium nitrite was added. After 20 hr. the solution was deionized over Dowex 50(H^+) and Amberlite XE-168(OH^-) and concentrated to a sirup. The sirup was taken up in ethanol, decolorized with charcoal, and the solution evaporated to a small volume. The crystals obtained were filtered to yield 2.5 g (58%) of crude 2,6-anhydro-D-*glycero*-D-*galacto*-heptitol, m.p. 138–140°. Recrystallization from ethanol gave 0.86 g. of pure hygroscopic material, m.p. 142–144° and $[\alpha]^{25}D$ −33.6° (*c* 1.5, water).

Anal. Calcd. for $C_7H_{14}O_6$: C, 43.29; H, 7.28. Found: C, 43.33; H, 7.28.

2,6-Anhydro-D-*glycero*-D-*galacto*-heptitol consumed 2 moles of periodate in 3 hr and gave an optically inactive solution. After 10 hr. the values were unchanged.

1-Deoxy-D-*manno*-heptulose (VI).—Five grams of 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol was reduced and the amine treated with nitrous acid as was described. 2,6-Anhydro-D-*glycero*-D-*galacto*-heptitol (IV) was removed from the reaction mixture by crystallization. Chromatography of the mother liquors showed the presence of IV (R_f 0.23) and 1-deoxy-D-*manno*-heptulose (R_f 0.30). The sirupy mixture (3.5 g.) was separated by chromatography on a cellulose column[20] by elution with 90% 1-butanol. Fractions containing only 1-deoxy-D-*manno*-heptulose were combined and evaporated to yield 0.76 g. (17.3%) of sirup. The sirup was dissolved in hot ethanol, and petroleum ether (b.p. 63–69°) was added to turbidity. Cooling and filtration gave 0.32 g. (8%) of VI, m.p. 87–89°. Recrystallization from ethanol–petroleum ether yielded a product having m.p. 90–91° and $[\alpha]^{25}D$ +24.2° (*c* 3.4, water, 30 min., constant over 8 hr.).

Anal. Calcd. for $C_7H_{14}O_6$: C, 43.29; H, 7.27. Found: C, 42.70; H, 7.43.

An iodoform test[21] on the compound was positive. Alkaline sodium hypoiodite solution converted the compound to iodoform, m.p. 120°.

An osazone was prepared in the usual manner.[22] From 0.47 g. of compound 0.26 g. of crystalline product was obtained, m.p. 135–137° dec. The material was difficult to recrystallize but several recrystallizations from ethanol–water raised the melting point to 176–178° dec.

Reduction of 1-Deoxy-D-*manno*-heptulose.—A solution of 0.5 g. of sodium borohydride in 20 ml. of water was added dropwise at room temperature to a stirred solution of 1.1 g. of 1-deoxy-D-*manno*-heptulose in 25 ml. of water. After 3.25 hr. processing the reaction mixture in usual manner yielded 0.30 g. (27%) of crystalline 1-deoxy-D-*glycero*-D-*manno*-heptitol, m.p. 173–175°. Recrystallization from methanol gave 0.12 g. of pure material, m.p. 181–182° and $[\alpha]^{25}D$ +1.14° (*c* 2.6, water).

Anal. Calcd. for $C_7H_{16}O_6$: C, 42.84; H, 8.09. Found: C, 43.0; H, 8.19.

Zissis, *et al.*,[9] report m.p. 181–182° and $[\alpha]^{25}D$ +1.1° in water for 1-deoxy-D-*glycero*-D-*manno*-heptitol.

Evaporation of the mother liquors gave a sirupy residue (0.48 g.), which failed to crystallize.

2,6-Anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol (XI).—A solution of 13.1 g. of 1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol[23] in 131 ml. of water was refluxed for 48 hr. Chromatography of the reaction mixture showed the presence of XI (R_f 0.36), a reducing compound, presumably galactose (R_f 0.12), and two minor unidentified products (R_f 0.45 and R_f 0.55). Evaporation to dryness and crystallization of the residue from 90% ethanol gave 7.36 g. (62%) of XI. Recrystallization from the same solvent yielded 6.45 g. (55%) of pure product, m.p. 199.5–200.5° and $[\alpha]^{25}D$ +36.0° (*c* 2.9, water).

Anal. Calcd. for $C_7H_{13}O_7N$: C, 37.65; H, 5.87; N, 6.28. Found: C, 37.56; H, 5.55; N, 6.24.

When 1-deoxy-1-nitro-D-*glycero*-L-*gluco*-heptitol[23] was heated in aqueous solution as before, the main product was again 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol (65%), m.p. 199.5–200.5° and $[\alpha]^{25}D$ +36.0° (*c* 2.9, water)

2,6-Anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol consumed 2 moles of periodate in 2 hr. with the production of 2 moles of formic acid and no formaldehyde. The values were unchanged after 24 hr. and at this time the specific optical rotation (based on dialdehyde) was −17.6° (*c* 2.1).

Equilibration of 2,6-Anhydro-1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol (XI) in Hot Aqueous Solution.—A solution of 0.57 g. of XI in 5.7 ml. of water was refluxed for 20 hr. Chromatographic examination of the solution showed four components, R_f values: 0.14, 0.36, 0.45, and 0.55. The chromatograms were identical with those taken during the formation of XI as described previously.

Acknowledgment.—The authors wish to acknowledge the generous support of the U. S. Public Health Service (Grant No. GM-08849) during the course of this work.

(16) J. C. Sowden and R. Schaffer, *J. Am. Chem. Soc.*, **73**, 4662 (1951).

(17) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Interscience Publishers, Inc., New York, N. Y., 1947, p. 428.

(18) "Handbook of Chemistry and Physics," 40th Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1958, p. 1086.

(19) J. R. Dryer, "Methods of Biochemical Analysis," Vol. 3, Interscience Publishers, Inc., New York, N. Y., 1956, p. 111.

(20) ChroMax column (size, 8.0 × 44.5 cm.), LKB-Produkter, Stockholm, Sweden.

(21) A. Lieben, *Ann.*, **7**, 218 (1870).

(22) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Interscience Publishers, Inc., New York, N. Y., 1947, p. 430.

(23) J. C. Sowden and D. R. Strobach, *J. Am. Chem. Soc.*, **82**, 1954 (1960).

Sorboses. II. Reaction Mechanism of Acetonization of 1,2-O-Isopropylidene-α-L-sorbopyranose[1]

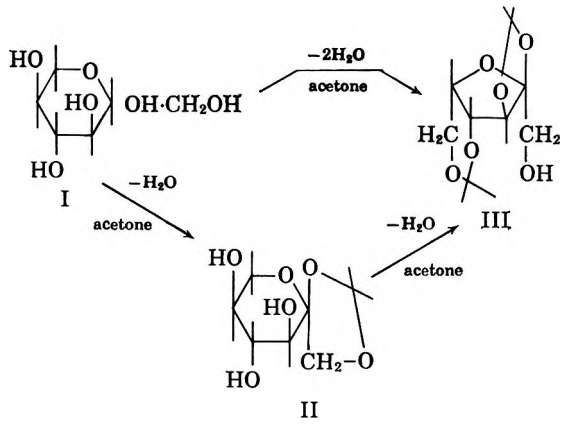
KANJI TOKUYAMA, ETSUKO HONDA, AND NOBUYUKI HŌKI

Shionogi Research Laboratory, Shionogi and Company, Ltd., Fukushima-ku, Osaka, Japan

Received April 22, 1963

Acetonization of 1,2-O-isopropylidene-α-L-sorbopyranose (II) was studied kinetically. The reaction mechanism was proposed to be cyclic as follows: II → $[II]_2$ → diacetonized furanose (III) + L-sorbose (I), which in turn reverted to II.

The acetonization of L-sorbose (I) is a very important reaction for the production of l-ascorbic acid. It has been known that the reaction in acetone solution without acids gave 1,2-O-isopropylidene-α-L-sorbopyranose (II)[2] and with acids gave 2,3:4,6-di-O-isopropylidene-α-L-sorbofuranose (III), along with 2,3-O-isopropylidene-α-L-sorbofuranose (IV) as a by-product.[3] Recent results from our laboratory,[4] which demonstrated the formation of the pyranoside (II) and its subsequent transformation into furanoside (III) during the acid-catalyzed acetonization of I, prompted us to investigate the reaction mechanism of the acid-catalyzed acetonization of II.



To determine the rate order of acid-catalyzed acetonization of the pyranoside (II), a convenient method might be titration of the acetone of III formed during the course of the reaction. However, several known methods[5,6] gave poor results in our hands, because the loss of the acetonized sugars was too great on removal of the solvent from an alkaline solution. Thus we decided to use Karl Fischer's method[7] of titrating water formed during the reaction. Although it appears that the formation of water due to dimerization of the solvent may disturb the titration, dimerization was only observed after the reaction of acetonization was over, as shown in Fig. 1. Therefore, reaction of the pyranoside (II) in acetone with a catalytic amount of sulfuric acid was followed successfully by the latter method. The results are shown in Fig. 1 and 2. Plots of concentration function $x/a(a-x)$ against time were linear as shown in Fig. 3, except that it showed a slight downward curvature at the final stage. Therefore, it was

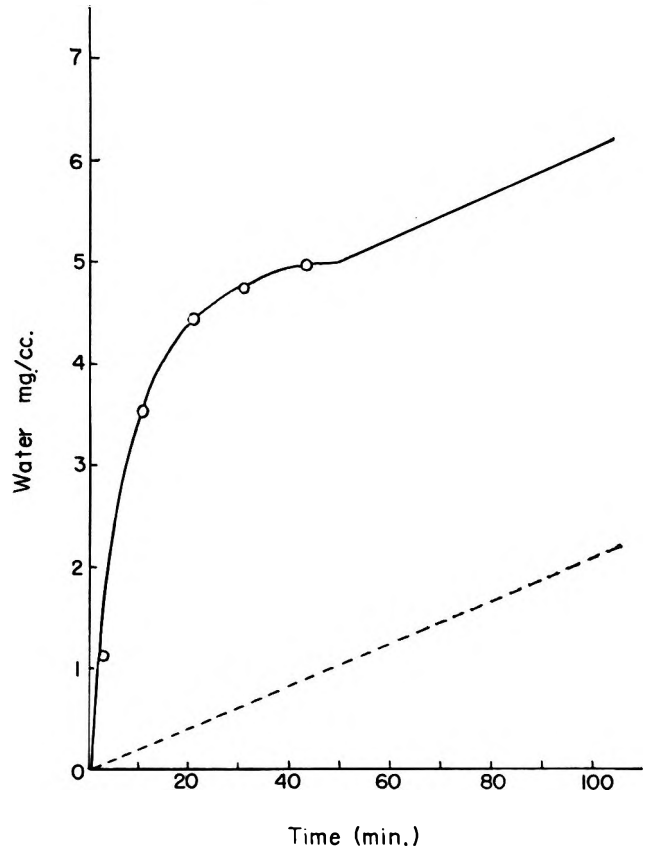


Fig. 1.—Increase of water in acid-catalyzed acetonization of II at 20°: II, 30.2, and sulfuric acid, 1.16 moles/l. ———, increase of the water; - - - - -, increase of the water in absence of II.

considered that the reaction was second order and the rate was proportional to the square of the concentration of the reactant, II. The second order in pyranoside (II) suggests that two molecules of the pyranoside (II) participate in the sequence leading to the rate-determining step. Presumably the two molecules of the pyranoside (II) were converted into a dimer $[II]_2$. The rate constant also was found to be proportional to the concentration of sulfuric acid. These constants are shown in Table I.

Gas chromatographic investigations at the end of the reaction showed three products, II, III, and IV. Therefore, the reaction process was probably *via* a pathway of II → III → IV or II → IV → III.

The reaction rates of III → IV and IV → III in acetone with sulfuric acid were measured. They were carried out by titrating the water increase or decrease, but the reactions were too fast to allow measurements of the rates in the concentrated acid solution employed above. Since changes from III to IV and the reverse

(1) Part I: K. Tokuyama, M. Kiyokawa, and N. Hōki, *Bull. Chem. Soc. Japan*, **36** (11) (1963).
(2) H. Ohle, *Ber.*, **71**, 762 (1938).
(3) T. Reichstein, *Helv. Chim. Acta*, **17**, 3111 (1934).
(4) S. Sato, private communications.
(5) R. A. Kramarov, *Farmatsiya* (Sofia), **12**, 18 (1940).
(6) J. M. R. Romers and G. G. Trigo, *Chim. Ind.* (Paris), **86**, 256 (1961).
(7) K. Fischer, *Z. angew. Chem.*, **48**, 394 (1935).

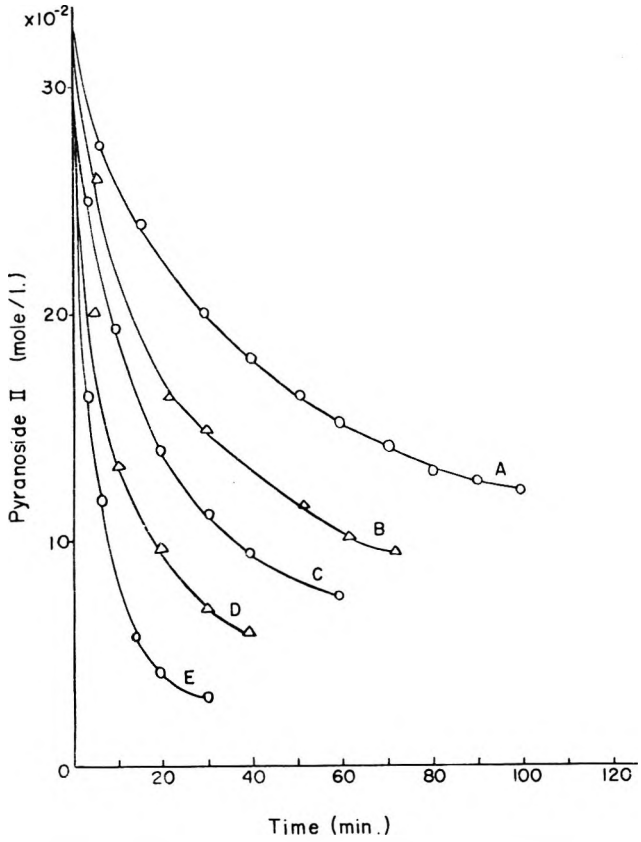


Fig. 2.—Decrease of II in acid-catalyzed acetonization of II at 30°: sulfuric acid (A) 0.44, (B) 0.58, (C) 0.74, (D) 0.85, and (E) 1.15 moles/l.

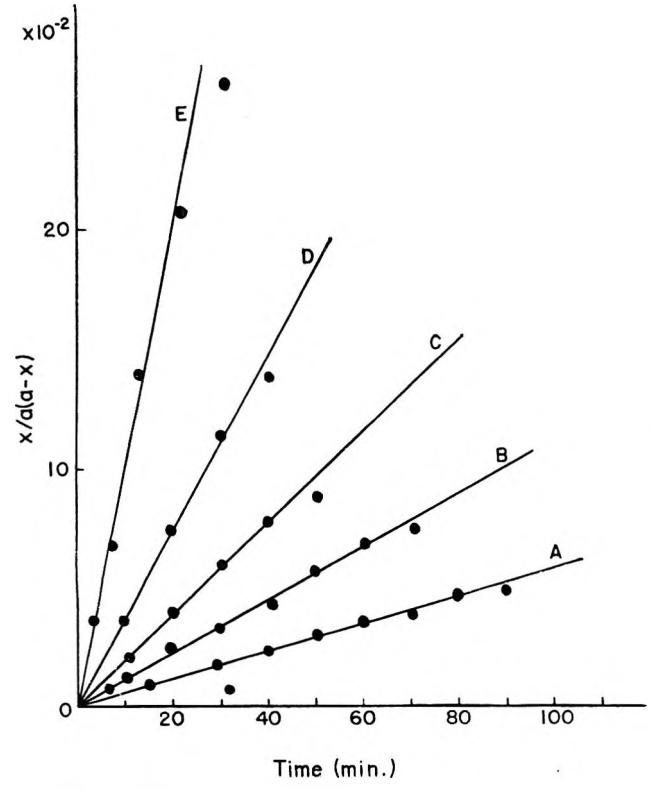


Fig. 3.—Values of concentration function against time at 30°: sulfuric acid (A) 0.44, (B) 0.58, (C) 0.74, (D) 0.85, and (E) 1.15 moles/l.

were considered to be very fast equilibria, they were not rate-determining steps in the total pathway. Since the total rate was second order by measurement of the water, if the reaction process is assumed to be the pathway of II → IV → III, the reaction of II → IV would be a second-order reaction in which water must be formed. However, the formation of water can not be expected during the course of II → IV. Therefore, the reaction process of acetonization should be *via* the pathway of II → III → IV. In this pathway the reaction of II → III is second order and the reaction of III → IV reaches equilibrium very fast. As the reaction progresses, equilibrium will consume the water produced by the second-order reaction. This is why the plots of the concentration function showed a slight downward curvature on the final stage, as shown in Fig. 3.

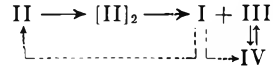
TABLE I

THE RATE CONSTANTS OF THE REACTION OF II → III

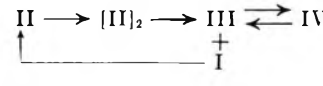
Reaction temp., °C.	Sulfuric acid, mole/l.	Rate constants × 10^{-3}, l./mole sec.
20	0.45	0.68
20	0.58	1.27
20	0.72	2.00
20	0.89	4.50
20	1.16	12.17
30	0.44	1.00
30	0.58	1.83
30	0.74	3.43
30	0.85	6.50
30	1.15	17.17
40	0.45	2.00
40	0.59	3.83
40	0.73	5.83
40	0.86	11.37

The results of the reactions of III → IV and IV → III in slightly acid solution were shown in Fig. 4. They seem to be zero order at the initial stages, but further studies would be required for complete interpretation.

Thus the reaction process of acetonization of II is considered as the following.



If this proposal is reliable, sorbose (I) must be detected during the course of the reaction. As expected, positive evidence was obtained by a Fehling's test of the reaction mixture. I also was noticed by paper partition chromatography of the reaction mixture. The rate of decrease of I in the reaction mixture by Bertrand's method[8] was obtained as zero order as shown in Fig. 4. Because, if I is directly transformed into IV, the over-all rate of the reaction becomes zero order, which is inconsistent with the aforementioned results. The reaction process of acetonization of the pyranoside (II) was suggested by us as the following.

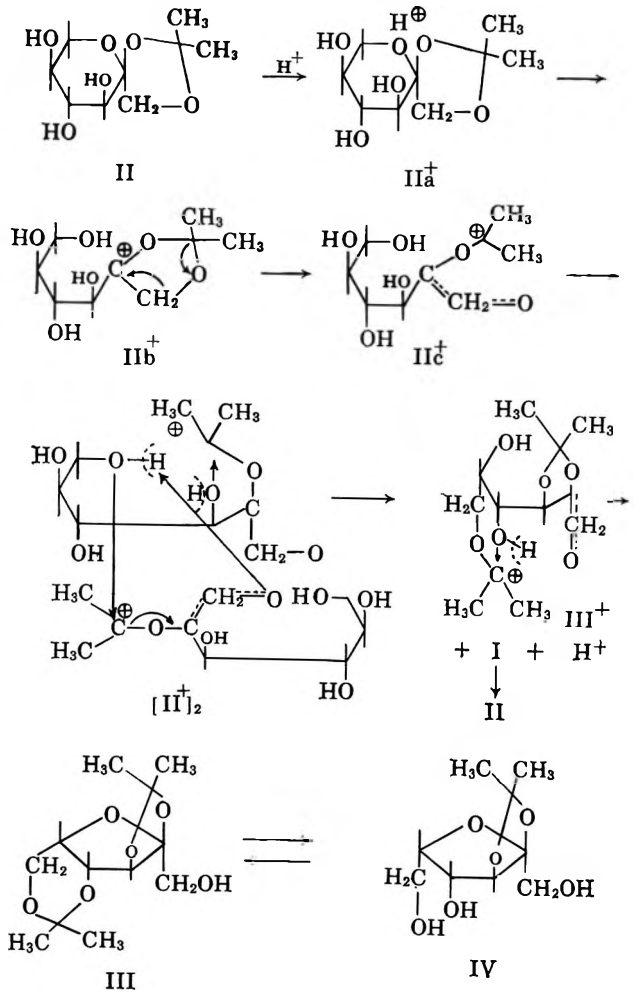


As indicated, aceonization of the pyranoside (II) is a cyclic pathway. When this cycle starts from I, the reaction is the same as acetonization of I. It also was found that acetonization of I does not take a simple pathway, such as I → IV → III.

Considering our reaction mechanisms, it may be expected that the furanoside (III) is prepared from the

(8) G. Bertrand, *Bull. soc. chim. France*, **35**, 1285 (1906).

CHART I



pyranoside (II) in the absence of acetone. When I, II, III, or IV was allowed to stand in dioxane containing 2% of sulfuric acid for a long time, all solutions except that of IV exhibited the same absorption band at 280 mμ. The bands disappeared by making the dioxane solutions alkaline and only the starting sugars were detected in the solutions. So, it seems likely that the absorption band at 280 mμ is due to the protonated forms of the sugars. In the acidic dioxane solution with a higher concentration of the pyranoside (II), the solution turned from colorless to violet *via* pink, and labile crystals separated, which then polymerized to a black tar. The changes in ultraviolet absorption spectra of the solutions are shown in Fig. 5. In the first stage the absorption band at 280 mμ appeared and then an absorption band at 225 mμ appeared. The labile crystals exhibited both bands. If the reaction mixture was made alkaline at the stage that the second band at 225 mμ appeared, I, II, III, and IV were identified. From these results it seems reasonable that the protonated form of the pyranoside (II^+) exhibits the first absorption band at 280 mμ and the protonated form of the dimer $[II^+]_2$ exhibits the second absorption band at 225 mμ. The labile crystals would be $[II^+]_2$, but it was too labile to be isolated in a pure state for further investigations. From the aforementioned, it may be considered that the pyranoside (II) is converted into the pyranoside ion (II^+) and then dimerized to $[II^+]_2$.

On the basis of all data presented, the mechanism of

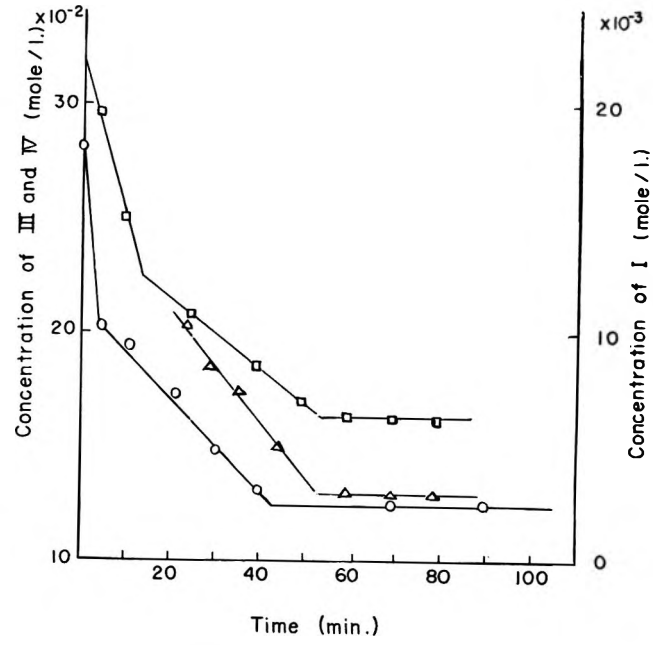


Fig. 4.—Results of the reactions of III → IV, IV → III, and I → II in acid solution –O–O–, decrease of III in the reaction of III → IV at 30° (sulfuric acid, 0.0078 mole/l.); –□–□–, decrease of IV in the reaction of IV → III at 30° (sulfuric acid, 0.0080 mole/l.); –Δ–Δ–, decrease of I in acetonization of II at 30° (sulfuric acid, 0.58 mole/l.).

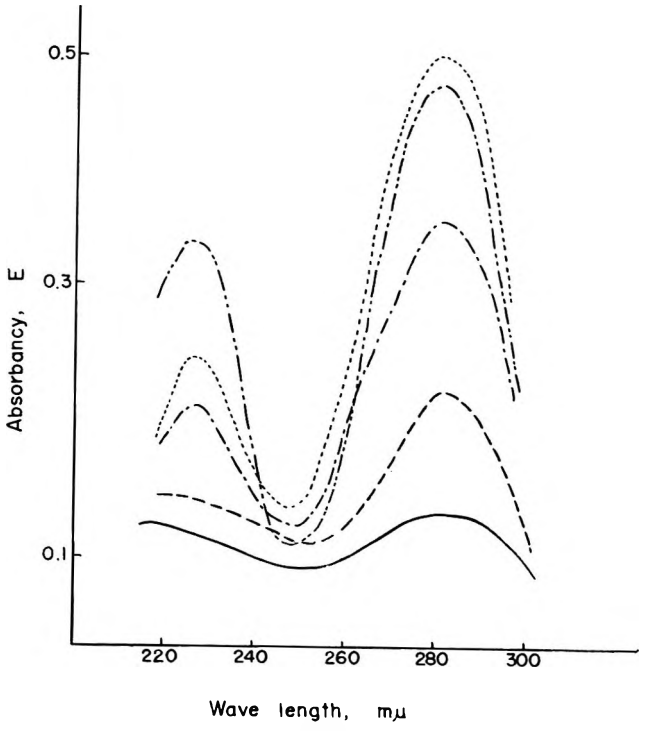


Fig. 5.—Changes in ultraviolet absorption spectra of the reaction mixture of II (0.10 g.), dioxane (1.86 g.), and sulfuric acid (0.038 g.) at 30°. ———, after 11 min.; – – – –, after 22 min.; –·–·–, after 38 min. ·····, after 49 min.; –··–··, after 60 min.

acetonization of the pyranoside (II) is summarized in Chart I.

Experimental

Materials.—1,2-O-Isopropylidene-α-L-sorbopyranose (II), m.p. 142°, $[\alpha]^{20}D$ −85.2° (*c* 1.503, water)[2]; 2,3:4,6-O-isopropylidene-α-L-sorbofuranose (III), m.p. 78°, $[\alpha]^{18.5}D$ −18.1° (*c* 1.380, acetone)[3]; and 2,3-O-isopropylidene-α-L-sorbofuranose (IV),

m.p. 91°, $[\alpha]^{20}D$ +7.02° (*c* 1.42, water),[9] were prepared by the usual methods.

Kinetic Measurements of the Reactions of II → III, III → IV, IV → III, and I → II.—Sulfuric acid was weighed into 50 g. of acetone in a standard flask which was then placed in a thermostat at the appropriate temperature. To the solution was added about 0.4 g. of the water to keep the water in the solution constant, and then 5 g. of the sugars. (1) Samples (1 ml.) were titrated by Karl Fischer's method.[7] The data are shown in Fig. 1, 2, 3, and 4, and Table I. (2) Samples (1 ml.) were titrated by Bertrand's method.[8] The data are shown in Fig. 4 and Table II.

TABLE II

THE RATE CONSTANTS OF THE REACTION OF I → II

Reaction temp., °C.	Sulfuric acid, mole/l.	Rate constants × 10^{-5}, mole/l. sec.
30	0.71	0.61
40	0.73	3.20

After the reactions were over, the solutions were poured into a saturated solution of sodium carbonate to make the solution alkaline, evaporated to dryness *in vacuo*, and extracted with acetone. Evaporation of the solvent gave a brown sirup. (1) II, III, and IV were obtained from the sirup prepared from the reaction of II → III, and were detected by gas chromatography (conditions: column, 1.5 m. × 6 mm. silicone 550 on Chromsorb.; temp., 200°; flow rate, hydrogen 100 ml./min.; retention times of the sugars: II, 13.25 min., III, 16.5 min., IV, 20.5 min.). (2) III and IV were obtained from the sirup prepared from the reactions of III → IV and IV → III, and were detected by gas chromatography.

The reaction of 0.1 g. of II, 0.038 g. of sulfuric acid, and 1.86 g. of dioxane was allowed to stand at 30°. The color of the solution changed from colorless to pink (after 30 min.) and then violet (after 1 hr.). After about 30 min., crystals started to form, which then polymerized to a black tarry product. After 1 hr., the reaction mixture was made alkaline, evaporated to dryness *in vacuo*, and extracted with chloroform. From the extract, II, III, and IV were detected by gas chromatography and, from the residue, I, II, III, and IV were detected by paper chromatography (*n*-BuOH–AcOH–H_2O, 4:1:5, ascending method). In order to reveal the position of the sugars, the paper was sprayed with 1 *N* hydrochloric acid, dried at room temperature, sprayed again with benzidine solution,[10] and heated at 90–95° for 5–10 min. The sugars appeared as brown spots. The R_f values were I, 0.25; II, 0.65; III, 0.88; IV, 0.68.

Acknowledgment.—The authors are deeply grateful to Dr. Ken'ichi Takeda, Director, and Dr. Kaname Hamamoto, assistant director of this laboratory, for encouragement and advice throughout this work.

(9) T. I. Temnikova and V. V. Sklyarava, *Zh. Prikl. Khim.*, **21**, 1131 (1954); *Chem. Abstr.*, **49**, 2952 (1955).

(10) R. H. Horrocks, *Nature*, **164**, 144 (1949).

Diacyl Peroxide–Olefin Reactions. Epoxidation of Tetramethylethylene by an Aroyl Peroxide[1]

FREDERICK D. GREENE AND WALDEMAR ADAM

Department of Chemistry, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Received August 19, 1963

Reaction of *m,m'*-dibromobenzoyl peroxide and tetramethylethylene in benzene at 45° affords tetramethylethylene oxide (72%), *m,m'*-dibromobenzoic anhydride (75%), *m*-bromobenzoic acid (13%), and a small amount of allylic *m*-bromobenzoates. Oxygen-18 labeling experiments show that the tetramethylethylene oxide oxygen is derived exclusively from the peroxygen bond of the peroxide. From kinetic evidence, utilizing the stable free-radical galvinoxyl, it is concluded that the reaction proceeds by direct reaction between olefin and peroxide; contributions from free-radical chain processes are negligible.

Reaction between *m,m'*-dibromobenzoyl peroxide and *p,p'*-dimethoxy-*trans*-stilbene has been shown to afford a mixture of *meso*- and *d,l*-dihydroanisoin bis-*m*-bromobenzoates.[2] The reaction occurs principally *via* a nonchain, bimolecular reaction between peroxide and olefin. In this paper, evidence is presented for a direct reaction between this diacyl peroxide and a purely aliphatic olefin, tetramethylethylene, in which, in marked contrast to the cited case, the major course of the reaction is single oxygen atom transfer from peroxide to olefin.

Results

Products.—Tetramethylethylene and *m,m'*-dibromobenzoyl peroxide undergo a moderate reaction at 45° in benzene to give tetramethylethylene oxide (72%), *m,m'*-dibromobenzoic anhydride (75%), *m*-bromobenzoic acid (13%), and a neutral oil, assigned the composition of a mixture of the allylic esters, 2,3-dimethyl-but-3-ene-2-yl *m*-bromobenzoate and 2,3-dimethyl-but-2-ene-1-yl *m*-bromobenzoate on the basis of the spectroscopic, hydrolytic, and hydrogenolysis data given in the Experimental section.

Kinetics.—Rate studies were conducted in benzene in the absence of oxygen. By use of olefin in excess, the rate of the peroxide–olefin reaction exceeded the rate of unimolecular decomposition of peroxide by more than 100-fold. The kinetic data are summarized in Table I.

TABLE I

REACTION OF *m,m'*-DIBROMOBENZOYL PEROXIDE (P) WITH TETRAMETHYLETHYLENE (TME) IN BENZENE AT 44.8°

Run no.	Reactants, $M \times 10^2$ P	TME	G[c]	$k_1 \times 10^5$ M^{-1} sec.$^{-1}$ P[b]	$k_1 \times 10^5$ sec.$^{-1}$ G[a,c]
1	1.00	0	0	*d*	
2	1.00	0	0.095	*e*	
3	0	100	0.95		23.2
4	5.00	111	0	4.71	
5	5.00	97	0	4.70	
6	5.00	47	0	4.72	
7	5.00	100	0.95	5.13	24.0
8	5.00	112	0.90	4.83	
9	5.00	100	0	1.0[f]	
10	5.00	100	0	9.1[g]	

[a] Galvinoxyl, see ref. 2 and 3. [b] Titrimetric. [c] Spectroscopic. [d] k_1 for peroxide decomposition = 1.84 × 10^{-7} sec.$^{-1}$. [e] k_1 = 1.98 × 10^{-7} sec.$^{-1}$. [f] At 30.3°. [g] At 54.8°.

(1) This work was supported by the research program of the Atomic Energy Commission under Contract No. AT-(30-1)-905. Reproduction is permitted for any purpose of the United States Government.

(2) F. D. Greene, W. Adam, and J. E. Cantrill, *J. Am. Chem. Soc.*, **83**, 3461 (1961).

TABLE II

DISTRIBUTION OF OXYGEN-18 FROM THE REACTION OF *m,m'*-DIBROMOBENZOYL PEROXIDE-*carbonyl*-O^{18} WITH TETRAMETHYLETHYLENE

Compound	Atom % excess O^{18} per molecule Expt. A	Expt. B
Tetramethylethylene oxide	0.00	0.00
m,m'-Dibromobenzoic anhydride	1.596	1.602
m-Bromobenzamide[a]	0.501	0.537
m-Bromobenzoic acid[a]	1.100	1.069
m-Bromobenzoic acid	0.31[b,c]	
m-Bromobenzoic anhydride	0.47[b,c]	

[a] From ammonolysis of anhydride (ref. 5). [b] From equilibration experiment of unlabeled anhydride with *m*-bromobenzoic acid of 1.81 atom % excess O^{18}. [c] Ratio of O^{18} between acid and anhydride observed, 0.66; calcd. for complete equilibration, 0.67.

Although the principal products of the reaction—epoxide and anhydride—are suggestive of a direct reaction rather than a chain reaction, it was desired to ascertain whether chain reaction was of any importance here. In the case of *m,m'*-dibromobenzoyl peroxide and *p,p'*-dimethoxy-*trans*-stilbene, experiments employing the hindered phenoxyl radical galvinoxyl[2,3] indicated that the major course of that peroxide–olefin reaction proceeded by direct reaction, on which was superimposed a radical chain reaction of short chain length. The suitability of galvinoxyl for that study originated in the inertness of galvinoxyl towards the reactants, a condition that does not extend to tetramethylethylene. In spite of the concomitant reaction of galvinoxyl with tetramethylethylene,[4] the kinetic data for this peroxide–olefin reaction in the presence of galvinoxyl are informative on the nature of the reaction. In the presence of all three components (peroxide, olefin in large excess, and galvinoxyl), galvinoxyl exerts only a small effect (a small increase, see Table II of ref. 2) on the rate of disappearance of peroxide; the rate of disappearance of galvinoxyl in the presence of both tetramethylethylene and the peroxide is essentially the same as in the presence of olefin alone. (For runs 7 and 3, in 30 min. the extent of consumption of galvinoxyl was 35.4% and 35.5%, respectively. The extent of destruction of peroxide in run 7 in 30 min. was 8.84%; the extent of unimolecular decomposition of peroxide in 30 min. under the conditions of run 7 is calculated to be 0.034%.) Thus, in the presence of excess olefin, the galvinoxyl–olefin and peroxide–olefin reactions appear to proceed independently of each other. Since ample galvinoxyl was present in the reaction mixture, one concludes that the reaction of the peroxide with tetramethylethylene does not provide scavengeable radicals, thereby excluding radical chain mechanisms from consideration for the peroxide–olefin reaction. Further refinement of mechanism was sought in studies employing oxygen-18. Oxygen-18 data for the reaction of *m,m'*-dibromobenzoyl peroxide-*carbonyl*-O^{18} with tetramethyl ethylene (Table II) show that the oxygen in the tetramethylethylene oxide is derived exclusively from oxygen of the peroxygen bridge of the peroxide. The distribution of oxygen-18 in anhydride was determined by cleavage to amide and acid under conditions that have been shown not to effect equilibration of the oxygen atoms during the ammonolysis.[5] The ratio of oxygen-18 in acid to amide is 2.2, 2.0, close to the value calculated for complete equilibration (O^{18}-acid/O^{18}-amide: 2.0). Such equilibration might occur under the conditions of the experiment by interchange of anhydride with the small amount of *m*-bromobenzoic acid produced by the peroxide–olefin reaction. In a control experiment (Table II, last two entries) complete equilibration *did* occur between acid labeled with oxygen-18 and the anhydride in 30 min. at 80° in benzene. (The acid was not sufficiently soluble to duplicate the actual peroxide–olefin reaction conditions of 45°, 6 hr.)

Discussion

It is of interest to compare the results of this system with those in several closely related reactions of peroxygen compounds from the following standpoints: (1) product composition, (2) point of attack of the nucleophile on diacyl peroxides, and (3) relative reactivity.

Product Composition.—With the aliphatic olefin, tetramethylethylene, the major products from reaction with the acyclic peroxide (*m,m'*-dibromobenzoyl peroxide) are derived from single oxygen transfer leading to epoxide and anhydride. Involvement of allylic hydrogens (formation of unsaturated ester plus acid) occurs but is of minor importance. In the reaction of the cyclic peroxide (phthaloyl peroxide) over-all involvement of allylic hydrogens is of major importance; the principal products are allylic monoesters of phthalic acid.[6] Towards diarylethylenes both the acyclic peroxide (*m,m'*-dibromobenzoyl peroxide) and the cyclic peroxide (phthaloyl peroxide) behave similarly in that the major products are 1:1 adducts. The acyclic peroxide affords a 2:1 mixture of *d,l*- and *meso*-dihydroanisoin bis-*m*-bromobenzoate[2]; phthaloyl peroxide affords a mixture of diester and lactone ortho ester of dihydroanisoin.[7] (In the reaction of phthaloyl peroxide with *cis*- and *trans*-stilbene the stereochemistry was shown to be that of *cis* addition.[8])

The principal example of single oxygen transfer in other types of peroxygen compounds is the reaction of peracids with olefins. This type of process also has been observed as a minor pathway in the reaction of phthaloyl peroxide with olefins.[6a]

Point of Nucleophilic Attack.—For the diacyl peroxide–tetramethylethylene reaction of this study, the oxygen-18 data establish that the oxygen transferred originates from the peroxygen link. Whether the oxygen transfer occurs by a cyclic process (eq. 1), analogous to that suggested for the epoxidation of olefins by peracids,[9] or by ion-pair paths[10] cannot be said, since the facile interchange between anhydride and

(3) G. M. Coppinger, *J. Am. Chem. Soc.*, **79**, 501 (1957).

(4) From a product study of the galvinoxyl–tetramethylethylene reaction, hydrogalvinoxyl was isolated in low yield. No other discrete product was obtained from the residual tar.

(5) (a) M. A. Greenbaum, D. B. Denney, and A. K. Hoffmann, *J. Am. Chem. Soc.*, **78**, 2563 (1956); (b) D. B. Denney and M. A. Greenbaum, *ibid.*, **79**, 979 (1957); **79**, 3701 (1957).

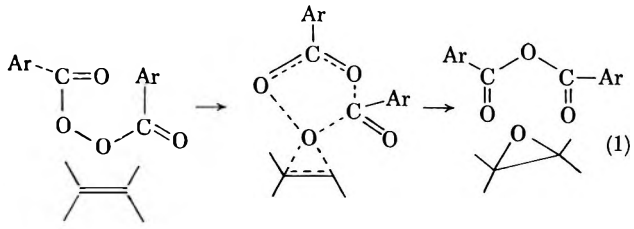
(6) (a) F. D. Greene and W. W. Rees, *ibid.*, **80**, 3432 (1958); (b) **82**, 890 (1960).

(7) Unpublished results of these laboratories.

(8) F. D. Greene *J. Am. Chem. Soc.*, **78**, 2250 (1956).

(9) P. D. Barlett, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **11**, 47 (1950).

(10) M. A. Greenbaum, D. B. Denney, and A. K. Hoffmann, *J. Am. Chem. Soc.*, **78**, 2563 (1956).



(1)

acid (which is formed as a side product) effaces the oxygen-18 distinction between oxygen atom transfer by these two paths.

The preferential attack of a nucleophile on a peroxygen atom of a diacyl peroxide, demonstrated in this work for the peroxide–olefin reaction, previously has been established for the reaction of aroyl peroxides with triphenylphosphine[10] (forming anhydride and triphenylphosphine oxide) and with tributylphosphine,[6b,11] for the reaction of benzoyl peroxide with the α-ethoxyethyl radical[12] (forming α-ethoxyethyl benzoate), with the triphenylmethyl radical[13] (forming triphenylmethyl benzoate), and with dibenzylamine[14] (forming N,N-dibenzylhydroxylamine benzoate). This pattern may also obtain in the reaction of sodio acetoacetate with benzoyl peroxide.[15]

Relative Reactivity.—A number of comparisons on the effect of variation in olefin structure on rate of reaction with peroxygen compounds in the series, perbenzoic acid, phthaloyl peroxide, and *m,m'*-dibromobenzoyl peroxide[16] are summarized in Table III. Towards all three of these peroxygen compounds, electron-donating groups on the olefin enhance the rate of reaction.[17] Two features of note in this table are (1) the enhanced reactivity of peracid towards the aliphatic olefins, and (2) the enhanced reactivity of phthaloyl peroxide and *m,m'*-dibromobenzoyl peroxide towards *trans-p,p'*-dimethoxystilbene (associated in part, with a greater sensitivity to electron-donating substituents for the reaction of the stilbenes with these peroxygen compounds *vs.* reaction with the peracid).

TABLE III

RELATIVE REACTIVITY OF PEROXYGEN COMPOUNDS TOWARD OLEFINS IN BENZENE AT 30° ($k_2 \times 10^3$, M^{-1} SEC.$^{-1}$)

Olefin	Perbenzoic acid	Phthaloyl peroxide	*m,m'*-Dibromobenzoyl peroxide
Tetramethylethylene	3000[a]	20[b]	0.01[c]
Cyclohexene	31[d]	0.2[b]	<0.0001[c]
trans-4,4'-Dimethoxystilbene	12.8[e]	1700[f]	0.23[g]
trans-4-Methoxystilbene	3.14[e]	30[b]	0.007[g]
trans-Stilbene	0.66[e]	0.6[b]	

[a] Estimated from the data cited in ref. 17. [b] Estimated from the data of ref. 6a. [c] An upper limit for k_2. The rate constant for unimolecular decomposition of peroxide under these conditions is estimated to be 4×10^{-8} sec.$^{-1}$ These data indicate little enhancement by cyclohexene on the rate of decomposition of this peroxide. [d] Ref. 17. [e] Ref. 18. [f] Ref. 7. [g] Estimated from the data of ref. 2.

For peracid epoxidations, from the known dependence of rate on olefin and on peracid structure,[17,18] one may estimate the rate of epoxidation of tetramethylethylene by *m*-bromoperbenzoic acid in benzene at 30° to have a k_2 of 11 M^{-1} sec.$^{-1}$. Thus, although both *m,m'*-dibromobenzoyl peroxide and *m*-bromoperbenzoic acid hand over a single oxygen atom to tetramethylethylene the latter is a million times more effective than the former.

Experimental

Oxygen-18 analyses were performed by Dr. Josef Nemeth, University of Illinois. The oxygen-18 data are summarized in Table II and were calculated by the equations of Miller and Anderson.[19]

***m,m'*-Dibromobenzoic anhydride** was prepared by the action of water on the acid chloride in pyridine. Several recrystallizations from hexane afforded material of m.p. 98–99°.

Anal. Calcd. for $C_{14}H_8Br_2O_3$: C, 43.80; H, 2.10; Br, 41.62. Found: C, 43.99; H, 2.19; Br, 41.86.

Tetramethylethylene oxide was prepared by the action of ethereal perbenzoic acid on tetramethylethylene (b.p. 73°) and collected from a g.l.p.c. 550 silicone column, b.p. 93° (lit. b.p. 93°); infrared in carbon tetrachloride, 3000 (s), 2980 (s), 1468 (m), 1372 (s), 1202 (s), 1168 (s), 1137 (s), 895 (w), 840 (s) cm.$^{-1}$; n.m.r. in deuteriochloroform, single band at 8.78 τ.

***m,m'*-Dibromobenzoyl Peroxide-*carbonyl*-O^{18}.**—To a solution of sodium peroxide in 38 ml. of water, cooled to 0°, was added a solution of 6.55 g. (0.03 mole) of *m*-bromobenzoyl chloride-O^{18} (prepared from the acid by the action of thionyl chloride) in 10 ml. of cyclohexane within 10 min., keeping the temperature of the reaction mixture below 5°. After 30 min. of additional stirring, the reaction mixture was filtered on a sintered glass funnel and washed well with water. The peroxide was dissolved in chloroform and precipitated by addition of several volumes of methanol. Repeated crystallization afforded 4.18 g. (0.0105 mole), m.p. 125.5–126°, of *m,m'*-dibromobenzoyl peroxide-*carbonyl*-O^{18} better than 99% pure, by iodometric titration.

Reaction of *m,m'*-Dibromobenzoyl Peroxide with Tetramethylethylene.—To a dry, constricted test tube was added 2.0 g. (0.005 mole) of *m,m'*-dibromobenzoyl peroxide and 5 ml. of tetramethylethylene. The tube was degassed on the vacuum line and sealed under reduced pressure. It was heated at 80° for 10 min. to dissolve the peroxide and then placed in a constant temperature bath at 44.8° for 6 hr. After removal from the bath the tube was centrifuged. The supernatant liquid was removed from the white precipitate by means of a dropper. To the solid, 2 ml. of tetramethylethylene was added, and the test tube was centrifuged again. The tetramethylethylene and the liquid reaction product were combined.

A. Tetramethylethylene Oxide.—The combined tetramethylethylene wash and liquid reaction products were distilled at aspirator pressure, trapping the volatile reaction products in a Dry Ice–acetone-cooled container. The volatile reaction products, 4.55 g., were analyzed on a 550 silicon oil column at 60.5°. In addition to unchanged tetramethylethylene, a new peak was present in the chromatogram. The compound was collected and identified as tetramethylethylene oxide by identity of the infrared spectrum and retention time on the column with the authentic substance. Quantitative study by means of v.p.c. showed that the solution was 7.9% tetramethylethylene oxide (72% yield based on initial moles of benzoyl peroxide).

B. *m*-Bromobenzoic Acid.—The solid reaction product obtained from the centrifugation of the reaction mixture and the residue from the distillation experiment were dissolved in ether and separately extracted with 5% aqueous sodium bicarbonate. The basic extracts were neutralized with hydrochloric acid, extracted with methylene chloride, and dried over anhydrous magnesium sulfate. After filtration and removal of the solvent at reduced pressure, a total of 0.259 g. (13% yield based on initial moles of peroxide), m.p. 156–157°, of *m*-bromobenzoic acid was

(11) The reaction of this phosphine with *t*-butyl perbenzoate also has been studied: D. B. Denney, W. F. Goodyear, and B. Goldstein, *J. Am. Chem. Soc.*, **82**, 1726 (1961).

(12) D. B. Denney and G. Feig, *ibid.*, **81**, 5322 (1959); J. C. Martin and E. H. Drew, *Chem. Ind.* (London), 929 (1959).

(13) W. von E. Doering, K. Okamoto, and H. Krauch, *J. Am. Chem. Soc.*, **82**, 3579 (1960).

(14) D. B. Denney and D. Z. Denney, *ibid.*, **82**, 1389 (1960); also see R. Huisgen and F. Bayerle u. *Ann.*, **630**, 138 (1960).

(15) S. O. Lawesson and C. Berglund, *Acta Chem. Scand.*, **13**, 1716 (1959).

(16) For leading references, see ref. 2 and 6a.

(17) D. Swern, *J. Am. Chem. Soc.*, **69**, 1692 (1947).

(18) B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955).

(19) W. G. Miller and L. Anderson, *Anal. Chem.*, **31**, 1668 (1959).

isolated. The identity of the acid was shown by mixture melting points with the authentic *m*-bromobenzoic acid.

C. *m,m'*-Dibromobenzoic Anhydride.—The neutral ether solution, from which the *m*-bromobenzoic acid was extracted was dried over anhydrous magnesium sulfate. After filtration, and removal of the solvent at reduced pressure, 1.8 g. of a white residue was obtained. Fractional recrystallization from *n*-hexane afforded 1.35 g. (70% yield based on initial moles of peroxide), m.p. 90–94°, of a crystalline precipitate. An infrared spectrum in carbon tetrachloride was virtually identical with *m,m'*-dibromobenzoic anhydride. The anhydride was purified by recrystallization from *n*-hexane, m.p. 98–99°, m.m.p. 98–99°.

The solvent was evaporated from the mother liquor and the residue was recrystallized until the final mother liquor showed no anhydride absorption (1790 and 1720 cm.$^{-1}$) in the infrared spectrum. In this manner, another 0.1 g. (5% yield based on the initial moles of peroxide), m.p. 89–96°, of *m,m'*-dibromobenzoic anhydride was obtained. The total anhydride yield thus was 75%.

D. Characterization of the Residual Oil.—The mother liquor, after removal of all *m*-bromobenzoic anhydride and evaporation of the solvent consisted of a yellowish, sweet-smelling oil. An infrared spectrum of this oil in carbon tetrachloride showed ester absorption at 1720 (s), *gem*-dimethyl group absorption at 1380 and 1365 (m), and terminal methylene absorption at 900 cm.$^{-1}$ (m).

1. Saponification of the Residual Oil with Potassium Hydroxide.—To a solution of 10 ml. of 10% aqueous potassium hydroxide was added 0.200 g. of the residual oil. Under a nitrogen atmosphere, the reaction mixture was heated at reflux for 10 hr. The reaction mixture was cooled and extracted with methylene chloride. The methylene chloride solution was dried over anhydrous magnesium sulfate. An infrared spectrum of the neutral extract in chloroform indicated that all the ester was saponified (no absorption at 1720 cm.$^{-1}$). No well defined material could be isolated from the neutral extract.

The basic aqueous solution was acidified, and the precipitate was collected and dried over phosphorus pentoxide at high vacuum to yield 0.120 g. of *m*-bromobenzoic acid, m.p. 156–158°.

2. Hydrogenation of the Residual Oil.—To a solution of 0.179 g. of the residual oil in 3 ml. of freshly distilled tetrahydrofuran was added 0.018 g. of platinum oxide. A total of 20 ml. (STP) of hydrogen was taken up. The reaction mixture was filtered and the solvent removed at reduced pressure. The residue was dissolved in ether and extracted with 5% aqueous sodium bicarbonate. The basic aqueous extract was acidified and filtered. The precipitate, after drying over phosphorus pentoxide at high vacuum, was 0.035 g. of *m*-bromobenzoic acid, m.p. 154–157°, m.m.p. 154–156°. The neutral ether solution was dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent, an infrared spectrum in carbon tetrachloride of the residue indicated ester absorption at 1720 (s) and *gem*-dimethyl group absorption at 1380 and 1365 cm.$^{-1}$ (m).

Reaction of *m,m'*-Dibromobenzoic Anhydride-O^{18} with Ammonia.—The *m,m'*-dibromobenzoic anhydride was obtained by allowing *m,m'*-dibromobenzoyl peroxide-*carbonyl*-O^{18} to react with tetramethylethylene under the conditions of the previous product study. The anhydride was rigorously purified by fractional crystallization from *n*-hexane until a melting point of 98–99° was obtained. A 96-mg. sample of the *m,m'*-dibromobenzoic anhydride-O^{18} was ammonolyzed in 20 ml. of ammonia at −33° and the acid and amide were worked up by the published procedure.[5] The *m*-bromobenzamide was recrystallized from an ether–pentane mixture affording 28 mg., m.p. 153–155°. Recrystallization of the amide from methanol–water afforded 23 mg., m.p. 153–155°.

The basic aqueous solution was acidified with hydrochloric acid and the precipitate collected. Recrystallization from *n*-hexane gave 0.046 g., m.p. 154–156°, of *m*-bromobenzoic acid. Repeated crystallization from *n*-hexane raised the melting point to 155–157°. Recrystallization from a methanol–water mixture afforded 0.028 g., m.p. 155–157°, of acid. The *m*-bromobenzamide and *m*-bromobenzoic acid were dried over phosphorus pentoxide at high vacuum for 3 days prior to analysis for oxygen-18. (A mixture melting point of amide and acid was 120–130°.)

Exchange Reaction of *m*-Bromobenzoic Acid-O^{18} with *m,m'*-Dibromobenzoic Anhydride.—The *m,m'*-dibromobenzoic anhydride (0.72 g. or 1.88 mmoles) and *m*-bromobenzoic acid (0.13 g. or 0.65 mmole) were added to 2.5 ml. tetramethylethylene (concentration at which the reaction of labeled *m,m'*-dibromobenzoyl peroxide with tetramethylethylene was studied). After degassing the tube was sealed and heated at 80° for 45 min. On cooling, a precipitate formed; 15 ml. of ether was added and the resulting solution was extracted with cold aqueous sodium bicarbonate solution (a control experiment established that washing with cold aqueous sodium bicarbonate does not effect the hydrolysis of *m,m'*-dibromobenzoic anhydride in ether). The basic extracts were washed with ether and then neutralized with hydrochloric acid. Several recrystallizations from hexane and a mixture of methanol–water afforded acid of m.p. 155–156°.

Galvinoxyl was prepared and purified by the method described previously.[2]

Kinetics.—The procedure described previously[2] was employed. A representative run is reported in Table IV.

TABLE IV

REACTION OF *m,m'*-DIBROMOBENZOYL PEROXIDE[a] WITH TETRAMETHYLETHYLENE[b] IN THE PRESENCE OF GALVINOXYL[c] AT 44.8° IN BENZENE

Time (sec. × 10^{-4})	$S_2O_3^{-2}$,[d] ml.	O.D.$_t$ (λ, 434 mμ)	$k_1 \times 10^5$ sec.$^{-1}$[e]
0.0	10.43	0.236	
1.8	9.45	0.186	5.38
3.6	8.65	0.142	5.18
5.4	7.84	0.102	5.30
7.2	7.07	0.076	5.40
9.0	6.45	0.076	5.35
10.8	5.85	0.044	5.35
14.4	4.75	0.035	5.45
18.0	4.00	0.033	5.31
21.6	3.25	0.032	5.40

[a] 0.05 *M* initial concentration. [b] 1.12 *M* initial concentration. [c] 0.00190 *M* initial concentration. [d] Corrected for galvinoxyl titer. [e] $k_1 = 5.35 \pm 0.0535 \times 10^{-5}$ sec.$^{-1}$, $k_1 = 4.78 \times 10^{-5}$ M^{-1} sec.$^{-1}$, % average deviation = 1.00%.

The Liquid Phase Oxidation of the Lower Olefins[1]

WILLIAM F. BRILL AND BRUNO J. BARONE

Petro-Tex Chemical Corporation, FMC Chemical Research and Development Center, Princeton, New Jersey

Received July 12, 1963

The nature of the epoxides, aldehydes, and ketones obtained as major products by the autoxidation of the lower olefins indicates that reaction at the double bond is the predominant primary process occurring in the oxidation of most olefins. The formation of different products from 1-butene and 2-butene, notably, is incompatible with oxidation by a mechanism emphasizing α-hydrogen abstraction. Reactivity may be estimated from structure using empirical rules. The dependency of oxidation rate on olefin concentration, in concentrated benzene solutions, is very strong.

Although the liquid phase autoxidation of many unsaturated compounds has been studied, the simple low molecular weight olefins, whose study should be uniquely able to contribute to the understanding of olefin oxidation, have been largely neglected. This paper reports the oxidation of olefins with five carbons or less. The effect of structure on the products and reactivity were studied in benzene or without solvent using oxygen above atmospheric pressure.

The formation of epoxide as the major product from propylene and butene and of glycol from isobutylene has been reported.[2] The catalytic oxidation of butenes in acetic acid[3] and the related oxidation of butenes in the dense vapor phase[4] yielded mostly glycol esters and acids. Since this work was completed a study of the kinetics and products for the oxidation of butene-1 has been described which stresses the importance of hydroperoxide as a primary product.[5]

Experimental

Olefins were Phillips's pure grade and were charged into the reactor from a weighing bomb. Benzene was purified by fractionation.

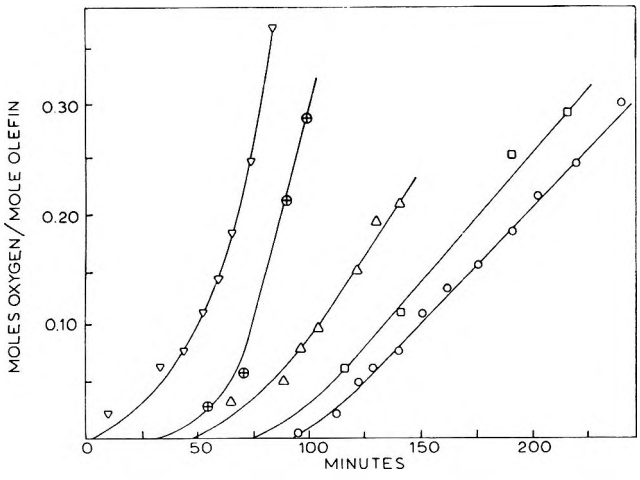


Fig. 1.—Oxygen absorption of olefins at 120°, 50 mole % in benzene: ▽, cis-2-butene; ⊕, 3-methyl-1-butene (displaced 25 min.); △, 1-butene (displaced 50 min.); □, isobutylene (displaced 75 min.); ○, propylene.

Oxidations were conducted in a 1.4-l. autoclave, 4.5 in. in diameter and 5.5 in. deep, equipped with cooling coils, a Teflon-coated liner, baffles, and a reflux condenser. A Magnedrive stirrer (Autoclave Engineers, Inc., Erie, Pa.) allowed magnetic stirring at 1000 r.p.m. The entire apparatus was well barricaded as occasional explosions occurred.

U.S.P. oxygen was fed from a 3-l. calibrated reservoir equipped with a 16-in. test gage to the reactor using a dome loaded regulator to maintain a constant set reaction pressure. An exit gas was maintained to monitor gaseous products and prevent their accumulation. The oxygen vented was measured with a wet test meter after trapping organic vapors and removing carbon dioxide. A complete material balance including gaseous reactants and products was obtained from each reaction.

The maximum rates were obtained from plots of oxygen absorbed against time. Typical absorption curves are shown in Fig. 1.

Major products were isolated by gas chromatography, by fractionation, or a combination of both. Identification utilized the infrared and mass spectra and retention times. Where the known epoxides were not available for comparison, as for the methylbutenes, the appropriate distillate or the crude oxidate was oxidized with periodic acid until the peak corresponding to the epoxide disappeared on gas chromatography and new peaks corresponding to the expected carbonyl products appeared. Hydroxy esters and diesters were prepared by reaction of carboxylic acids with the appropriate epoxide.

Product yields were calculated from gas chromatographic area analysis. Peak areas produced by injecting constant volume samples of known concentrations in benzene were used to confirm epoxide values. In some cases, the benzene solvent itself was used as an internal standard. Direct titration for epoxide with hydrogen bromide in acetic acid[6] gave values usually within 10% of those obtained by peak area analysis; except for propylene oxidation products where values were 30% lower (average from four different crude products). Propylene also showed a slight phase separation, analysis of both phases being required to calculate theoretical yields.

Results and Discussion

The relative reactivities of the olefins studied fall in an order which is generally consistent with the rules proposed by Bolland[7] for correlating structure with the rate of α-hydrogen abstraction in autoxidations. From a study of a series of olefins starting with hexenes, he concluded that replacement of hydrogens at either terminal carbon in propene by alkyl groups increases the rate of abstraction. Similar replacement at the middle carbon atom is without effect. The quantitative agreement of the measured and calculated rates (see Table I) appears much poorer than that obtained by Bolland. This may be due partly to the inapplicability of over-all rates which are influenced by differences in initiation. If it is considered that initiation primarily results from hydroperoxide decomposition,

(1) Reported in part at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., March, 1963.

(2) (a) J. Gardner and N. Robertson, U. S. Patent 2,780,635 (1957); (b) H. Shingu, U. S. Patent 2,985,668 (1961); (c) A. F. Millidge and W. Webster, U. S. Patent 2,741,623 (1956); (d) C. E. Schweitzer, U. S. Patent 2,644,837 (1953); (e) N. Robertson, *et al.*, U. S. Patent 2,780,654 (1957); (f) Y. Kaminya, *Kogyo Kagaku Zasshi*, **64**, 1513 (1961).

(3) W. F. Brill, unpublished work.

(4) J. C. Snyder and A. V. Grosse, Preprints of the Petroleum Division, National Meeting of the American Chemical Society, Houston, Tex., March, 1950, p. 271.

(5) A. Chauvel, G. Clement and J. C. Balaceanu, *Bull. soc. chim. France*, 1774 (1962).

(6) A. J. Durbetaki, *Anal. Chem.*, **28**, 2000 (1956).

(7) J. L. Bolland, *Trans. Faraday Soc.*, **46**, 358 (1950).

TABLE I

EFFECT OF STRUCTURE ON RELATIVE RATE

Olefin	Calcd.[a]	Observed[b]
C—C=C	0.5	<1
C		
C—C=C	1	1
C=C—C—C	1.6	1.2
C		
C=C—C—C	2.1	2.7
C—C=C—C	3.2	4.2
C		
C=C—C—C	5.4	2.9
C		
C—C=C—C	8.7	8.2

[a] Using Bolland's rules[7] for calculating "k_3." [b] From the maximum measured rate with 50 mole % olefin in benzene using $d(O_2)/dt = k_2(\text{olefin})^2$ with concentrations expressed in moles/kg.

the anomalous position of 3-methyl-1-butene, the only olefin possessing a tertiary hydrogen, appears to be related to the fact that it alone forms hydroperoxide as a major product. It is interesting that 2,4-dimethyl-2-pentene, the only olefin containing a tertiary hydrogen which has been fitted to Bolland's scheme, is reported to have anomalously low reactivity.[8]

The dependency of the observed maximum rate for a given olefin on the olefin concentration is very strong. With increasing benzene dilution the drop in rate is, in fact, so strong that at olefin concentrations most useful for kinetic treatment no reaction or an inconveniently slow reaction occurs. On the other hand, the more reactive olefins are oxidized so rapidly in the absence of solvent that the reaction temperature can not be adequately controlled. The effect of concentration is illustrated by the second-order oxidation rates for isobutylene shown in Table II. The only reasonably adequate empirical rate constants could be obtained by assuming third-order dependency after approximating molar concentrations.

The data in Table II also indicate that dependency on oxygen pressure does not appear until pressures as low as 200 p.s.i. are encountered. The magnitude of the effect of catalyst or initiator also is illustrated. The presence of stirred calcium oxide, a common condition in synthesizing epoxides from olefins by oxidation, has little effect on the rate.

TABLE II

OXIDATION OF ISOBUTYLENE AT 120°

Pressure,[a] p.s.i.	Catalyst[b]	Concn.,[c] moles/kg.	k_2[d] × 10^{-5}, kg. mole^{-1} sec.$^{-1}$
400 (35)		17.7	6.5
(210)		7.1	5.3
(291)		3.3	2.1
600 (485)		2.9	2.1
200 (78)		3.2	1.4
500 (399)	AIBN	3.1	6.3
600 (371)	CaO	2.9	1.2
400 (202)	CoA CaO	7.5	11.1
600 (493)	CoA	3.0	7.9
400 (196)	CoN MgO	7.8	5.0
300 (96)	CoN MgO	7.8	5.1
300 (118)	CoN MgO	6.7	5.3

[a] Gage pressure (estimated partial pressure of oxygen). [b] AIBN is azobisisobutyronitrile, 0.3 wt. %; CoA is cobaltic acetylacetonate, 0.16 wt. %; CoN is cobalt naphthenate, 0.16 wt. %; CaO and MgO, 5 wt. %. [c] In benzene. [d] From $d(O_2)/dt = k_2(\text{olefin})^2$.

Products.—As reported for the higher molecular weight olefins where the reaction products have been carefully examined,[9] oxidation of the liquid petroleum olefins produces epoxides with the oxirane ring at the position previously occupied by the double bond. Yields in some case may be better than 50% on olefin changed. Carbonyl compounds containing less carbon atoms than the original olefins also may be produced as major products, even though they are susceptible to further oxidation (Table III). It is particularly interesting that alcohol is not usually a significant product and that all the hydroxy compounds formed in more than a few per cent yield are glycols and hydroxy esters which can arise from the epoxide. Only for the single case of 3-methyl-1-butene where a tertiary hydroperoxide may be produced, is hydroperoxide the major product.

The order of increasing yield of epoxide for the various olefins appears to be the same as the order of increasing oxidizability, presumably indicating a common structural effect on epoxide formation and oxidation rate. However, the epoxide found at the conversion of these experiments may reflect their relative reactivity to addition, rearrangement, or oxidative cleavage.

For propylene oxide, the importance of ring opening was apparent from the amounts of glycol and glycol derivatives found in the oxidation of propylene. The amount of product arising from ring opening does not appear to be entirely related to the expected reactivity of the epoxide.[10] A more reasonable correlation can be made with the tendency of the olefin to yield formic acid which is far more reactive toward epoxides than other carboxylic acids. Propylene oxide was found to be stable to oxidation under conditions equivalent to those encountered in the oxidation of propylene. When propylene oxide was added to other olefins it survived the oxidation of the mixture. Other oxides have not yet been studied in this manner but recent reports of radical reactions of epoxides[11] indicate that other structures may be expected to be resistant to further oxidation.

The detailed product analysis for propylene, given in Table III, indicates that while approximately equal quantities of formic and acetic acid formed, most of the formic acid added to the epoxide. The formation of large amounts of methanol and methyl esters distinguishes the oxidation of propylene from that of other olefins. The presence of suspended base during the oxidation not only failed to improve epoxide yields but drastically diminished glycol and glycol derivatives. The initiator concentration and the use of catalyst was found to have little effect on the products formed.

Isobutylene gives acetone, which is unusually resistant to further oxidation, in yields which may be greater than 50%. Unlike propylene, epoxide yields,

(8) L. Bateman, *Quart. Rev.* (London), **8**, 147 (1954).

(9) E. G. E. Hawkins and D. C. Quin, *J. Appl. Chem.* (London), **6**, 1 (1956), and references therein.

(10) R. E. Parker and N. S. Issacs, *Chem. Rev.*, **59**, 737 (1959).

(11) (a) T. Wallace and R. J. Gritter, *J. Org. Chem.*, **26**, 282 (1962); (b) C. Walling and P. S. Fredricks, *J. Am. Chem. Soc.*, **84**, 3326 (1962).

TABLE III

OXIDATION PRODUCTS[a]

Olefin[b]	Propylene	Isobutylene	1-Butene	*cis*-2-Butene[c]	2-Methyl-1-butene	2-Methyl-2-butene
Catalyst[d]	DDM	CaO			MgO CoN	MgO CoN
Conversion, %	36.0	32.2	18.4	18.6	52.5	55.4
Epoxide	8.2	18.4	19.4	48.2[e]	32.6	49.2
Glycol	3.9	7.1				
Monoformate	10.7	1.2	3.9			
Diformate	5.2	6.6	1.7			
Monoacetate	2.3	0.8				
Methanol	26.8					
Methyl esters	8.0					
Acetaldehyde				34.5		
Acetone		41.7			6.0	34.8
Propionaldehyde			15.9			
Methyl ethyl ketone			10.1		30.9	
Crotonaldehyde			7.6	10.4		
Acrolein				6.9		
Biacetyl				4.6		
Formic acid	5.1					
Acetic acid	21.6	5.9	9.9	6.9		
Acrylic acid	3.7		3.6			
Propionic acid	0.2		12.5			
Butyric acid			1.5	2.5		

[a] Theoretical yield of products based on olefin reacted. [b] 3-Methyl-1-butene gave 44% hydroperoxide, 9% epoxide, 9% acetone, and 2.5% isobutyraldehyde at 30% conversion. [c] *trans*-2-Butene gave the same products as *cis*-2-butene. Yields were 30% *trans* epoxide, 9% *cis* epoxide, and 30% acetaldehyde at 33% conversion. No propionaldehyde was detected. [d] At 120°; 50 mole % olefin in benzene; DDM is 60% methyl ethyl ketone peroxide, 0.7 wt. %; CoN is cobalt naphthenate (6% cobalt), 0.2 wt. %; CoA is cobalt acetylacetonate, 0.2 wt. %; MgO is light magnesium oxide, 5.5 wt. %; CaO, 5.5 wt. %. [e] 19.5% *cis* epoxide and 28.7% *trans* epoxide.

and even glycol and glycol ester yields, are improved by oxidation of isobutylene in the presence of added base. Both the large amount of ester formed and extrapolation of yields back to zero conversion indicate that epoxide is actually formed as a primary product in yields above 30%. However at practical conversions, careful control of reaction conditions is necessary to obtain up to 20% epoxide.

A comparison of the products from 1-butene and *cis*- or *trans*-2-butene is particularly interesting since if the course of oxidation is determined by abstraction of α-hydrogen, the oxidation of both the α- and β-olefin would proceed through similar butenyl radicals.

$$CH_3\dot{C}HCH{=}CH_2 \leftrightarrow CH_3CH{=}CH{-}\dot{C}H_2$$

All products except those formed by direct attack on the double bond would therefore be the same from each olefin. As shown in Table III, the products found in significant quantities from each olefin are very different, crotonaldehyde and acetic acid being the only common products. The major products from 1-butene, other than epoxide, are propionaldehyde and propionic acid and methyl ethyl ketone while the major product from *cis*- or *trans*-2-butene is acetaldehyde. While oxidation of epoxide may partially account for these results, it does not seem likely that aldehydes be produced from epoxide by a radical oxidation. It is even more difficult to project a scheme for the formation of propionaldehyde from 1-butene by oxidation initiated at the α-hydrogen. Assuming reaction at the α-position without isomerization, the expected products, other than acetaldehyde, would be unsaturated. Similarly, the 2-butene would yield propionaldehyde or unsaturated products.

The product distributions from 2-methyl-1-butene and 2-methyl-2-butene are analogous to those from the corresponding unsubstituted butenes. The formation of methyl ethyl ketone from the α-olefin and acetone from the β-olefin as major products is incompatible with α-hydrogen abstraction with formation of the common 2-methyl butenyl radical. The radical $(CH_3)_2C{=}CH{-}\dot{C}H \leftrightarrow (CH_3)_2\dot{C}{-}CH{=}CH_2$ also can be formed from 2-methyl-2-butene. Statistically it can not account for more than one-third of the products formed by abstraction but it is a likely precursor for acetone.

Mechanism.—It has been shown that epoxides arise during the oxidation of 2,4,4-trimethyl-1-pentene and cyclohexene by free-radical attack on the double bond and not by secondary oxidation involving hydroperoxide.[12] The products from 2,4,4-trimethyl-1-pentene were explained by a mechanism in which two molecules of epoxide and one of ketone are formed by the sequence shown.

$$RCH{=}CHCH_2OO\cdot + RCH{=}CHCH_3 \longrightarrow \underset{\displaystyle RCH\overset{O}{\diagup\diagdown}CHCH_3}{} + RCH{=}CHCH_2O\cdot \quad (1)$$

$$RCH{=}CHCH_2O\cdot \longrightarrow RCH{=}CH\cdot + CH_2O \quad (2)$$

$$RCH_2CH\cdot + O_2 \longrightarrow RCH{=}CHOO\cdot \quad (3)$$

$$RCH{=}CHOO\cdot + RCH{=}CHCH_3 \longrightarrow \underset{\displaystyle RCH\overset{O}{\diagup\diagdown}CHCH_3}{} + RCH{=}CHO\cdot \quad (4)$$

The results reported in the present paper indicate that double bond oxidation is the more important process for all olefins which do not possess an extremely reactive hydrogen. However, the proposed mechanism does not explain the major carbonyl products observed with the butenes. Since it requires that products other than epoxide arise through a common allylic radical, the high yield of propionaldehyde from 1-butene and methyl ethyl ketone from 2-methyl-1-

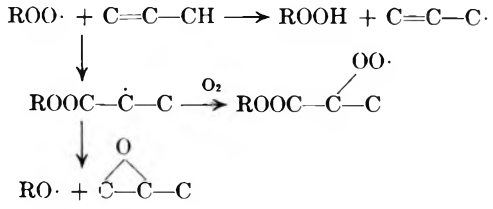
(12) W. F. Brill, *J. Am. Chem. Soc.*, **85**, 141 (1963).

butene remains to be explained. Unless it can be demonstrated that these products result from the oxidation of epoxide, an additional sequence will be necessary to explain completely all the products obtained from olefins. Copolymerization of olefin with oxygen, followed by cleavage of the polyperoxide formed to two molecules of aldehyde as suggested by Mayo to explain the oxidation of styrene to benzaldehyde and formaldehyde[13] may be appropriate.

$$RO\cdot + n CH_2{=}CHC_2H_5 + nO_2 \longrightarrow RO(CH_2CHOO)_n\cdot \longrightarrow RO\cdot + nCH_2O + nC_2H_5CHO$$

The relationship between the reaction sequences leading eventually to the production of allylic hydroperoxide, the epoxide corresponding to the olefin oxidized, and aldehydes by fission at the double bond is illustrated.

If it is accepted that three reaction pathways, all of which are probably available for most olefins, are required to explain oxidation products, the effect of structure on reactivity becomes difficult to interpret in terms of α-hydrogen–carbon bond strengths as has been done.[7] However, as alkyl substitution α to a double bond may be expected to favor the electrophilic addition of oxygen radicals,[14] as well as α-hydrogen abstraction, the observed effect of structure on reactivity is still appropriate.



Acknowledgment.—The authors wish to acknowledge the assistance of Mr. John O'Neill, Jr. The encouragement of Dr. L. Marshall Welch and Dr. Louis J. Croce is especially appreciated.

(13) F. R. Mayo, *J. Am. Chem. Soc.*, **80**, 2465 (1958).

(14) R. J. Cvetanovic, *Can. J. Chem.*, **38**, 1678 (1960).

Chemistry of Isocyanic Acid. III. Reaction of Isocyanic Acid with Olefins

F. W. HOOVER AND H. S. ROTHROCK

Contribution No. 890 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington 98, Delaware

Received June 17, 1963

The synthesis of isocyanates has been effected by the addition of isocyanic acid to *m*- and *p*-diisopropenylbenzenes, isoprene, styrene, α-methylstyrene, and other olefins. Several of the isocyanates obtained are new.

Organic isocyanates have been prepared by such routes as phosgenation of amines, decomposition of acid azides, dehydration of hydroxamic acids, reaction of inorganic cyanates with esters of inorganic acids, and thermal decomposition of ureas.[1]

In previous papers in this series, the preparation of isocyanates by the reaction of isocyanic acid with carbonyl compounds[2] and with α,β-unsaturated ethers[3] was described. We now report the synthesis of isocyanates by the addition of isocyanic acid to certain olefins as illustrated.

$$C_6H_5C(CH_3){=}CH_2 + HNCO \xrightarrow{H^+} C_6H_5C(CH_3)_2NCO$$

In Table I are listed some of the olefins studied and the isocyanates obtained.

In addition to the products described in Table I, isocyanates were obtained in low yields from divinylbenzene, dicyclopentadiene, vinylacetylene, 1-methyl-3-methylene-1-phenylcyclobutane, 1-methylcyclohexene, 2,3-dimethyl-1,3-butadiene, and *p*-methoxy-α-methylstyrene. In general, the most reactive olefins were those having terminal double bonds with at least one electron-releasing group, such as methyl or phenyl, on the 2-carbon. Isopropenylbenzenes were considerably more reactive than the other olefins studied.

TABLE I

ISOCYANATES FROM OLEFINS AND ISOCYANIC ACID

Olefin	Isocyanate	Yield,[a] %
$C_6H_5C(CH_3){=}CH_2$	$C_6H_5C(CH_3)_2NCO$	41
$C_6H_5CH{=}CH_2$	D,L-$C_6H_5CH(CH_3)NCO$	5
$C_6H_4(C(CH_3){=}CH_2)_2$ (*m*)	$CH_2{=}C(CH_3)C_6H_4C(CH_3)_2NCO$ (*m*)	30
	and	
	$OCNC(CH_3)_2C_6H_4C(CH_3)_2NCO$ (*m*)	35
$C_6H_4(C(CH_3){=}CH_2)_2$ (*p*)	$CH_2{=}C(CH_3)C_6H_4C(CH_3)_2NCO$ (*p*)	9
	and	
	$OCNC(CH_3)_2C_6H_4C(CH_3)_2NCO$ (*p*)	16
$CH_2{=}CHC(CH_3){=}CH_2$	$CH_2{=}CHC(CH_3)_2NCO$	3
$(CH_3)_2C{=}CH_2$	$(CH_3)_3CNCO$	10

[a] Based on the amount of olefin charged.

The reaction of isocyanic acid with isoprene gave α,α-dimethylallyl isocyanate (II) in low yield. An alternative route to II was found in the reaction of silver cyanate with γ,γ-dimethylallyl chloride (I). This reaction also gave the isomer (III) in about an equal amount. Interestingly, treatment of α,α-dimethylallyl chloride (IV) with silver cyanate gave mainly III with only a small amount of II.

$$(CH_3)_2C{=}CHCH_2Cl \xrightarrow{AgOCN} \underset{\text{I}}{} CH_2{=}CHC(CH_3)_2NCO + (CH_3)_2C{=}CHCH_2NCO$$
$$\text{II} \qquad\qquad \text{III}$$

$$CH_2{=}CHC(CH_3)_2Cl \xrightarrow{AgOCN} \text{III (main product)} + \text{II}$$
$$\text{IV}$$

The addition of isocyanic acid to olefins has been effected under autogenous pressure at 100–110° in a

(1) R. Arnold, J. Nelson, and J. Verblanc, *Chem. Rev.*, **57**, 47 (1957).

(2) F. W. Hoover, H. B. Stevenson, and H. S. Rothrock, *J. Org. Chem.*, **28**, 1825 (1963).

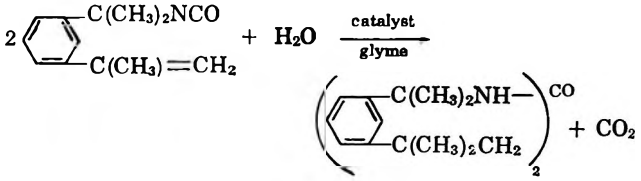
(3) F. W. Hoover and H. S. Rothrock, *ibid.*, **28**, 2082 (1963).

solvent. The reaction is strongly promoted by cationic catalysts, for example, *p*-toluenesulfonic acid, hydrogen chloride, and salts of strong acid with weak bases (*e.g.*, ammonium tosylate and octylammonium 2,2,2-trifluoroethylsulfonate). Trimerization of the isocyanic acid and polymerization of the olefin are competitive reactions, and the type of solvent used affects the extent of these reactions. Aromatic solvents have given the best yields of isocyanates. Basic solvents, such as tetrahydrofuran and diethyl ether, help to stabilize isocyanic acid against trimerization but reduce the rate of addition of HNCO to the double bond. Other polar solvents, such as acetonitrile and nitrobenzene, enhance olefin polymerization and give lower yields of isocyanate.

The addition of isocyanic acid to olefins apparently proceeds by a carbonium-ion mechanism, judged by the nature of the effective catalysts, the types of operable olefins, and the structure of isocyanates obtained.

$\alpha,\alpha,\alpha',\alpha'$-Tetramethyl-*m*-xylylene diisocyanate formed polymers with diamines and with glycols. The aliphatic diamines reacted very rapidly with this isocyanate, whereas 2,4-toluenediamine and other weakly basic amines reacted relatively slowly. Reactions with glycols were slow at room temperature but were quite rapid at 80° when catalyzed with stannous octoate.

m-Isopropenyl-α,α-dimethylbenzyl isocyanate, $\alpha,\alpha,\alpha',\alpha'$-tetramethyl-*m*-xylylene diisocyanate, and other tertiary isocyanates react slowly with water unless a mutual solvent and catalysts, such as tetraethylammonium cyanide and benzyltrimethylammonium hydroxide, are employed. However, under suitable conditions, a fairly rapid reaction with water can be effected to give the corresponding urea.



Experimental[4]

$\alpha,\alpha,\alpha',\alpha'$-Tetramethyl-*m*-xylylene Diisocyanate and *m*-Isopropenyl-α,α-dimethylbenzyl Isocyanate.—A mixture of 320 g. of *m*-diisopropenylbenzene (obtained from Hercules Powder Company), 860 g. of isocyanic acid,[2] 3000 ml. of toluene, and 14 g. of ammonium tosylate was heated in a 1-gal. (working capacity) stainless steel autoclave equipped with a three-blade, propeller type, motor-driven stirrer for 2 hr. at 100°. The cyanuric acid (710 g.) formed was removed by filtration. Simple distillation of the filtrate gave 319 g. of a mixture of isocyanates, b.p. 92° (0.5 mm.) to 110° (1 mm.). There also was obtained 70 g. of a viscous residue. The infrared spectrum of the residue showed strong absorption at 4.4 μ (NCO).

The mixture of isocyanates was redistilled through an 18-in. Nester spinning-band column[5] (about 15 plates) having an inside diameter of 10 mm. There was obtained 103 g. of monoisocyanate, b.p. 83–85° (0.9 mm.), 23 g. of a mixture of 73% monoisocyanate and 23% diisocyanate, b.p. 85–100° (0.9 mm.), and 167 g. of diisocyanate, b.p. 100–106° (mainly 106°) at 0.9 mm. The yields of the mono- and diisocyanates (based on *m*-diisopropenylbenzene) were 30 and 35%, respectively.

Anal. Calcd. for $C_{13}H_{15}NO$ (monoisocyanate): C, 77.57; H, 7.51; N, 6.96. Found: C, 77.20; H, 6.97; N, 7.22.

The infrared spectrum showed absorption at 3.25 μ (=CH–); 3.35 and 3.4 (saturated CH); 4.44 (–NCO); 6.15 (C=C); 6.25, 6.34, and 6.73 (aromatic C=C); 7.21, 7.32, and 7.33 [$(CH_3)_2C$]; and 12.52 (*meta* disubstitution).

The proton n.m.r. spectrum showed absorption at 1.57 p.p.m. ($C(CH_3)_2$), 2.08 (CH_3C=C), 5.05 (C=CH split, probably *cis* to CH_3), 5.37 (C=CH, probably *trans* to the CH_3 group), 7.23 (aromatic), and 7.56 (aromatic) in the ratio of 6:3:1:1:3:1, respectively.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$ (diisocyanate): C, 68.83; H, 6.60; N, 11.46. Found: C, 69.14; H, 6.66; N, 11.55.

The infrared absorption spectrum showed absorption at 3.27 μ (=CH); 3.35, 3.4, and 3.46 (saturated CH); strong 4.45 (–NCO); 6.23, 6.3, and 6.72 (aromatic C=C); 7.21 and 7.32 [$>C(CH_3)_2$]; and 12.57 (*meta* disubstitution).

The proton n.m.r. spectrum showed hydrogens at 1.66 p.p.m., 7.42, and 7.75 in the ratio of 12:3:1, respectively.

The purity of these products was determined by gas chromatographic analysis with a 1-m. column packed with 10% squalene on 40–60-mesh Chromosorb W (helium flow of 100 ml./min.).

The reaction of $\alpha,\alpha,\alpha',\alpha'$-tetramethyl-*m*-xylylene diisocyanate (0.42 g.) with hexamethylenediamine (0.20 g.) in dimethylformamide gave a polyurea. This reaction proceeded rapidly as evidenced by the rapid increase in solution viscosity and a large exotherm. The polymer, isolated by precipitation with acetone, melted at 200–227° and gave an infrared spectrum characteristic of a urea structure.

A low molecular weight polyurethane having isocyanate end groups was obtained by heating a mixture of 48.0 g. of polytetramethylene oxide glycol (mol. wt., 963), 19.5 g. of $\alpha,\alpha,\alpha',\alpha'$-tetramethyl-*m*-xylylene diisocyanate, and 0.05 g. of stannous octoate at 80° for 1.5 hr. Chain extension of this polymer was effected by treatment with hexamethylenediamine or 2,4-toluenediamine and by exposing thin films to moisture in the presence of tetraethylammonium cyanide catalyst. The products obtained with hexamethylenediamine and with water were rubbery, and the product obtained with 2,4-toluenediamine was relatively hard and tough.

$\alpha,\alpha,\alpha',\alpha'$-Tetramethyl-*p*-xylylene Diisocyanate (VI) and *p*-Isopropenyl-α,α-dimethylbenzyl Isocyanate (V).—A mixture of 350 g. (2.2 moles) of *p*-diisopropenylbenzene (Hercules Powder Company), 860 g. (20 moles) of isocyanic acid, 4 g. of ammonium tosylate, 7 g. of hydroquinone, and 3000 ml. of toluene was treated under the conditions previously described for *m*-diisopropylbenzene. On simple distillation, there was obtained 136 g. of crude diisocyanate, b.p. 90–110° (1 mm.), and 190 g. of nondistillable residue which gave strong infrared absorption at 4.4 μ (NCO). Redistillation through a Nester still gave 38 g. (9% based on olefin) of V, b.p. 83° (0.55 mm.), and 86 g. (16%) of VI, b.p. 110° (0.55 mm.) and m.p. 78°. Analyses were made on center cuts.

Anal. of V. Calcd. for $C_{13}H_{15}NO$: C, 77.57; H, 7.51; N, 6.96. Found: C, 77.77; H, 7.57; N, 7.33.

Anal. of VI. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.46. Found: C, 69.19; H, 6.76; N, 11.43.

The infrared absorption spectrum of the diisocyanate showed absorption at 3.27 μ (=CH), 3.35 and 3.40 (saturated CH), 4.43 (–NCO), 6.15 and 6.63 (aromatic –C=C–), 7.22 and 7.32 (*gem*-dimethyl), and 12.06 (*para* disubstitution).

The proton n.m.r. spectrum of the diisocyanate in deuteriochloroform showed hydrogens at 1.67 p.p.m. and 7.43 in the ratio of 3:1.

When this reaction was carried out in the absence of a catalyst, 21% of the olefin was converted to monoisocyanate, virtually none to diisocyanate, and 15% to polymer. The remainder of the olefin was recovered.

α,α-Dimethylbenzyl Isocyanate.—A mixture of 2237 g. (19 moles) of α-methylstyrene, 1200 g. (28 moles) of isocyanic acid, 14 g. of ammonium tosylate, 7 g. of hydroquinone, and 3 l. of toluene was heated in an autoclave for 3 hr. at 100°. Distillation gave 1250 g. (41% based on olefin) of α,α-dimethylbenzyl isocyanate, b.p. 44° (0.75 mm.), $n^{25}D$ 1.5050; lit.[6] b.p. 50–52° (0.16 mm.), $n^{25}D$ 1.5038.

Anal. Calcd. for $C_{10}H_{11}ON$: N, 8.69. Found: N, 8.86.

(4) All melting and boiling points are uncorrected. N.m.r. data were obtained on a Varian A60 spectrometer. N.m.r. data reported as parts per million (lower field) from tetramethylsilane (internal). Unless otherwise stated, no solvent was used.

(5) U. S. Patent 2,712,520 (1955).

(6) A. Lambert, J. D. Rose, and B. C. L. Weedon, *J. Chem. Soc.*, 42 (1949).

The infrared spectrum showed absorption at 3.25 μ and 3.28 (=CH), 3.35 and 3.40 (saturated CH), 4.44 (-NCO), 6.21 (aromatic -C=C-), 7.19 and 7.30 (>C(CH_3)$_2$), and 13.13 and 14.35 (monosubstituted aromatic bands).

The proton n.m.r. spectrum showed hydrogens at 1.51 p.p.m. and 7.37 (multiple splitting) in the ratio of 6:5. Reaction of this isocyanate with aniline gave the urea, m.p. 195–197°, lit.[6] m.p. 193–194°.

After standing 2 weeks in excess ethanol at room temperature, α,α-dimethylbenzyl isocyanate was converted (89%) to ethyl N-α,α-dimethylbenzyl carbamate, b.p. 88° (0.45 mm.), n^{25}D 1.5100.

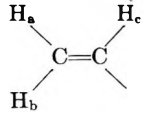
Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 69.52; H, 8.27; N, 6.76. Found: C, 69.71; H, 8.34; N, 6.99.

The infrared spectrum was in agreement with the urethane structure.

α,α-Dimethylallyl Isocyanate.—A mixture of 2000 ml. of xylene (toluene free), 1020 g. (15 moles) of isoprene, 840 g. (19.5 moles) of isocyanic acid, 14 g. of ammonium tosylate, and 5 g. of hydroquinone was heated with stirring in an autoclave for 3 hr. at 100°. The product was filtered, and the filtrate distilled through a column packed with glass helices. On redistillation through a 24-in. Podbielniak column, there was obtained 35 g. of α,α-dimethylallyl isocyanate, b.p. 104.5°, n^{25}D 1.4100. The infrared spectrum showed bands at 2.7 μ (common to tertiary NCO), 4.43 (NCO), 6.1 (CH_2=CH-), 7.26 and 7.35 (*gem*-dimethyl), and 10.1 and 10.8 (CH_2=CH-), consistent with the proposed structure.

Anal. Calcd. for C_6H_9NO: C, 64.80; H, 8.10; N, 12.60. Found: C, 64.84; H, 8.22; N, 12.62.

The proton n.m.r. resonance spectrum showed peaks at 1.31 p.p.m. (methyl hydrogens) and several peaks from 4.8 to 6.1 (vinyl hydrogens). The ratio of methyl to vinyl hydrogens was 2:1 The chemical shifts and coupling constants of the vinyl hydrogens



were approximately H_a, 4.92 p.p.m.; H_b, 5.16; and H_c, 5.81; $J_{H_bH_c}$ = 17 c.p.s.; $J_{H_aH_c}$ = 9.8; and $J_{H_aH_c}$ = 1.4.

Reaction with 2-ethylhexylamine gave N-2-ethylhexyl-N'-α,α-dimethylallylurea, CH_2=$CHC(CH_3)_2NHCONHCH_2CH(C_2H_5)C_4H_9$, an oil.

Anal. Calcd. N, 11.65. Found: N, 11.11.

The infrared spectrum was consistent with the urea structure.

Alternatively, α,α-dimethylallyl isocyanate was obtained from the reaction of silver cyanate with $(CH_3)_2C$=$CHCH_2Cl$, prepared from isoprene and hydrogen chloride.[7] The tertiary chloride, CH_2=$CHC(CH_3)_2Cl$, gave predominantly $(CH_3)_2C$=$CHCH_2NCO$ and only minor amounts of the tertiary isocyanate. Thus, γ,γ-dimethylallyl chloride (13.5 g., 0.14 mole) was added dropwise over a period of 20 min. to a stirred mixture of 100 ml. of ether and 30 g. (0.2 mole) of silver cyanate during which time the temperature rose from 23° to 31°. The mixture was then heated under reflux for 10 min. After removal of the solid by filtration, distillation yielded 5 g. (32%) of CH_2=$CH(CH_3)_2NCO$, b.p. 104–105° (infrared spectrum same as that of an authentic sample), and 6 g. (39%) of $(CH_3)_2C$=$CHCH_2NCO$, b.p. 139–140°, n^{25}D 1.4393.

Anal. Calcd. for C_6H_9NO (b.p. 139–140°): N, 12.60. Found: N, 12.72.

The infrared spectrum of the higher boiling isocyanate showed bands at 3.4 μ (CH), 4.43 (NCO), 6.02 (-C=C-), and 11.5 (CR_1R_2=CHR_3), consistent with the proposed structure.

(7) A. J. Ultée, *J. Chem. Soc.*, 530 (1948).

***t*-Butyl Isocyanate.**—A mixture of 200 ml. of toluene, 43 g. (1.0 mole) of isocyanic acid, 28 g. (0.5 mole) of isobutylene, and 0.5 g. of *p*-toluenesulfonic acid was heated in a stainless steel bomb for 8 hr. at 100–110°. Distillation of the product through a Vigreux column and then through a precision still gave about 5 g. (10% on isobutylene) of *t*-butyl isocyanate, b.p. 85–86° lit.[8] 85°; about 18 g. of isobutylene was recovered. The proton resonance spectrum of the isocyanate showed only methyl hydrogens. The infrared spectrum was consistent with this structure.

α-Phenylethyl Isocyanate.—A mixture of 300 ml. of toluene, 54 g. (0.52 mole) of styrene, 84 g. (1.9 moles) of isocyanic acid, 1 g. of ammonium tosylate, and 1 g. of hydroquinone was heated 3 hr. at 100°. Distillation through a Vigreux column gave 2.4 g. (5.6%) of D,L-α-phenylethyl isocyanate, b.p. 38° (0.4 mm.); for L-α-phenylethyl isocyanate, lit.[9] b.p. 82–83° (12–14 mm.).

Anal. Calcd. for C_9H_9NO: N, 19.52. Found: N, 19.15.

Reaction with ammonia gave D,L-$C_6H_5CH(CH_3)NHCONH_2$, m.p. 140° (m.p. of L-α-phenylethylurea 121–122°, melting point of D,L-mixture not reported).

Anal. Calcd. for $C_9H_{12}N_2O$: N, 17.06. Found: N, 16.73.

***p*-Methoxy-α,α-dimethylbenzyl Isocyanate.**—A solution of 12.5 g. (0.085 mole) of *p*-methoxy-α-methylstyrene and 5 ml. of toluene was added dropwise over a period of 32 min. to a stirred mixture of 19.2 g. (0.45 mole) of isocyanic acid, 30 ml. of toluene, and 0.1 g. of *p*-toluenesulfonic acid. The temperature rose to 34° and was held at this temperature for an additional 50 min. Distillation through a Vigreux column gave 3 g. of a mixture [b.p. 75–92° (0.5 mm.)], containing *p*-$CH_3OC_6H_4C(CH_3)_2NCO$ (89%) on the basis of infrared and nitrogen analyses.

Anal. Calcd.: N, 7.3. Found: N, 6.5.

Reaction with aniline gave the urea, *p*-$CH_3OC_6H_4C(CH_3)_2$-$NHCONHC_6H_5$, m.p. 169–171°.

Anal. Calcd. for $C_{17}H_{20}O_2N_2$: C, 71.82; H, 7.09; N, 9.85. Found: C, 72.29; H, 7.08; N, 9.92.

The infrared spectrum showed absorption at 3.0 μ, 3.4, 6.05, 6.25, 6.7, 12.1, 13.3, and 14.45.

Reaction Variables.—With the reaction of isocyanic acid with α-methylstyrene as a prototype, the effect of various catalysts and solvents has been explored. Catalysts in decreasing order of effectiveness are *p*-toluenesulfonic acid, ammonium *p*-toluenesulfonate, iodine, hydrogen chloride, ammonium perfluoroisobutyrate, silver perfluoroisobutyrate, and octylammonium-2,2,2-trifluoroethylsulfonate.

Several types of solvents were employed, and the best yields of isocyanates were obtained with aromatic hydrocarbons, such as toluene or benzene. With tetrahydrofuran, the rate of isocyanic acid trimerization was only 3% compared to 30% with toluene under otherwise comparable conditions. With acetonitrile, the amount of high-boiling residue was several times that obtained with toluene and the yield of distillable isocyanates was only about one-half.

Reaction of Tertiary Isocyanates with Water.—The following example illustrates the procedure for preparing ureas from tertiary isocyanates. A mixture of 25 g. of α,α-dimethylbenzyl isocyanate, 50 ml. of water, 0.02 g. of tetraethylammonium cyanide, and 250 ml. of 1,2-dimethoxyethane was prepared at 25°. The temperature rose to about 35° on standing and within 15 min. a precipitate began to form. After the mixture had stood overnight, water was added, and the solid (21.5 g., 94%), m.p. 225–227°, lit.[5] m.p. 226–227°, was removed by filtration.

Similarly, *m*-isopropenyl-α,α-dimethylbenzyl isocyanate was converted to (m-$C_3H_5C_6H_4C(CH_3)_2NH)_2CO$, m.p. 171–173°, in 100% yield.

Anal. Calcd. for $C_{25}H_{22}N_2O$: N, 7.46. Found: N, 7.56.

This compound in chloroform readily added chlorine to give partial saturation (81%) of the double bonds.

(8) W. Siefken, *Ann.*, **562**, 75 (1949).

(9) T. L. Cairns, *J. Am. Chem. Soc.*, **63**, 870 (1941).

The Reaction of Fenton's Reagent with Phenoxyacetic Acid and Some Halogen-Substituted Phenoxyacetic Acids[1]

RONALD F. BROWN, SAUNDERS E. JAMISON, UPENDRA K. PANDIT, JACK PINKUS, GEORGE R. WHITE, AND HANS P. BRAENDLIN

The Department of Chemistry, University of Southern California, Los Angeles 7, California

Received June 3, 1963

Phenoxyacetic acids have been shown to react readily with hydrogen peroxide in the presence of ferrous ion to give carbon dioxide, formaldehyde, phenols, and 1,2-diphenoxyethanes. Evidence in the form of the diphenoxyethanes as products, of formaldehyde-d_2 from phenoxy-d_2-acetic acid, and of monophenols as products favor attack by hydroxyl at the carboxyl group of the acids. Quantitative determination of the production or consumption of carbon dioxide, ferric ion, and diphenoxyethanes are reported. A slightly modified Merz–Waters type of mechanism has been employed as a basis for discussion.

Phenoxyacetic acids bearing halogen substituents in the *para* position exhibit activity as plant growth regulators. Additional substituents modify the activity in either direction, but phenoxyacetic acids lacking a *para* substituent show negligible activity.[2] The variations in biological activity of the variously substituted phenoxyacetic acids could not be correlated with variations in heterolytic reactivity as indicated by studies of ether hydrolysis rates,[3a] ester hydrolysis rates,[3b] or by comparison with acid dissociation constants.[4]

Therefore, it appeared to be of interest to study the homolytic reactivity of these compounds. The anaerobic treatment with hydrogen peroxide in the presence of ferrous ions, known as Fenton's reaction,[5] was chosen for study of the homolytic reactivity, since the work of Merz and Waters[6] suggested that quantitative reactivity data might be readily available in this system. The method also appeared attractive because it presented an analogy to biological oxidative processes.[7]

The effectiveness of Fenton's reagent in the oxidation of organic compounds is attributed to the action of a high energy intermediate formed by the interaction of the inorganic materials. Contrary views have been expressed as to the nature of the active intermediate. Both hydroxyl radical[8] and a tetravalent iron cation[9] have been proposed and are considered to arise, respectively, through reactions 1 and 2.

$$\mathrm{Fe(II) + H_2O_2 \longrightarrow Fe(III) + HO^- + HO\cdot} \quad (1)$$

$$\mathrm{Fe(II) + H_2O_2 \longrightarrow Fe(IV) + 2HO^-} \quad (2)$$

Kolthoff and Medalia[10] showed that the radical hydroxylation of organic compounds and other homolytic reactions previously observed with this reagent could be explained equally well on the basis of initiation by either reaction 1 or 2, but suggested that their observation of the absence of a salt effect in the reaction of Fenton's reagent with ethanol favored reaction 1. In favor of reaction 2, Cahill and Taube[11] found evidence in isotope fractionation studies that the course of oxidation of ferrous ion by hydrogen peroxide resembled that of stannous ion and others in which two-electron transfer is structurally available rather than that of titanous ion in which it is not available. However, in common with most of the workers in the field, we shall employ the hydroxyl radical formulation.

Previous work[6] indicated that the wide variety of organic compounds susceptible to attack by Fenton's reagent comprised aliphatic ethers and acids along with a large number of aromatic compounds, including benzene itself. Thus all of the structural features of the phenoxyacetic acids appeared to offer vulnerable sites for attack, with different degrees of susceptibility. In the present work the phenoxyacetic acids were found to yield carbon dioxide, formaldehyde, and the related phenols and diaryloxyethanes as primary products of reaction with Fenton's reagent. The indidated stoichiometric relationships are summarized in eq. 3.

$$\begin{aligned}(2a)\mathrm{Fe^{+2}} + (2a)\mathrm{H^+} + (b + 2c)\mathrm{ArOCH_2COOH} + \\ (a + b + c)\mathrm{H_2O_2} \longrightarrow (2a)\mathrm{Fe^{+3}} + (b)\mathrm{ArOH} + \\ (b)\mathrm{HCHO} + (c)\mathrm{ArOCH_2CH_2OAr} + (b + 2c)\mathrm{CO_2} + \\ (2a + b + 2c)\mathrm{H_2O}\end{aligned} \quad (3)$$

The product recovery data are presented in Table I in terms of the relationships indicated in eq. 3. The tabulated data indicate the unlikelihood that other as yet unidentified primary products might be formed to any major extent.

Secondary attack on formaldehyde would reduce the yield not only of formaldehyde but also of carbon dioxide relative to hydrogen peroxide consumption. If eq. 4 be multiplied by the coefficient d and added to eq.

$$\mathrm{2H_2O_2 + HCHO \longrightarrow 3H_2O + CO_2} \quad (4)$$

$$\begin{aligned}(2a)\mathrm{Fe^{+2}} + (2a)\mathrm{H^+} + (b + 2c)\mathrm{ArOCH_2COOH} + \\ (a + b + c + 2d)\mathrm{H_2O_2} \longrightarrow (2a)\mathrm{Fe^{+3}} + (b)\mathrm{ArOH} + \\ (b - d)\mathrm{HCHO} + (c)\mathrm{ArOCH_2CH_2OAr} + (b + 2c + d)\mathrm{CO_2} + \\ (2a + b + 2c + 3d)\mathrm{H_2O}\end{aligned} \quad (5)$$

3, eq. 5 results; eq. 3 gives $(b + 2c)/(a + b + c)$ for the ratio of carbon dioxide formed to hydrogen peroxide consumed, and eq. 5 gives a ratio of $(b + 2c + d)/(a + b + c + 2d)$ obviously less than the former ratio if d has a finite value. After the first few runs the conversions (based on hydrogen peroxide added) were held to the range 5–20% in order to minimize secondary

(1) This work was supported by a contract with the U. S. Army Chemical Corps, Fort Detrick, Frederick, Md., and by a contract with the U. S. Atomic Energy Commission. It is based in part on a dissertation submitted by S. E. Jamison to the Graduate School of the University of Southern California in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

(2) R. L. Weintraub, J. W. Brown, and J. A. Thorne, *J. Agr. Food Chem.*, **2**, 996 (1954).

(3) (a) R. F. Brown and E. F. Claflin, *J. Am. Chem. Soc.*, **80**, 5960 (1958); (b) R. F. Brown and H. C. Newsom, *J. Org. Chem.*, **27**, 3010 (1962).

(4) N. V. Hayes and G. K. Branch, *J. Am. Chem. Soc.*, **65**, 1555 (1943).

(5) H. J. H. Fenton, *J. Chem. Soc.*, **65**, 899 (1894).

(6) (a) J. H. Merz and W. A. Waters, *Discussions Faraday Soc.*, **2**, 179 (1947); (b) *J. Chem. Soc.*, S15 (1949); (c) 2427 (1949).

(7) D. J. Mackinnon and W. A. Waters, *ibid.*, 323 (1953).

(8) F. Haber and J. Weiss, *Proc. Roy. Soc.* (London), **A147**, 332 (1934).

(9) W. C. Bray and M. Gorin, *J. Am. Chem. Soc.*, **54**, 2124 (1932).

(10) (a) I. M. Kolthoff and A. I. Medalia, *ibid.*, **71**, 3777 (1949); (b) **71**, 3784 (1949); (c) A. I. Medalia and I. M. Kolthoff, *J. Polymer Sci.*, **4**, 377 (1949).

(11) A. E. Cahill and H. Taube, *J. Am. Chem. Soc.*, **74**, 2312 (1952).

TABLE I

REACTION OF PHENOXYACETIC ACIDS WITH FENTON'S REAGENT[a]

Compound[b]	Mmoles × 10^2	Fe^{+2},[c] mmoles × 10^2	H_2O_2,[c,d] mmoles × 10^2	ΔFe^{+2}, mmoles × 10^2	CO_2, mmoles × 10^2	ArOH, mmoles × 10^2	HCHO, mmoles × 10^2	$(ArOCH_2)_2$,[e] mmoles × 10^4	$\frac{\Delta H_2O_2}{\Delta H_2O_2 - 0.5\Delta Fe^{+2}}$
POA	50	100	38.3	37.6	20		16.1		1.96
	150	100	13.0	11.7			6.2		1.82
	100	100	9.9	6.8	7.6				1.52
	100	100	13.3	9.3		8.8			1.54
	87	47	11.8	4.5				5.0	1.24
	181	47	11.8	3.8				16.6	1.19
2-FPOA	100	100	11.8	10.7	7.1				1.83
	100	100	9.8	9.0	6.3			130[f]	1.85
	17.5	46.4	1.57	1.2				6.4	1.62
	29.9	46.4	1.57	1.2				6.5	1.59
4-FPOA	100	100	11.0	12.5	4.7				2.31
	100	100	14.1	16.2	5.9			6.4[f]	2.34
	48.8	46.4	10.0	10.6				5.3	2.14
	73.8	46.4	10.0	10.6				8.1	2.12
	99.2	46.4	10.0	10.2				18.5	2.05
2,4-DiFPOA	100	100	9.9	11.0	4.3			2.4[f]	2.26
2-ClPOA	26	100	4.6	3.9		2.7			1.77
	7.5	46.4	2.72	3.8				8.6	3.26
	12.3	46.4	2.66	3.5				8.9	2.90
	13.6	46.4	2.76	3.1				12.3	2.28
4-ClPOA	26.7	100	4.7	4.3		3.0			1.81
	26.7	100	9.4	10.9		4.4			2.35
	9.3	46.4	3.76	4.5				2.3	2.53
	16.2	46.4	3.74	4.3				2.5	2.34
	18.7	46.4	3.71	4.1				1.1	2.24
	6.3	24.4	2.52	2.4				3.5	1.89
	9.0	24.4	2.49	2.9				4.0	2.35
	10.6	24.4	2.50	2.2				5.6	1.76
	13.3	24.4	2.48	2.2				8.8	1.81

[a] The volume of each solution before the hydrogen peroxide addition was 70 ml. The final volume was close to 75 ml. The sulfuric acid concentration varied from the initial 0.143 *N* to the final 0.133 *N* in each run. All runs made at room temperature, approximately 25°. [b] POA is the abbreviation for phenoxyacetic acid. [c] Initial amounts. [d] Also ΔH_2O_2, the amount consumed. [e] Determined by infrared spectrophotometry. [f] Determined by weighing of residues after extraction purification.

reactions. Even so, in those runs on 4-fluoro- and 2,4-difluorophenoxyacetic acid in which carbon dioxide was measured, $\Delta CO_2 - (\Delta H_2O_2 - \Delta Fe^{+2}/2)$ gave −0.0005, −0.001, and −0.001 mmole showing that the result represents $(c - d)$ from eq. 5 rather than c from eq. 3. This explanation also may apply to the value for c, 0.013 mmole, obtained by direct weighing of the residue on extraction of the reaction product of 2-fluorophenoxyacetic acid, which exceeds the value of 0.010 mmole, calculated from measurements of carbon dioxide and ferric ion formation. Moreover, in the experiments on the substrates from which the carbon dioxide yield indicated little or no dimer formation, slight if any turbidity was observed to develop in the course of the reaction, while those reactions yielding the appropriate high level of carbon dioxide also formed considerable precipitate. The precipitation reflects the formation of diaryloxyethanes, since they are the least soluble of the products in the reaction medium. Moreover, the identification was made positive by isolation and comparison in several instances with authentic materials. Infrared spectroscopy was employed subsequently to measure the concentration of these dimeric products in a series of runs which also are reported in Table I. It is interesting to note that, of the substances tested, the biologically active acids, which contain *para* substituents, formed in general a much smaller proportion of diaryloxyethanes than did the biologically inactive acids which lacked the *para* substituent. Although we have postulated four pathways for the disappearance of the phenoxymethyl radical so that, if applicable, the amount of diaryloxyethane formed would be inversely related to the concentrations of ferric ion, hydrogen peroxide, and hydroxyl radical, we found little variation in the fraction of total substrate reacted, which resulted in formation of the diether (except for 2,4-dichlorophenoxyacetic acid which varied widely and was interpreted as a solubility effect). Thus, for phenoxyacetic acid, 2 ± 1% of the amount which reacted became 1,2-diphenoxyethane; for the 2-fluoro acid, 13 ± 1%; 4-fluoro, 5 ± 3%; 2-chloro, 18 ± 2%; 4-chloro, 6 ± 3%; and for 2,4-dichlorophenoxyacetic acid, 22 ± 12%. This surprising difference between those compounds bearing an *ortho* substituent and the others may be ascribed, perhaps, to chelation with ferric ion by the *ortho*-substituted phenoxymethyl radicals following.

Such a complex could lead on the one hand to the reaction represented by k_6 or on the other hand to chelation of a second radical about the iron. Such accumulation of radicals about the iron could be thought of as a pseudocage effect, bringing the radicals together in

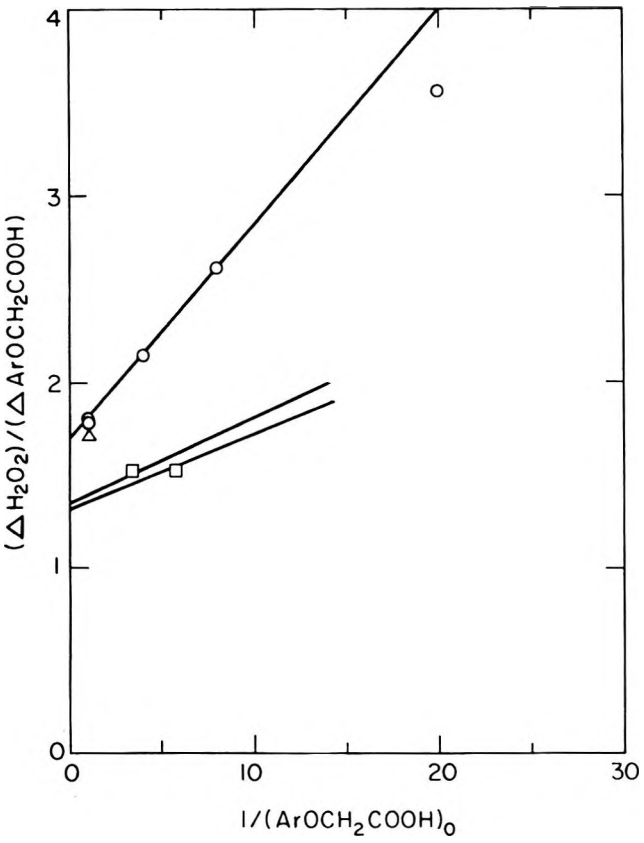


Fig. 1.—Plot of the ratio of hydrogen peroxide consumed to 2-fluorophenoxyacetic acid consumed against the reciprocal of the initial concentration (in mmoles per 75 ml.) of 2-fluorophenoxyacetic acid: ○, for initial concentration of ferrous ion, 1 mmole (in 75 ml.); △, 0.5 mmole; ⊡, 0.464 mmole. The lines are drawn for $k_2/k_3 = 0.068$, $k_5/k_4 = 52.5$ in eq. 6 with $k_2(Fe^{+2})_0 \gg k_9(ArOCH_2\cdot)$.

such a fashion as to facilitate the formation of diphenoxyethane.

The attempts at measurement of yields of phenol, identified as its tribromo derivative in the phenoxyacetic acid reaction product, appear to have given results that are distinctly high. The spectral procedure used was insufficiently precise, apparently because of inadequate removal of interfering substances (notably, unchanged phenoxyacetic acid). However, the results do correspond in order of magnitude to those obtained for the other products in more precise analyses and thus may be considered to provide additional confirmation of the applicability of eq. 3 or 5.

Following in the path of the already cited studies by Merz and Waters,[6] Mackinnon and Waters,[7] Kolthoff and Medalia,[10] and to which may be added the investigations by Baxendale and Magee[12] of the reaction of benzene with Fenton's reagent, the following scheme appears to indicate the reaction steps in the present system if the complicating secondary reactions are omitted. Despite the complications introduced by the inclusion of the steps indicated by k_5 and k_8, this mechanism satisfies the stoichiometry of eq. 3 and will serve as a basis for discussion.

$$Fe^{+2} + H_2O_2 + H^+ \xrightarrow{k_1'} Fe^{+3} + HO\cdot + H_2O \qquad k_1 = k_1'(H^+)$$

$$Fe^{+2} + HO\cdot + H^+ \xrightarrow{k_2'} Fe^{+3} + H_2O \qquad k_2 = k_2'(H^+)$$

$$ArOCH_2COOH + HO\cdot \xrightarrow{k_3} ArOCH_2COO\cdot + H_2O$$

$$ArOCH_2COO\cdot \xrightarrow{k_4} ArOCH_2\cdot + CO_2$$

$$ArOCH_2COO\cdot + Fe^{+2} + H^+ \xrightarrow{k_5'} ArOCH_2COOH + Fe^{+3} \qquad k_5 = k_5'(H^+)$$

$$ArOCH_2\cdot + Fe^{+3} + H_2O \xrightarrow{k_6'} ArOCH_2OH + Fe^{+2} + H^+ \qquad k_6 = k_6'(H_2O)$$

$$ArOCH_2\cdot + H_2O_2 \xrightarrow{k_7} ArOCH_2OH + HO\cdot$$

$$ArOCH_2\cdot + ArOCH_2\cdot \xrightarrow{k_8} ArOCH_2CH_2OAr$$

$$ArOCH_2\cdot + HO\cdot \xrightarrow{k_9} ArOCH_2OH$$

$$ArOCH_2OH + H^+ \xrightarrow{k_{10}} ArOH + HCHO + H^+$$

From the reactions given, there is readily derived, assuming that HO· and $ArOCH_2COO\cdot$ are steady states, eq. 6 as the correlation of the rates of disappearance of peroxide and organic substrate. If the assumption be made that $k_2(Fe^{+2}) \gg k_9(ArOCH_2\cdot)$—namely, that Fe^{+2} is superior to $ArOCH_2\cdot$ in competition for HO·— and that $k_4 \gg k_5(Fe^{+2})$—namely, that the decarboxylation of $ArOCH_2COO\cdot$ predominates over the reaction with Fe^{+2}—then eq. 6 reduces to eq. 7,

$$\frac{d(H_2O_2)}{d(ArOCH_2COOH)} = \left[1 + \frac{k_5(Fe^{+2})}{k_4}\right]\left[1 + \frac{k_2(Fe^{+2}) + k_9(ArOCH_2\cdot)}{k_3(ArOCH_2COOH)}\right] \qquad (6)$$

$$\frac{\Delta(H_2O_2)}{\Delta(ArOCH_2COOH)} = 1 + \frac{k_2(Fe^{+2})_0}{k_3(ArOCH_2COOH)_0} \qquad (7)$$

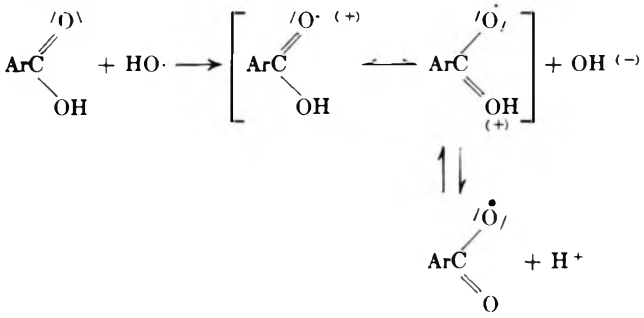
the relationship originally introduced by Merz and Waters[6] for the action of Fenton's reagent on various substrates. This shows that, for reactions meeting the qualifications given, the ratios shown may be plotted to give a line with an intercept of unity and a slope which is the ratio of constants representing the relative affinities of ferrous ion and the substrate for the hydroxyl radical. None of our data fitted this limitation and eq. 7 failed to hold. If $ArOCH_2COO\cdot$ should be so stable that the lifetime before decarboxylation increases the relative rate of reaction with ferrous ion, k_5, then the intercept of a plot of the ratios will give a line with an intercept of $1 + k_5(Fe^{+2})/k_4$ and the slope will be increased by the same factor providing the ferrous ion concentration is held constant while the ratios are being varied. If, in addition, k_9 should be so large that $k_2(Fe^{+2})$ no longer is very much greater than $k_9(ArOCH_2\cdot)$ then the plot of ratios would become nonlinear and the slope and intercept would have a simple interpretation only if certain other requirements are met. Actually, most of our data give straight line plots as shown, for example, in Fig. 1 for 2-fluorophenoxyacetic acid. The graph also shows the effect of variation in the initial ferrous ion concentration, the point for 0.5 mmole being seriously out of place. The point at $1/(ArOCH_2COOH)_0 = 20$ also does not fit the plot, but in this instance the initial concentration of peroxide exceeded the initial concentration of substrate so that part of the peroxide must have been consumed in a secondary reaction with formaldehyde. Figure 2 illustrates the variation in slope and intercept for

(12) J. H. Baxendale and J. Magee, *Discussions Faraday Soc.*, **14**, 160 (1953).

varying substrates at constant ferrous ion concentration.

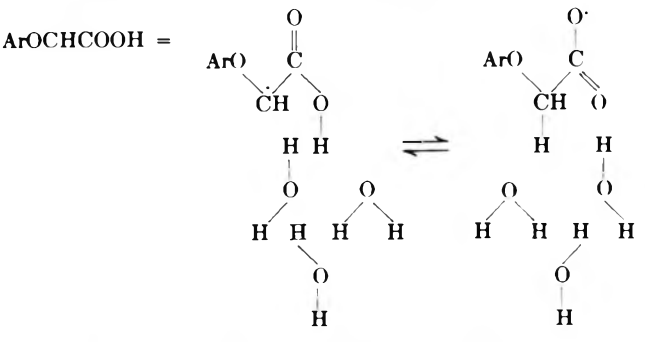
It may be recalled that Kolthoff and Medalia[10] explained the failure of acetic acid to undergo oxidation by Fenton's reagent on the basis of reduction by ferrous ion of acetoxy radical to acetate ion. In the absence of stabilizing substituents on the methyl group in acetoxy radical, ferrous ion apparently can suppress the tendency to decarboxylation. This suppression of acetoxy decarboxylation was complete at concentrations of ferrous ion considerably lower (0.51×10^{-3} M) than any used in the experiments described herein. Thus even the *para*-substituted phenoxy group appears to make an appreciable contribution to the ability of the carboxy radical to decarboxylate.

The similarity of reactivity of the various substrates may imply a similarity in process involved such as electron abstraction by the hydroxyl radical from either ferrous ion or the substrate phenoxyacetic acid rather than hydrogen atom abstraction from the hydration shell of the ferrous ion or from the substrate. Thus we envisage the process indicated by k_3 as proceeding as follows.



Although the concept of initial attack by electron abstraction at the carboxyl group offers the simplest explanation of the product distribution, the C–H bond α to an ether oxygen or to a carbonyl group is typically quite susceptible to free-radical attack.[13] Such attack can be formulated to give the observed products if it is assumed that initial removal of an α-hydrogen is followed by proton migration from the carboxyl group, possibly facilitated by bridging through solvent water, or conversely, that α-hydrogen is lost after initial electron removal. That neither occurs was demonstrated as follows.

$$ArOCH_2COOH + HO\cdot \longrightarrow ArO\dot{C}HCOOH + H_2O$$



If the acid in which the two α-hydrogens had been replaced by deuteriums were used, the product formaldehyde would retain both deuterium atoms if α-hydrogen were not involved. The product formaldehyde would have one deuterium replaced by hydrogen if α-hydrogen involvement occurred. Dideuterated phenyoxyacetic acid was prepared and the formaldehyde produced was isolated as the dimedone derivative, which was burned. The resulting water was reduced to furnish a gaseous sample for analysis in a mass spectrometer,[14] but the results were not decisive. The experiment was repeated when a Beckman IR-7 spectrophotometer became available.[15]

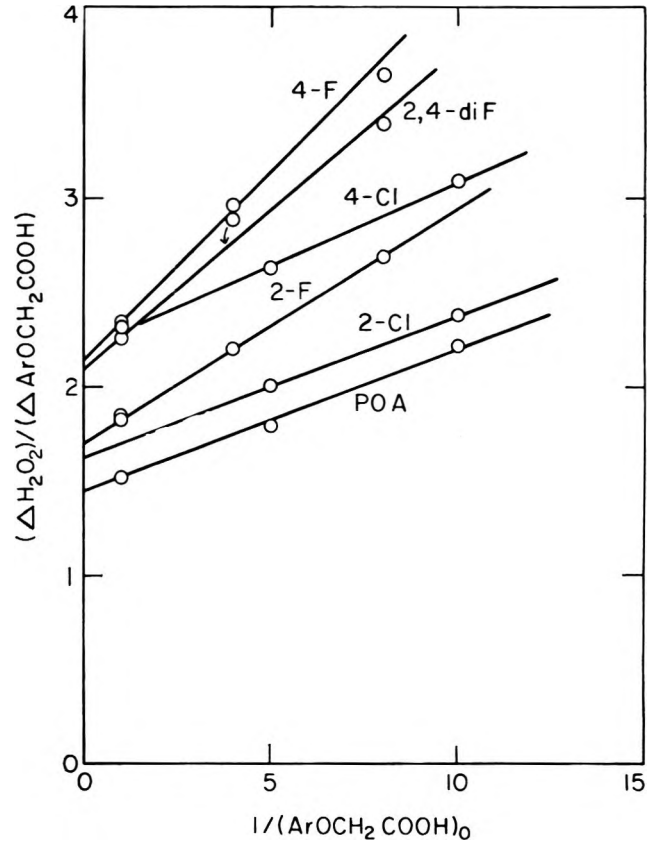


Fig. 2.—Plot of the ratio of hydrogen peroxide consumed to various substituted phenoxyacetic acids consumed against the reciprocal of the initial concentrations (in mmoles per 75 ml.) of the various substrates. All were at ferrous ion concentration of 1 mmole (in 75 ml.). The lines are merely graphical straight lines drawn for identification.

The infrared absorption spectra of chloroform solutions of the dimedone derivatives of formaldehyde, formaldehyde-d_2, and of the formaldehyde product from reaction of deuterated phenoxyacetic acid were compared in the 950–2300-cm.$^{-1}$ region. Three bands were chosen for quantitative examination. The HCHO derivative absorbed at 976 cm.$^{-1}$ (ϵ 10.3), 1085 (160), and had no band at 2117 while the DCDO derivative absorbed at 952 cm.$^{-1}$ (ϵ 24), 1064 (130), and 2117 (3.3). The product derivative spectrum was identical with that from DCDO with ϵ 23.2, 127, and 3.3 for the three bands. The identity of the absorption at 2117 cm.$^{-1}$ may be regarded as critical, representing a C–D vibration assignment[16] whereas the bands at 952 and 1064 are in the "fingerprint" region without specific

(13) W. E. Cass, *J. Am. Chem. Soc.*, **69**, 500 (1947).

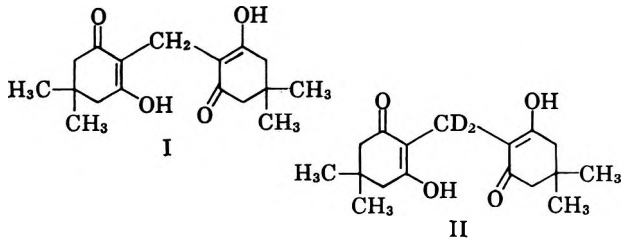
(14) R. B. Alfin-Slater, S. M. Rock, and M. Swislocki, *Anal. Chem.*, **22**, 421 (1950).

(15) Made possible by Grant G14665 of the National Science Foundation, which we are happy to acknowledge.

(16) B. Nolin and R. N. Jones, *J. Am. Chem. Soc.*, **75**, 5626 (1953); *Can. J. Chem.*, **34**, 1382 (1956). See also E. S. Ebers and H. H. Nielsen, *J. Chem. Phys.*, **6**, 311 (1938); R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954).

assignment.[17] The possible objection that the latter two bands may be due to an interaction between the six-membered rings of the bismethone which may be altered by the introduction of only one deuterium on the linking carbon is ruled out by the 2117-cm.$^{-1}$ band datum. Thus the evidence for the lack of attack at the α-position was strengthened, but the low intensities of the bands chosen left a residual doubt.

Turning to n.m.r., it was reasoned that the formaldehyde bismethone (I), but not the formaldehyde-d_2 bismethone (II), should exhibit distinct absorption for



I

II

the bridged methylenic protons. This was verified; substance I gave three peaks: A at −2.14, B at −4.61, and C at −6.36 p.p.m. relative to tetramethylsilane. The relative area ratios[18] were A:B:C = 6.00:3.89:0.91. Substance II gave a spectrum identical with I but with ut the C peak, which was assigned to the bridged methylenic protons. The product, isolated from the reaction of phenoxy-d_2-acetic acid with Fenton's reagent as the bismethone, gave a spectrum identical with that from II. The accumulation of evidence points conclusively to the strange resistance by phenoxyacetic acid to attack on the α-protons by Fenton's reagent.

In contrast, Garrison, *et al.*,[19] present evidence that aqueous hydroxyl radical attack is directed preponderantly to the methyl rather than the carboxyl group in acetic acid. This has been confirmed by Coffman, Jenner, and Lipscomb[20] who also observed both α- and β-attack by Fenton's Reagent on propionic and isobutyric acids leading to dimeric products. The yields of coupled products fell off drastically as the concentrations of substrate or of hydrogen peroxide decreased so that our observation of the formation of any diaryloxyethanes was a surprise to us. There is no cage effect operating here to cause dimerization so one recourse is to postulate relative stability to the phenoxymethyl radicals. Russell[21] points out that ". . . hydrogen atoms alpha to ether linkages are often attacked by peroxy radicals . . . " while Walling[22] in a discussion of relative stability of radicals points out that an adjacent carbonyl group is better than an adjacent alkoxy group in stabilizing a radical, or (>C–COOR) > (>C–OR). The point of attack by a radical on a substrate molecule is difficult to predict because of the lack of understanding of the effects of various factors (electronic, structural, steric, etc.) on the activation energy and the pre-exponential factor. The stabilization of the resulting new radical will have an effect in lowering the expected activation energy. Thus, since we found the aryloxymethyl radical to be relatively stable, one might predict that anisole should be somewhat susceptible to attack by radicals on the methyl group to form the phenoxymethyl radical even though benzene ring attack would produce a methoxyphenyl radical. Frazer-Reid and co-workers[23] using an excess of Fenton's reagent on anisole at 0° and high concentrations identified guaiacol and hydroquinone as products, the latter probably arising by a demethylation *via* attack on the methyl group preceded by or followed by ring attack. On the other hand Norman and Radda[24] employed the "model peroxidase" conditions (ferrous ion with hydrogen peroxide under nitrogen with added phosphate buffer, ascorbic acid, and ethylenediaminetetracetic acid in aqueous acetone) on anisole and also with various deletions such as omission of acetone or ascorbic acid, etc., and up to 4% reaction. They detected no dihydroxy products and found only ring attack. This system has been discussed by Grinstead[25] who pointed out the relative oxidation–reduction potential changes involved in chelation and who found both salicyclic and benzoic acids to be subject to attack. Recently, Hamilton and Friedman[26] investigated the reaction of anisole with hydrogen peroxide using Fenton conditions as well as the model peroxidase system and the use of catechol and hydroquinone as intermediate carriers instead of ascorbic acid. They found the yield of ring hydroxylated products under Fenton conditions to be only 20% which was 86% *ortho*. Here again no mention is made of phenol, formaldehyde, or of 1,2-diphenoxyethane as products to be expected from attack on the methyl group.

Of interest also is the report of Friess and co-workers[27] who studied the reaction of perbenzoic acid in chloroform with anisole and a series of polymethoxybenzenes. Unfortunately for our purpose, they used an excess of perbenzoic acid in nearly every instance so that primary products could not be identified and in particular did not identify any products from demethylation along with oxidation to quinones. Again, no effort was made to isolate neutral products; thus if any diphenoxyethane were formed it remained undetected in the recovered anisole fraction.

That an adjacent amino group does not shift attack away from the α-position was shown by Maxwell and Peterson[28] in an extensive study of the aerobic reaction of Fenton's reagent with glycine. They concluded that the initial attack was at the α-hydrogen and that the

(17) S. C. Burkett and R. M. Badger, *J. Am. Chem. Soc.*, **72**, 4397 (1950); R. N. Jones, B. Nolin, and G. Roberts, *ibid.*, **77**, 6331 (1955).

(18) Although not of immediate importance, the n.m.r. spectra were of general interest. The absence of any splitting pattern (A had a tiny, almost questionable, shoulder) may be attributed to the absence of any adjacent protons in either I or II. Peak A was assigned to the twelve methyl protons, supported by the 6:1 relationship to the two bridged methylenic protons (peak C). The surprise came in the collapse of the nominally ten ring protons into a single peak (B) of eight methylenic protons. The averaging effect of the enolic double bond position would explain the identical absorptions, but the enolic hydrogens could not be found even though the down-scale limit of the instrument was reached.

(19) W. M. Garrison, W. Bennett, S. Cole, H. R. Haymond, and B. M. Weeks, *J. Am. Chem. Soc.*, **77**, 2720 (1955).

(20) D. D. Coffman, E. L. Jenner, and R. D. Lipscomb, *ibid.*, **80**, 2864 (1958).

(21) G. A. Russell, "Peroxide Reaction Mechanisms," J. O. Edwards, Ed., John Wiley and Sons, Inc., New York, N. Y., 1962, p. 117.

(22) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 122.

(23) B. Frazer-Reid, J. K. N. Jones, and M. B. Perry, *Can. J. Chem.*, **39**, 555 (1961).

(24) R. O. C. Norman and G. K. Radda, *Proc. Chem. Soc.*, 138 (1962).

(25) R. R. Grinstead, *J. Am. Chem. Soc.*, **82**, 3464, 3472 (1960).

(26) G. A. Hamilton and J. P. Friedman, *ibid.*, **85**, 1008 (1963).

(27) S. L. Friess, A. H. Soloway, B. K. Morse, and W. C. Ingersoll, *ibid.*, **74**, 1305 (1952).

(28) C. R. Maxwell and D. C. Peterson, *ibid.*, **79**, 5110 (1957).

ratio of rate constants for the competition between ferrous ion and glycine for the hydroxyl radical was 80.

The susceptibility to attack at various sites on a substrate molecule by radicals remains a question for exploration. The sensitivity of the phenoxyacetic acids to attack at the carboxyl group followed by extensive decomposition offers a new probe for the study of free-radical reactions. In subsequent papers we will report in more detail our results pertinent to the mechanism and to other substrates and other radical systems.

Experimental[29]

The phenols and phenoxyacetic acids were prepared by standards methods.[3] Authentic samples of the 1,2-diphenoxyethanes were prepared in low yield (15–25%) from ethylene bromide and the phenol as described by Cope.[30] Five of the ethers do not seem to have been described previously.

1,2-Bis(2-fluorophenoxy)ethane had m.p. 116.5–117°.

Anal. Calcd. for $C_{14}H_{12}O_2F_2$: C, 67.20; H, 4.80; mol. wt., 250. Found: C, 67.09; H, 5.12; mol. wt., 247 (Rast).

1,2-Bis(4-fluorophenoxy)ethane had m.p. 85–86.5°.

Anal. Calcd. for $C_{14}H_{12}O_2F_2$; C, 67.20; H, 4.80; mol. wt., 250. Found: C, 67.28; H, 4.96; mol. wt., 250 (Rast).

1,2-Bis(2-chlorophenoxy)ethane had m.p. 103–105°.

Anal. Calcd. for $C_{14}H_{12}O_2Cl_2$: C, 59.38; H, 4.27; Cl, 25.04. Found: C, 58.39, 60.05; H, 4.52, 4.64; Cl, 25.24.

1,2-Bis(4-chlorophenoxy)ethane had m.p. 130–131.5°.

Anal. Calcd. for $C_{14}H_{12}O_2Cl_2$: C, 59.38; H, 4.27; Cl, 25.04. Found: C, 59.18; H, 4.17; Cl, 25.28.

1,2-Bis(2,4-dichlorophenoxy)ethane had m.p. 131–133°.

Anal. Calcd. for $C_{14}H_{10}O_2Cl_4$: C, 47.76; H, 2.86; Cl, 40.29. Found: C, 47.78; H, 3.12; Cl, 40.50.

All of the diethers absorbed at 8.00 ± .01 μ (1250 ± 2 cm.$^{-1}$). The molecular extinction coefficients were determined from the data at three concentrations in carbon tetrachloride, which gave linear plots through the origin. Because of uncertainty in path length, nominally 0.01 cm., the coefficients probably are in error as to absolute values, but the relative values and their use in determining unknown concentrations were not affected since the same cell was used throughout. The molecular extinction coefficients used were 729.6 ± 2.2 for 1,2-diphenoxyethane, 812.6 ± 1.5 for 1,2-bis(2-fluorophenoxy)ethane, and 800.2 ± 6.6 for the 4-fluoro, 478.1 ± 7.5 for the 2-chloro, 794.3 ± 9.2 for the 4-chloro, and 378.7 ± 3.7 for the 2,4-dichloro analogs.

Phenoxy-d_2-acetic acid was prepared from a solution of potassium phenoxyacetate (6.68 g., 0.033 mole) and sodium hydroxide (1.05 g., 0.026 mole) in 98% deuterium oxide (8.5 ml.) which was refluxed for 24 hr., transferred to another flask, and concentrated *in vacuo* to a solid so that 5 ml. of deuterium oxide were removed. More deuterium oxide (6.5 ml.) was added to the residue which was then refluxed for 26 hr. The 6.5 ml. of deuterium oxide was recovered by evaporation as before.

A portion (*ca.* 1 g.) was removed from this residue (50 hr. total refluxing) and worked up in a manner similar to that described subsequently for the main product formed after 70 hr. refluxing.

The main residue was diluted with deuterium oxide (5 ml.) and refluxed for 20 hr. (70 hr. total reflux time) during which a solid deposited. The reaction mixture was dissolved in 0.1 *N* hydrochloric acid (310 ml.) and the acid solution extracted with six 50-ml. portions of ether. After drying over sodium sulfate, filtration, and evaporation under reduced pressure, the combined ethereal extracts gave an oil which crystallized on trituration with benzene. Recrystallization from benzene gave phenoxy-d_2-acetic acid, m.p. 99–100°; ν_{max} 2100 cm.$^{-1}$ (ϵ 11.6), 2169 (2.7), 10% in chloroform. The infrared absorption spectrum of phenoxyacetic acid (10% in chloroform) showed no absorption in the region 2000–2300 cm.$^{-1}$.

Anal. Calcd. for $C_8H_8D_2O_3$: C, 62.33; H + D, 6.54. Found: C, 62.92; H + D, 6.54.

The phenoxy-d_2-acetic acid isolated after 50 hr. refluxing had ν_{max} 2100 cm.$^{-1}$ (ϵ 11.0), 2169 (2.0), showing no further exchange to have occurred (within experimental error) during the extra 20 hr. refluxing undergone by the main product; combined yield, 1.37 g., 25%.

A mass spectrometric determination[31] showed that material which had undergone a 17-hr. period of exchange contained at least 96% of the theoretical two deuterium atoms per molecule.

Distilled water which had been boiled for 15–30 min. and cooled under nitrogen was used throughout in the preparation and dilution of all solutions. More elaborate treatment did not improve reproducibility of results.

Procedure.—In general, 10 ml. of a standardized solution of ferrous sulfate or of ferrous ammonium sulfate (usually 0.05 to 0.10 *N*) in 0.1 *N* sulfuric acid as solvent was added to 60 ml. of a solution of a known weight of a phenoxyacetic acid (kept in storage over phosphorus pentoxide in the dark) in 0.1 *N* sulfuric acid contained in a 250-ml. filter flask mounted on a magnetic stirrer. The flask was fitted with a two-hole rubber stopper. One of the holes carried a glass tube connected to a nitrogen source and which delivered nitrogen below the surface of the solution in the flask. The other hole carried a glass plug which could be interchanged with the tip of a buret which had been elongated to reach close to the surface of the solution. The outlet arm of the flask was connected to a three-way stopcock so that the exit gases could be vented to an aspirator (or to the room) or passed through an absorption train consisting of bubble counter, water absorber, and two carbon dioxide absorbers as used in a semi-micro carbon–hydrogen combustion train. The nitrogen was purified according to Fieser[32] and was passed through 0.1 *N* sulfuric acid before entering the reaction flask.

If carbon dioxide was not to be measured, with the plug in place, the flask was evacuated through the aspirator while nitrogen was shut off and the contents were stirred. When bubbles of dissolved gas ceased to appear, the stopcock was turned to isolate the flask and nitrogen introduced to atmospheric pressure. The evacuation and restoration of pressure by nitrogen was repeated. Then with a small excess pressure maintained in the flask, the plug was replaced by the buret tip. With nitrogen flow maintained through the flask, and with the stirrer in operation, a standardized solution of hydrogen peroxide was added from the buret as rapidly as possible without exceeding a dropwise rate. The flow of nitrogen and the stirring was continued for about 5 min. after the hydrogen peroxide addition was complete. In every instance an insoluble product was formed ranging from a faint turbidity to an actual precipitate depending upon the reactant and concentrations used.

The standardized hydrogen peroxide was prepared fresh every day from a 30% solution by dilution of 1 ml. to 500 ml. with 0.1 *N* sulfuric acid which had been previously boiled and then cooled with soda lime protection. The diluted solution (about 0.05 *N*) was standardized against potassium permanganate or potassium iodide and sodium thiosulfate. No variation in concentration was noted during the day. The bottle of 30% solution was stored in a refrigerator after opening. When first opened, the solution was acidified with 1 ml. of 10 *N* sulfuric acid per 200 ml. Before each use, nitrogen was bubbled through the solution at 0° for 30 min.

Analytical and Identification.—If carbon dioxide was to be determined, the procedure was the same until the two evacuations had been completed. The nitrogen flow through the absorption train was begun and continued for 30 min. The absorption tubes were disconnected, weighed, and replaced in position. The buret replaced the plug and the hydrogen peroxide solution was added as before. The flow of nitrogen and stirring was continued for 30 min. when it was interrupted and the absorption tubes were removed and weighed. As a check, a further 30-min. period of flow was carried out. Results are given in Table I. The method was checked and the details worked out in runs in which standardized sodium carbonate solutions replaced the hydrogen peroxide. For about 10 mg. of carbon dioxide evolved recovery averaged 99 ± 2%.

If ferric ion was to be determined, the reaction mixture was diluted to 100 ml. and a suitable aliquot transferred to a 50-ml. volumetric flask. Sulfuric acid, 5 ml. of 10 *N*, and 5 ml. of 10%

(29) Melting points are corrected. Analyses by W. Schenck and R. S. Walpole, Department of Chemistry, University of Southern California; Elek Micro Analytical Laboratories, Los Angeles, Calif.; and by Dr. Joseph Alicino, Metuchen, N. J.

(30) A. C. Cope, *J. Am. Chem. Soc.*, **57**, 572 (1935).

(31) Analysis by Mr. V. Skipski, Department of Biochemistry, University of Southern California.

(32) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1955, p. 299.

potassium thiocyanate were added[33] and the contents diluted to the mark with water. The red solution was measured within 5 to 10 min. in a Klett-Summerson photoelectric colorimeter with a no. 54 filter. Readings were calibrated against suitable standards freshly prepared by the treatment of excess ferrous sulfate solutions with varying quantities of standardized hydrogen peroxide. The ferric ion concentration in the diluted reaction mixture remained constant up to 5 hr. after completion of the reaction. Results are given in Table I.

Formaldehyde was identified first from a reaction involving 0.2 g. (1.3 mmoles) of phenoxyacetic acid, 1.0 g. (2.5 mmoles) of ferrous ammonium sulfate in 200 ml. of 0.1 *N* sulfuric acid, and 10 ml. of 0.1 *N* (1.0 mmole) hydrogen peroxide. To the reaction mixture, 50 ml. of a solution of 1.2 g. of 2,4-dinitrophenylhydrazine in 300 ml. of 2 *N* hydrochloric acid was added. After standing overnight in the refrigerator, the product was collected and dried, m.p. 157–160°. Recrystallization from aqueous acetic acid gave a material of m.p. 161–162°. Admixture of authentic formaldehyde 2,4-dinitrophenylhydrazone of m.p. 164–165°, lit.[34] m.p. 167°, gave m.p. 157–160°. With 2- and 4-chlorophenoxyacetic acids it became necessary to modify the isolation by extracting the reaction mixture with ether, followed by addition to the aqueous phase of 5 g. of sodium hydroxide in 10 ml. of water. The mixture was centrifuged and the supernatant liquid acidified with 6 *N* hydrochloric acid. Addition of 50 ml. of the 2,4-dinitrophenylhydrazine solution yielded a crude precipitate, m.p. 155–158°, in both instances. Recrystallization from aqueous acetic acid gave material, m.p. 159–161°, with no lowering upon mixture with the pure substance.

Formaldehyde was determined, for example, by removal of 35 ml. of the 100 ml. of the diluted reaction mixture from 1.00 mmole of ferrous ion, 1.50 mmoles of phenoxyacetic acid, and 0.13 mmole of hydrogen peroxide in approximately 0.05 *N* sulfuric acid. The aliquot was made basic with two pellets of sodium hydroxide, filtered, and 25 ml. taken for analysis. The pH was adjusted to 4.6 with 1.0 *N* sulfuric acid and 0.04 *N* sodium hydroxide[35] and a solution of 10 mg. of dimedone (5,5-dimethyl-1,3-cyclohexanedione) in 10 ml. of water was added. After standing for 3 days, the product was collected in a weighed filtering crucible, dried, and weighed, m.p. 186–187°. Mixed with an authentic substance of m.p. 186–187°, lit.[36] m.p. 187°, it had m.p. 186–187°. The weight, 4.48 mg., was equivalent to 1.84 mg. (0.0613 mmole) of formaldehyde in the total reaction mixture. Neglecting the formation of any diether, the theoretical amount of formaldehyde formed was equivalent to 0.13 mmole of hydrogen peroxide consumed less one-half of the amount of ferric ion formed. A 5-ml. aliquot of the diluted reaction mixture was analyzed as already described and showed 0.117 mmole of ferric ion to be present, hence 0.0715 mmole (2.145 mg.) of formaldehyde. This gave a yield of 86%.

An independent determination was made on a 25-ml. portion of the diluted reaction mixture by extraction with four 25-ml. portions of ether, each of which was backwashed with 2 ml. of water which was added to the aqueous phase. The aqueous solution was diluted to 50 ml. and analyzed for formaldehyde by the chromotropic acid method[37] standardized with reference to formaldehyde solutions standardized by dimedone. The formaldehyde concentration in the 50-ml. solution was 0.0094 mg. per ml. which corresponded with 1.88 mg. (0.00627 mmole) total for a yield of 88%.

Formaldehyde-d_2 was purchased as a 20% solution in deuterium oxide from Isotope Specialities Company, Burbank, California. Formaldehyde bismethone and formaldehyde-d_2 bismethone were prepared by the method of Shriner, Fuson, and Curtin.[38] Solutions in chloroform, 10%, showed the following differences in infrared absorption spectra as determined on a Beckman IR-7 spectrophotometer[15]: formaldehyde bismethone, m.p. 190–191°, ν_{max} 976 cm.$^{-1}$ (ϵ 10.3), 1085 (160); formaldehyde-d_2 bismethone, m.p. 187–188°, ν_{max} 952 cm.$^{-1}$ (ϵ 24), 1064 (130), 2117 (3.3). A mixture of the two had m.p. 186–187°.

Formaldehyde-d_2 was identified by three methods after isolation of the bismethone. From a reaction of 0.1034 g. (0.67 mmole) of phenoxy-d_2-acetic acid, 1.02 mmoles of ferrous ion, and 0.363 mmole of hydrogen peroxide run in the usual fashion, the reaction mixture was extracted with four 25-ml. portions of ether. The combined ethereal extract was backwashed with three portions of water (2, 10, and 2 ml.) which were combined with the previous aqueous mixture. Sodium hydroxide (0.3 g.) was added and the mixture centrifuged, the residue washed with 10 ml. water which was centrifuged, and the supernatant liquids combined. Ether was removed from the aqueous mixture by evaporation at room temperature for 1 hr. at the water pump. The pH of the solution was adjusted as described previously and the bismethone precipitated and dried, 0.044 g. (0.15 mmole), m.p. 185–186°; ν_{max} 952 cm.$^{-1}$ (ϵ 23.2), 1064 (127), 2117 (3.3), 10% in chloroform, identical with formaldehyde-d_2 bismethone.

For deuterium analysis in the mass spectrometer, the isolated bismethone was diluted with undeuterated formaldehyde bismethone to an anticipated deuterium content of 0.1 to 1.0%. After combustion of the mixture in a stream of dry oxygen, the recovered water was reduced over zinc[14] at about 400° and the gas submitted for analysis in a Westinghouse modified type LV mass spectrometer.[39] Three water samples of known deuterium content were reduced and submitted for analysis at the same time to give correction factors of 0.99, 1.21, and 1.30. Using 1.30 gave 70–93% deuterium in the bismethone. The n.m.r. spectra were obtained on a Varian A-60.[40]

Phenol was identified in a typical reaction mixture from phenoxyacetic acid by extraction with three 50-ml. portions of ether which were combined and washed with two 10-ml. portions of water and with ten 10-ml. portions of 5% sodium bicarbonate solution. The ether layer then was extracted once with 10 ml. of 5% sodium hydroxide, which was acidified with hydrochloric acid and extracted with 25 ml. of ether. The ether was evaporated and the residue treated with 100 ml. of 0.1 *N* potassium bromate–potassium bromide solution. The precipitate was collected, washed with 50 ml. of 1% sodium bisulfite solution, dried, and recrystallized three times from ethanol to give 2,4,6-tribromophenol, m.p. 92–93°; mixture with pure material of m.p. 94–95° gave m.p. 92–93°, lit.[41] m.p. 95°.

Phenols were determined by extraction of an aliquot of a diluted reaction mixture with five 10-ml. portions of ether each of which was washed with 2 ml. of water. The combined ethereal layer was extracted with five 5-ml. portions of 1.0 *N* sodium hydroxide which were combined and evaporated for 1 hr. at the filter pump. The residual alkaline liquid was diluted to 50 ml., clarified by centrifugation, and used directly for examination by ultraviolet absorption according to Brown and Claflin.[38a] Results are given in Table I. In addition, such a solution from a reaction with 2-chlorophenoxyacetic acid was examined over the range 235 to 320 mμ. For every 5-mμ interval the absorbance was calculated as the sum of the absorbances of 2-chlorophenoxide ion and of 2-chlorophenoxyacetate ion of concentrations as determined at the absorption maximum. The calculated and observed curves agreed very well except for a discrepancy of about 20% in absorbances at 250–255 mμ. This agreement was taken as evidence that no other phenoxides were present.

The isolation of 1,2-diphenoxyethane as a reaction product was accomplished by filtration of a reaction mixture from, 8 g. of ferrous ammonium sulfate, 3 g. of phenoxyacetic acid, and 50 ml. of 0.25 *N* hydrogen peroxide (total volume, about 300 ml.). The precipitate was washed with two 14-ml. portions of warm (about 70°) water and dried. The products from eleven such reactions were combined by solution in 25 ml. of peroxide-free ether which was evaporated. The residue was digested with 25 ml. of 5% sodium bicarbonate solution at 50°, filtered, washed with 25 ml. of 5% sodium bicarbonate solution, and washed copiously with water. After drying, the material was dissolved in 25 ml. of petroleum hexane, decolorized, filtered, and evaporated. The colorless residue was crystallized from 0.1 ml. of methanol to give 5 mg. of product, m.p. and m.m.p. 95–96°,

(33) T. C. J. Ovenston and C. A. Parker, *Anal. Chim. Acta*, **3**, 277 (1949).

(34) C. D. Hodgman, Ed., "Tables for Identification of Organic Compounds," Chemical Rubber Publishing Co., Cleveland, Ohio, 1960, p. 68.

(35) J. H. Yoe and L. C. Reid, *Ind. Eng. Chem., Anal. Ed.*, **13**, 238 (1941).

(36) W. Weinberger, *ibid.*, **3**, 365 (1931).

(37) C. E. Bricker and H. R. Johnson, *ibid.*, **17**, 400 (1945).

(38) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1959, p. 220.

(39) We wish to acknowledge the help of Mr. R. Vanselow who performed the analysis on the instrument at the Department of Chemistry, University of California, Los Angeles 24, Calif.

(40) The purchase of this instrument was made possible by a generous grant from the National Science Foundation, which we are happy to acknowledge.

(41) See ref. 34, p. 41.

lit.[30] m.p. 98–98.5°. An infrared spectrum of a Nujol mull was superposable on a similar spectrum of authentic 1,2-diphenoxyethane.

The estimation of diphenoxyethanes was carried out by a single extraction of a 75-ml. aliquot of the diluted reaction mixture with 100 ml. of ether. The ethereal extract was washed with three 10-ml. portions of water, with three 10-ml. portions of 2% sodium hydroxide solution, and then with five 5-ml. portions of water or until the water wash was neutral to Universal Indicator paper. The ethereal solution was dried over anhydrous magnesium or calcium sulfate, filtered, and the residue washed with fresh portions of ether. The combined filtrates were evaporated under a stream of dried air, and the residue was taken up in 5 ml. of Spectro Grade carbon tetrachloride. This was evaporated to dryness and repeated once more. Finally the residue was dissolved in 0.5 ml. of the solvent for infrared examination. The extinction coefficients were determined on synthetic materials.

Polyfunctional Aliphatic Compounds. V. The Cyclization of Dinitriles by Halogen Acids. A New Synthesis of Imidazoles

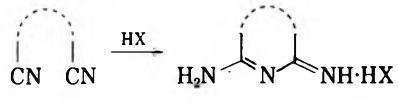
FRANCIS JOHNSON AND W. A. NASUTAVICUS

The Dow Chemical Company, Eastern Research Laboratory, Framingham, Massachusetts

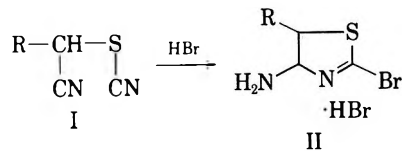
Received July 8, 1963

Dinitriles having the general structure, RN(CN)CH(CN)R, undergo cyclization to 2-bromo-4(5)-aminoimidazoles when treated with anhydrous hydrogen bromide. Where R and R′ are aryl groups these amino compounds are generally stable enough to be isolated as the free bases. Otherwise, the imidazoles can be obtained as their acetamino derivatives. A convenient method for the synthesis of the previously unavailable starting dinitriles utilizes the reaction of a monosubstituted cyanamide with an α-haloalkyl, or an α-[4-toluenesulfonyloxyl]alkyl cyanide in anhydrous dimethylformamide using triethylamine as an acid acceptor.

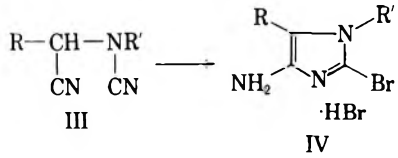
In previous publications[1–3] we have demonstrated that the halogen acid (X = Br or I) cyclization of dinitriles, *viz.*,



can be used for the synthesis of heterocyclic compounds in the pyridine,[1] isoquinoline,[2] and thiazole[3] series. The successful cyclization of α-cyanoalkyl thiocyanates (I) to 4-amino-2-bromothiazoles (II) suggested that

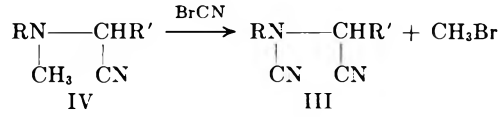


the analogous α-cyanoalkyl cyanamides (III) might lead to the corresponding imidazoles (IV).



Our findings, presented in this paper, now confirm this prediction and demonstrate, as anticipated, that the cyclization occurs in one specific direction, affording only derivatives of 4(5)-aminoimidazole.

α-Cyanoalkyl Cyanamides.—The chief difficulty in broadening the scope of the dinitrile cyclization to include imidazoles, lay in the unavailability of the precursors, namely α-cyanoalkyl cyanamides. For these aliphatic systems, only one recorded method of synthesis could be found in the literature. This, due to v. Braun,[4] involves the action of cyanogen bromide on N-alkyl-N-methylaminoacetonitriles (IV).



Where R is a simple alkyl group, selective cleavage of the methyl group occurs. Although this method proved suitable for the preparation of III, where R = alkyl and R′ = H, it was severely limited by the lack of easy methods of preparation of IV, where R = aryl or hydrogen and R′ = aryl, alkyl, or hydrogen. Therefore, a number of other approaches to III were tried, most with little success.

N-Phenyl-α-(4-methoxyphenyl)aminoacetonitrile did not react at room temperature with cyanogen bromide, and N-phenylaminoacetonitrile could only be induced to react with this reagent at temperatures above 90°. The sole product was N-(4-cyanophenyl)aminoacetonitrile.[5]

When α-phenylaminoacetonitrile (V) was treated with half an equivalent of cyanogen bromide in anhydrous ether the hydrobromide salt of V was rapidly precipitated, and from solution a sirup was obtained which could not be distilled or crystallized. Attempted chromatography only caused decomposition, and no α-cyanobenzyl cyanamide could be obtained.

A number of reactions using cyanamide (VI) itself were tried to no avail. A combination of benzaldehyde, hydrogen cyanide, and VI in the presence of anhydrous calcium sulfate did not lead to any α-cyanobenzyl cyanamide. On the other hand the reaction of α-cyano-2-chlorobenzyl 4-toluenesulfonate (VII) in the presence of triethylamine and VI afforded only the sulfone (VIII).

(1) F. Johnson, J. P. Panella, A. A. Carlson, and D. H. Hunneman, *J. Org. Chem.*, **27**, 2473 (1962).

(2) F. Johnson and W. A. Nasutavicus, *ibid.*, **27**, 3953 (1962).

(3) Part IV: F. Johnson and W. A. Nasutavicus, *ibid.*, **28**, 1877 (1963).

(4) J. v. Braun, *Ber.*, **40**, 3933 (1907).

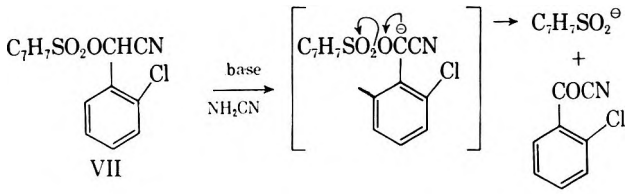
(5) Contrast N-methyl-N-phenylaminoacetonitrile which reacts with cyanogen bromide to give the bromo compound, N-methyl-N-(4-bromophenyl)aminoacetonitrile [J. v. Braun, *ibid.*, **41**, 2113 (1908)].

TABLE I

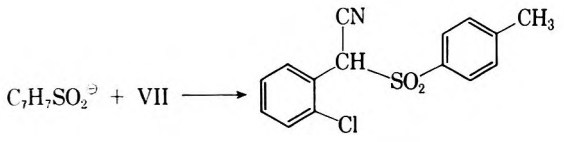
PREPARATION OF DINITRILES OF STRUCTURE $RCH(CN)N(CN)C_6H_5$

R	Crystd.[a] from	Yield, %	M.p., °C.	Analyses, % Calcd. C	H	N	Cl	Found C	H	N	Cl
H	ET	50	79–81	68.8	4.5	26.7		68.7	4.7	26.7	
C_6H_5	MC/E	62	105–107	77.2	4.8	18.0		77.1	5.0	17.8	
2-ClC_6H_4	ET	75	107–108	67.3	3.8	15.7	13.2	67.2	4.0	15.6	13.0
4-ClC_6H_4	MC/E	50.5	105–106	67.3	3.8	15.7	13.2	67.1	3.8	15.6	13.3
2,4-$Cl_2C_6H_3$	ET	40	98–100	59.6	3.0	13.9	23.5	59.6	3.0	13.6	23.6
2-$CH_3OC_6H_4$	ET	84	64–65	73.0	5.0	16.0		73.0	4.9	15.9	

[a] Solvent: ET = ethanol, MC = methylene chloride, E = ether.



VII

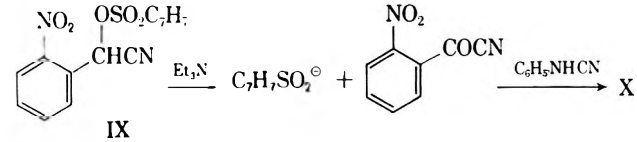


VIII

The mechanism of reactions of this type has been well documented.[3,6,7] When chloroacetonitrile was substituted for VII in the previous reaction only triethylcyanomethylammonium chloride could be isolated. Replacement of triethylamine by sodium acetate using ethanol as the solvent led to an oil, whose infrared spectrum indicated the presence of an >N–CN group but considerable absorption was present also in the 6-μ region. Attempted cyclization of this crude material in acetic acid followed by acetylation with acetic anhydride afforded only a trace of a bromine-containing material. The bulk of the product isolated by chromatography agreed well with $C_7H_{11}N_3O_4$. The n.m.r. spectrum of this substance in deuteriochloroform showed only two bands at −616 and −141 c.p.s. (with reference to tetramethylsilane at 0 c.p.s.) having relative intensities of 3:1. It exhibited bands in the infrared spectrum at 3.09, 3.16, 5.76, and 5.91 μ indicative of an imide group, but we have not been able to assign any structure to it.

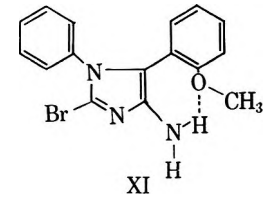
The reaction mixture of phenyl cyanamide and chloroacetonitrile in ethanol in the presence of sodium ethoxide darkened quickly and only tarry products could be obtained. Nevertheless when this reaction was carried out at room temperature in anhydrous dimethylformamide using triethylamine in place of sodium ethoxide, a good yield of N-cyano-N-phenylaminoacetonitrile was obtained. Using this procedure, phenyl cyanamide reacted with a range of α-chloroalkyl and α-[4-toluenesulfonyloxy]alkyl cyanides[3] to produce a number of the required dinitriles (III). These are listed in Table I. In only one case was a failure recorded. This involved α-cyano-2-nitrobenzyl 4-toluenesulfonate (IX), the only product that could be isolated being N-cyano-N-phenyl-2-nitrobenzamide (X). The latter was identified by comparison with an authentic specimen prepared from phenyl cyanamide and 2-nitrobenzoyl chloride.

Although phenyl cyanamide was the only monosubstituted cyanamide used in the preparation of III, we envisage that other aryl cyanamides could be utilized with equal success. However, attempts to extend the scope of this synthesis by using sodium dicyanamide in place of phenyl cyanamide met with uniform failure.



IX

Imidazoles.—When the α-cyanoalkyl cyanamides were treated with hydrogen bromide in an inert medium, reaction occurred rapidly in most instances, and the salt of the bromoaminoimidazole separated from solution. These materials were usually unstable to moisture and underwent a fast decomposition when added to mild base. The salts, however, could be converted easily to the corresponding acetamino compounds and most of the imidazoles were characterized as these derivatives. Where both 1- and 5-positions of the imidazoles were unsubstituted by aryl groups, the free amines could be isolated. The most stable was XI perhaps due to hydrogen bonding between the methoxyl and amino groups. The imidazoles prepared by hydrogen bromide induced cyclization are listed in Table II.



XI

Debromination of these compounds was accomplished easily as shown by the facile conversion of 4-acetamino-2-bromo-1-methylimidazole to 4-acetamino-1-methylimidazole when the former was shaken in solution with hydrogen and a palladium catalyst.

The constitution of these compounds as the 4-amino-2-bromoimidazoles and not the isomeric 2-amino-4-bromo compounds is suggested (a) by the instability of the free amines, a characteristic of 4(5)-aminoimidazoles[8] but not of 2-aminoimidazoles; and (b) by analogy with the cyclization of α-cyanoalkyl thiocyanates. The

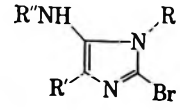
(6) E. C. Taylor, G. A. Berchtold, N. A. Goeckner, and F. G. Stroehmann, *J. Org. Chem.*, **26**, 2715 (1961).

(7) J. D. Loudon and I. Wellings, *J. Chem. Soc.*, 1780 (1959).

(8) K. Hofmann, "Imidazole and Its Derivatives," Part I, Interscience Publishers, Inc., New York, N. Y., 1953, pp. 142–143.

TABLE II

PREPARATION OF IMIDAZOLES FROM DINITRILES OF STRUCTURE RN(CN)—CH_2R'(CN)

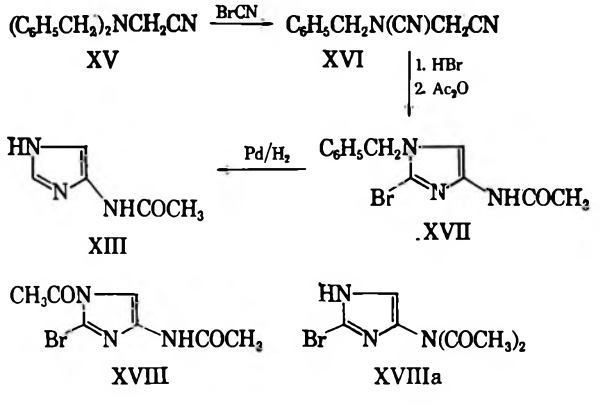


R	R'	R''	Method	Crystd.[a] from	Yield, %	M.p., °C.	Analyses, % Calcd. C	H	Br	N	Cl	Found C	H	Br	N	Cl
CH_3	H	CH_3CO	B	M	33	223–224	33.0	3.7	36.6	19.3		33.1	3.7	36.5	19.0	
C_2H_5	H	CH_3CO	B	MC/E	53	175–176.5	36.2	4.3	34.4	18.1		36.4	4.5	34.5	18.2	
C_4H_9	H	CH_3CO	B	MC/EA	47	138–140	41.6	5.4	30.7	16.2		41.6	5.2	30.8	16.0	
C_6H_5	H	CH_3CO	C	MC/E	82	200–202	47.2	3.6	28.5	15.0		47.0	3.5	28.4	14.9	
C_6H_5	C_6H_5	H	A	MC	82	195–210 dec.	57.3	3.9	25.4	13.4		57.3	3.9	25.7	13.2	
C_6H_5	2-ClC_6H_4	H	B[b]	M/E	10	249–252 dec.	51.7	3.2	22.9	12.0	10.2	51.5	3.4	22.7	11.9	10.1
C_6H_5	2-ClC_6H_4	CH_3CO	C	M	55	219–220	52.3	3.4	20.5	10.8	9.1	52.3	3.2	20.7	10.7	9.2
C_6H_5	4-ClC_6H_4	CH_3CO	C	MC	50	187–189	52.3	3.4	20.5	10.8	9.1	52.0	3.4	20.3	10.9	9.0
C_6H_5	2,4-$Cl_2C_6H_3$	H	A	MC/E	68	154–156	47.0	2.6	20.9	11.0	18.5	46.9	2.4	20.9	10.8	18.6
C_6H_5	2-$CH_3OC_6H_4$	H	A	MC	82.5	187–192 dec.	55.8	4.1	23.2	12.2		55.8	4.0	23.3	12.1	
$C_6H_5CH_2$	H	CH_3CO	B	MC/E	68	184–185	49.0	4.1	27.2	14.3		49.2	3.9	27.3	14.1	

[a] Solvent: M = methanol, MC = methylene chloride, EA = ethyl acetate. [b] Isolated by chromatography.

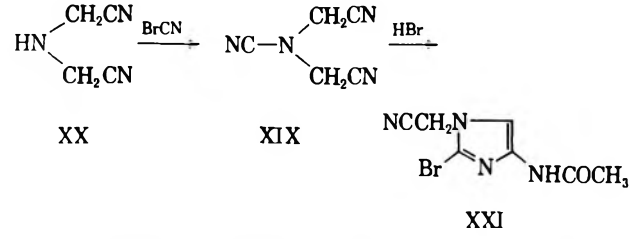
latter lead to 4-amino-2-bromothiazoles when treated with hydrogen bromide.[3] However, chemical evidence seemed desirable and an attempt was made to prepare 4(5)-acetamino-2-bromoimidazole (XII) with a view to converting it to the known 4(5)-acetaminoimidazole (XIII).

Treatment of aminoacetonitrile (XIV) with cyanogen bromide at 0° led to the rapid deposition of the hydrobromide of XIV together with a considerable quantity of highly colored gum. The liquid phase was removed and as attempted isolation of material from this led to further decomposition, it was treated directly with hydrogen bromide followed by acetic anhydride. The only product that could be isolated from this reaction was what appears to be the diacetylated imidazole (XVIII), and this only in very small amount. This structure is supported not only by a good elemental analysis but by its infrared spectrum which shows weak bands at 3.12 and 3.28 μ characteristic of a 4(5)-acetamino group in this series. Again imidazoles that we have examined having no substituent at the 1-position show a strong absorption at 3.10 μ. In addition strong bands are apparent at 5.75 (ring N-acetyl group) and 6.01 μ, the latter again characteristic of a 4(5)-acetaminoimidazole. Structure XVIIIa can be eliminated as a possibility because the 4(5)-diacetamino group could, by analogy with known examples in the thiazole series,[3] be expected to have only one absorption band at approximately 5.82 μ. However, the sequence of reactions shown finally led to the desired compound.



N,N-Dibenzylaminoacetonitrile (XV) was prepared[9] best by the action of chloroacetonitrile on dibenzylamine in the presence of triethylamine in anhydrous dimethylformamide. Cleavage of XV by cyanogen bromide occurred smoothly as did the subsequent cyclization and acetylation of XVI to give XVII. Hydrogenation of the latter to XVII, however, could not be accomplished in one step. It appears that the presence of bromide ion in solution inhibits the debenzylation reaction, for when this was removed, debenzylation occurred smoothly. The final product XIII had m.p. 225° in close agreement with that recorded (226°) for 4(5)-acetaminoimidazole,[10] but not with that (287°) of 2-acetaminoimidazole.[11] The infrared spectrum of XIII exhibited strong bands at 3.10 and 6.01 μ, in good agreement with what might be expected for a compound with this structure. The structures of the other imidazoles prepared were assigned by analogy with the direction of cyclization of XVI.

A number of other systems also were examined. N-Cyanoiminodiacetonitrile (XIX) prepared by the action of cyanogen bromide on XX underwent immediate reaction with hydrogen bromide. After acetylation the imidazole XXI could be obtained but the yield varied capriciously from 5–65%.



The structure assigned to XXI is supported by an elemental analysis and its infrared spectrum which exhibits a band at 5.95 (acetamino group) and a doublet at 6.34 and 6.44 μ characteristic of this type of imidazole. This spectrum, also, is strikingly similar to that

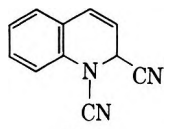
(9) The method described by R. A. Turner and C. Djerassi [*J. Am. Chem. Soc.*, **72**, 3081 (1950)] for the preparation of XV gave lower yields than the present procedure, and was often complicated by the appearance of N,N,N',N'-tetrabenzylmethylenediamine.

(10) G. Hunter and J. A. Nelson, *Can. J. Research*, **19B**, 296 (1941).

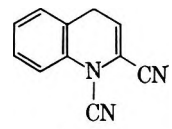
(11) R. G. Fargher and F. L. Pyman, *J. Chem. Soc.*, 217 (1919).

of 4-acetamino-2-bromo-1-methylimidazole, having corresponding bands at approximately 7.1, 7.2, 7.9, 10.0, and 13.5 μ. The lack of nitrile absorption in the spectrum of XXI was at first sight surprising but the complete absence of nitrile absorption in compounds such 2-acetoxy-2-cyanopropane has been noted previously.[12] This, however, appears to be the first reported occasion where an imidazole ring on the carbon atom bearing the nitrile group quenches the absorption of the latter. In addition the n.m.r. spectrum of XXI in trifluoroacetic acid shows absorptions at 473, 327, and 146.5 c.p.s. which integrated for proton ratios of 1:2:3. The positions of these bands are in good agreement with what might be expected for an imidazole proton, a methylene group flanked by an aromatic nucleus and a cyano group, and the hydrogens of an acetyl function. By way of comparison 4-acetamino-2-bromo-1-ethylimidazole showed n.m.r. absorption bands at 462 (proton at the 5-position), 265 (methylene quadruplet), 148 (acetyl methyl), and 98 c.p.s. (methyl triplet) in trifluoroacetic acid. However, no further chemical work on XXI has been attempted.

N,2-Dicyano-1,2-dihydroquinoline XXII prepared according to v. Braun[13] also was treated with hydrogen bromide. Reaction occurred immediately and a dark green muddy precipitate was deposited, but no crystalline product could be isolated. The isomeric dinitrile (XXIII) exhibited the same behavior.

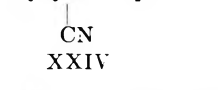


XXII

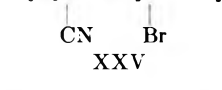


XXIII

In an attempt to determine if the cyclization procedure could be applied to groups isoelectronic with nitriles, N-phenyl-N-propargylcyanamide (XXIV), prepared by the action of propargyl bromide on phenylcyanamide in dimethylformamide, was treated with hydrogen bromide. A heavy white precipitate ap-



XXIV



XXV

peared but neutralization of this with mild base afforded only the hydrogen bromide addition product XXV which showed vinyl CH_2 absorption at 10.82 μ in its infrared spectrum.

Further work on the application of this dinitrile cyclization synthesis to other heterocyclic systems will be reported in subsequent publications.

Experimental

Melting points were determined on a Fisher-Johns melting point block and are not corrected. Infrared spectra were recorded on a Baird spectrophotometer Model No. A-55 as films or as Nujol mulls, and n.m.r. spectra were taken using a Varian A-60 instrument. Tetramethylsilane absorption was taken as the reference point of 0 c.p.s. in the n.m.r. spectra from the spectrophotometer. Hydrogen bromide in acetic acid was used as supplied by Eastman Kodak.

(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 256.

(13) O. Mumm and E. Herrendorfer, *Ber.*, **47**, 758 (1914).

Preparation of α-Cyanoalkyl Phenyl Cyanamides.—Phenyl cyanamide (0.02 to 0.04 mole) was dissolved in dry dimethylformamide (6 ml.) and triethylamine (0.2 to 0.4 mole) added. This mixture was then treated with a solution of the requisite halide or 4-toluenesulfonate. After a few minutes a precipitate of triethylamine salt began to appear. As soon as salt separation appeared complete (no more than 2 hr.) the total reaction mixture was poured into crushed ice. The solid which separated was rubbed until crystalline and then removed by filtration, dried, and recrystallized from the appropriate solvent.

N-Butyl-N-cyanomethyl Cyanamide.—Cyanogen bromide (10.6 g.) and N-butyl-N-methylaminoacetonitrile (12.6 g.) were combined and heated gently at 40° for 1.5 hr. The mixture was diluted with ether and the solid removed by filtration. The filtrate was heated to remove ether and the residual liquid (9.3 g.) distilled under reduced pressure. The fraction distilling at 95–115° (0.8 mm.) was collected (4.5 g.) and redistilled at 0.45 mm. to give the pure product (3 g.), b.p. 110°, $n^{25}D$ 1.4482.

Anal. Calcd. for $C_7H_{11}N_3$: C, 61.3; H, 8.1; N, 30.6. Found: C, 61.2; H, 8.0; N, 30.7.

The Action of Cyanamide and Triethylamine on α-Cyano-2-chlorobenzyl 4-Toluenesulfonate.—A solution of α-cyano-2-chlorobenzyl 4-toluenesulfonate (6.4 g.) in anhydrous dimethylformamide (10 ml.) was added to cyanamide (0.9 g.) and triethylamine (2.1 g.) in the same solvent (5 ml.). After 5 hr. the bronze-colored solution was poured into ice–water. The product, isolated by extraction with methylene chloride, was a colorless crystalline solid (2.7 g. 71%) and after recrystallization from methanol afforded pure α-cyano-2-chlorobenzyl 4-tolyl sulfone, m.p. 110–112°, lit.[7] m.p. 112°. Its infrared spectrum showed bands at 7.51 and 8.66 μ characteristic of a sulfone group.

Anal. Calcd. for $C_{15}H_{12}ClNO_2S$: C, 58.9; H, 4.0; Cl, 11.6; N, 4.6. Found: C, 58.9; H, 3.8; Cl, 11.6; N, 4.9.

N-Cyano-N-phenyl-2-nitrobenzamide. A.—Phenyl cyanamide (2.4 g.) in dry dimethylformamide (5 ml.) was treated with triethylamine (2 g.) followed by a solution of α-cyano-2-nitrobenzyl 4-toluenesulfonate (6.6 g.) in dimethylformamide (20 ml.). The mixture immediately became deep blue in color but changed to red within 3 hr. Addition of the solution to ice–water resulted in a partially crystalline red precipitate. This was removed by extraction with ether. Isolation of the product in the usual way followed by crystallization from ethanol led to the title compound (2.1 g., 40%), m.p. 116–118°. Its melting point was not depressed when mixed with the sample prepared later. Its infrared spectrum showed bands at 4.47, 5.81, and 6.56 μ.

Anal. Calcd. for $C_{14}H_9N_3O_3$: C, 62.9; H, 3.4; N, 15.7. Found: C, 63.3; H, 3.3; N, 16.0.

B.—Phenyl cyanamide (1.2 g.) in dry dimethylformamide (10 ml.) was treated successively with triethylamine (1.0 g. and 2-nitrobenzoyl chloride (1.9 g.). After 45 min. the solid precipitate was removed by filtration and recrystallized from ethanol to give the desired material, m.p. 116–117°. A mixture melting point with the specimen prepared as in a showed no depression.

Cyclization of Cyanoalkyl Cyanamides. A.—The dinitrile (0.01 mole) in methylene chloride (25–50 ml.) was treated with hydrogen bromide at 0° for 1.5 hr. The solvent and excess hydrogen bromide were removed at 30° under reduced pressure and the resulting solid added to saturated sodium hydrogen carbonate. After the subsidence of effervescence, the solid was removed, dried, and recrystallized from the appropriate solvent.

B.—The dinitrile (0.02 mole) if liquid, or dissolved in a minimum of acetic acid if solid, was added with cooling to a saturated solution (10 ml.) of hydrogen bromide in acetic acid. After stirring for 1 hr. an excess of a mixture of acetic anhydride and pyridine (3:1) was added. One and a half hours later the mixture was poured into saturated sodium hydrogen carbonate solution and the product isolated by methylene chloride extraction.

C.—This was the same as method A, except that the product was acetylated as in B.

4-Acetamino-1-methylimidazole.—4-Acetamino-2-bromo-1-methylimidazole (0.545 g.) and sodium acetate (0.205 g.) in ethanol (50 ml.) were stirred with hydrogen in the presence of a palladium-on-charcoal catalyst (90 mg., 10% Pd) at atmospheric pressure and room temperature. Hydrogen absorption ceased after 20 min. and the catalyst and solvent were then removed by the usual procedures. The residue was extracted with methylene chloride and the solution concentrated, then diluted with methanol to give 4-acetamino-1-methylimidazole (0.309 g., 89.5%), m.p. 249–252° dec.

Anal. Calcd. for $C_6H_9N_3O$: C, 51.7; H, 6.5; N, 30.2. Found: C, 51.7; H, 6.7; N, 30.5.

4-Acetamino-2-bromo-1-acetylimidazole.—Aminoacetonitrile (5.6 g.) in dry ether (30 ml.) was cooled to −60° and a solution of cyanogen bromide (5.3 g.) in the same solvent (30 ml.) added dropwise. The colorless solution was allowed to come to room temperature slowly and during this period it gradually darkened and an almost black gummy solid separated. The liquid phase was decanted and hydrogen bromide bubbled through it at ice bath temperatures. A copious yellow precipitate appeared and this was removed by filtration and added to acetic anhydride (10 ml.) and pyridine (2 ml.). Warming on the steam bath for 2 hr. followed by adding to sodium acetate solution led to a crude solid (0.5 g.). Repeated crystallization from ethyl acetate–ethanol gave the pure material, m.p. 192–193°.

Anal. Calcd. for $C_7H_8BrN_3O_2$: C, 34.2; H, 3.3; N, 17.1. Found: C, 33.9; H, 3.3; N, 17.0.

The Reaction of Chloroacetonitrile with Cyanamide.—Cyanamide (4.2 g.) was dissolved in ethanol (50 ml.) containing sodium acetate (8.2 g.) in suspension and the mixture stirred while chloroacetonitrile (7.5 g.) in ethanol (20 ml.) was added. Stirring was continued at room temperature until the aqueous phase gave only a slight test for organic chlorine (4 days). The precipitate (6.5 g.) was removed by filtration and the solvent evaporated to small bulk below 40°, and ethyl acetate added. After filtration to remove a small amount of suspended solid, the ethyl acetate and volatile materials were removed under reduced pressure. This afforded a sirup (5.3 g.) whose infrared spectrum showed bands at 4.44 and 5.90 μ. A sample of this material (3.4 g.) was added to a solution of hydrogen bromide (5.4 g., 30% hydrogen bromide) in acetic acid. After stirring for 1.5 hr., acetic anhydride (11.0 g.) was added and the mixture heated for 30 min. to effect solution of the precipitated solid. The liquid was then poured into saturated sodium acetate solution and, after stirring for a short period, the product was isolated by ethyl acetate extraction. This afforded brown crystals (1.9 g.) whose color was removed by percolation through a silica gel (15 g.) column in a 1:1 mixture of ethyl acetate methylene chloride. Two recrystallizations from acetone–ether gave the pure product (0.6 g.), m.p. 153–154°. It gave a negative Beilstein test.

Anal. Calcd. for $C_7H_{11}N_3O_4$: C, 41.8; H, 5.5; N, 20.9. Found: C, 41.8; H, 5.5; N, 21.0.

N,N-Dibenzylglycinonitrile.—Dibenzylamine (25 g.) and triethylamine (13.0 g.) were dissolved in anhydrous dimethylformamide (50 ml.), and chloroacetonitrile (10.5 g.) then added dropwise with stirring. Within 15 min. a precipitate began to appear and heat was evolved, but the solution was allowed to stand overnight. The dimethylformamide was removed under reduced pressure using a vacuum pump and the residue triturated with ice–water. The solid which formed was removed by filtration, dissolved in ether, and the ether solution stirred with magnesium sulfate and decolorizing charcoal. Filtration followed by concentration of the filtrate and dilution with petroleum ether afforded N,N-dibenzylglycinonitrile (21 g., 70%), m.p. 45–46°, lit.[9] m.p. 46–48°.

Using the procedure of Turner and Djerassi[9] the same product could be obtained in only 50% yield and isolation was more difficult.

N-Cyano-N-benzylglycinonitrile.—N,N-Dibenzylglycinonitrile (8.0 g.) in dry 1,2-dimethoxyethane (10 ml.) was treated with a solution of cyanogen bromide (4.24 g.) in the same solvent (20 ml.). The system was closed and the mixture heated for 48 hr. at 60–70°. The reaction solution was then added to a mixture of water and ethyl acetate. The organic layer was separated, dried over magnesium sulfate, and ethyl acetate and most of the benzyl bromide removed under reduced pressure. The resulting syrup was dissolved in benzene and chromatographed over silica gel (80 g.). Elution of the column with benzene afforded some benzyl bromide whereas benzene containing 10% methylene chloride gave starting material (about 1 g.). Further elution with the same solvents up to 100% methylene chloride removed unwanted materials (about 0.6 g.) which were discarded. Finally methylene chloride containing 10% ethyl acetate eluted the desired compound. Recrystallization from acetone–ether–petroleum ether (b.p. 30–60°) afforded pure N-cyano-N-benzylglycinonitrile (2.8 g., 48%), m.p. 63–64°. Its infrared spectrum showed a strong band at 4.46 μ.

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.2; H, 5.3; N, 24.5. Found: C, 70.3; H, 5.2; N, 24.2.

1-Benzyl-4-acetaminoimidazole.—1-Benzyl-2-bromo-4-acetaminoimidazole (1.8 g.) in ethanol (50 ml.) containing sodium acetate (0.65 g.) was shaken with hydrogen in the presence of a 10% palladium-on-charcoal catalyst (0.1 g.) at room temperature and pressure. Gas absorption ceased after 1 hr. and the catalyst and solvent were then removed. Water and methylene chloride were added and the organic layer separated and dried over magnesium sulfate. Evaporation of the solvent led to a solid which was recrystallized from methanol to give the pure product (1.15 g., 87%), m.p. 180–181°. Its infrared spectrum showed bands at 3.12, 3.17, 5.94, and 6.35 μ.

Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 67.0; H, 6.1; N, 19.5. Found: C, 66.9; H, 5.9; N, 19.3.

4(5)-Acetaminoimidazole.—1-Benzyl-4-acetaminoimidazole (0.6 g.) in glacial acetic acid (15 ml.) was stirred with a 10% palladium-on-charcoal catalyst (0.6 g.) in a hydrogen atmosphere overnight at room temperature and pressure. After the solution was filtered, the acetic acid was removed under reduced pressure and the solid product crystallized from methanol to give 4(5)-acetaminoimidazole (0.2 g.), m.p. 225° dec., lit.[10] 226°. For analysis, a sample was twice recrystallized from ethyl acetate.

Anal. Calcd. for $C_5H_7N_3O$: C, 48.0; H, 5.6; N, 33.6. Found: C, 48.0; H, 5.6; N, 33.5.

N-Cyanoiminodiacetonitrile.—A solution of iminodiacetonitrile (9.5 g.) and dry cyanogen bromide (5.8 g.) in monoglyme (100 ml.) was heated at 60° for 10 hr. The precipitated solid was removed by filtration and discarded. The filtrate was taken to dryness under reduced pressure and the residue crystallized from acetone–methylene chloride to give the pure product, m.p. 76–78° (2.7 g., 45%). The infrared spectrum showed a strong band at 4.45 μ.

Anal. Calcd. for $C_5H_4N_4$: C, 50.0; H, 3.16; N, 46.6. Found: C, 50.1; H, 3.4; N, 46.4.

4-Acetamino-2-bromo-1-cyanomethylimidazole.—To a cooled solution of N-cyanoiminodiacetonitrile (0.6 g.) in glacial acetic acid (10 ml.) there was added a 30% solution (11 g.) of hydrogen bromide in the same solvent. A heavy white precipitate formed immediately. After stirring for 1 hr., excess acetic anhydride (5 ml.) was added, and the solution heated for a further hour in a steam bath. The cooled solution was then poured into aqueous sodium acetate, and the precipitate removed by filtration. Recrystallization of this solid from methanol gave the desired compound (0.4 g.), m.p. 234–236°.

Anal. Calcd. for $C_7H_7BrN_4O$: C, 34.6; H, 2.9; Br, 32.9; N, 23.1. Found: C, 34.5; H, 3.0; Br, 32.9; N, 23.2.

N-Phenyl-N-propargyl Cyanamide.—To a cooled solution of phenyl cyanamide (2.4 g.) and triethylamine (2 g.) in anhydrous dimethylformamide (100 ml.), there was added dropwise propargyl chloride (1.6 g.) in the same solvent (10 ml.). The mixture was allowed to warm to room temperature and stood for 18 hr. The solution was poured into water and the gummy precipitate removed by filtration, dissolved in ethyl acetate, and this solution dried over anhydrous magnesium sulfate. Removal of the solvent led to a syrup which was dissolved in benzene and percolated through a silica gel (20 g.) column. Elution with methylene chloride–benzene (1:10) led to a solid (1.2 g.) which on crystallization from ether–petroleum ether (b.p. 30–60°) afforded the product, m.p. 46–47°. This material previously prepared[14] by the reaction of N-propargylaniline with cyanogen bromide was reported to have m.p. 48–49°.

Action of Hydrogen Bromide on N-Phenyl-N-Propargyl Cyanamide.—N-Phenyl-N-propargyl cyanamide (0.4 g.) was added to a 30–33% solution of hydrogen bromide in acetic acid (15 g.) and the mixture stirred for 20 hr. at room temperature. The reaction mixture was poured into an excess sodium hydrogen carbonate solution and the whole extracted with ethyl acetate. Isolation of the product in the usual way led to a sirup which crystallized. Recrystallization from ether–petroleum ether (b.p. 30–60°) afforded pure N-(2-bromoallyl)-N-phenyl cyanamide, m.p. 72–73°. Its infrared spectrum showed bands at 4.48 and 10.82 μ.

Anal. Calcd. for $C_{10}H_9BrN_2$: C, 50.7; H, 3.8; Br, 33.7; N, 11.8. Found: C, 50.4; H, 3.8; Br, 33.9; N, 11.6.

Acknowledgment.—The authors wish to thank Dr. C. K. Fitz who carried out all microanalyses.

(14) J. v. Braun and L. Tauber, *Ann.*, **458**, 102 (1927).

Acid Hydrolysis of γ-Hydroxybutyramide

R. BRUCE MARTIN, REGINA HEDRICK, AND ALICE PARCELL

Cobb Chemical Laboratory, University of Virginia, Charlottesville, Virginia

Received July 1, 1963

In order to characterize further the unusually rapid rate of acid hydrolysis of γ-hydroxybutyramide compared with butyramide, results are reported for hydrolysis rates over ranges of temperature and acidity. Hydrolysis of protonated γ-hydroxybutyramide proceeds with an activation energy of 14.6 kcal./mole and a pre-exponential term log A = 7.2. Both of these values are less than those obtained for ordinary amides. Plots of the logarithm of the observed first-order rate constant *vs.* the logarithm of activity of water yield abnormally low ω-values from 0.3 to 0.7 in perchloric acid and sulfuric acid at three temperatures. It is suggested that the results can be explained by nucleophilic attack of the hydroxy oxygen at the carbonyl carbon of the protonated amide and water-mediated proton transfer from this oxygen to the nitrogen atom. Pyrrolidone undergoes acid hydrolysis about 10^2 times slower than the corresponding straight-chain amide.

In comparing rates of hydrolysis of a series of hydroxy acid amides with their alkyl analogs of similar chain length, Zürn[1a] observed that in 1.0 N hydrochloric acid γ-hydroxybutyramide, δ-hydroxyvaleramide, and ε-hydroxycapronamide were hydrolyzed eighteen or more times faster than normal butyramide, valeramide, and capronamide, respectively. In this paper we undertook a further study of this augmentation in rate for γ-hydroxybutyramide over ranges of acidity and temperature.

Experimental

γ-Hydroxybutyramide was synthesized from γ-butyrolactone and concentrated aqueous ammonia. Melting point of the amide was 52–53° compared with lit.[1a] m.p. 46° and lit.[1b] m.p. 53–54°.

Anal. Calcd. for $C_4H_9NO_2$: C, 46.5; H, 8.8; N, 13.6. Found: C, 46.6; H, 8.8; N, 13.5.

Hydrolysis rates were calculated directly from the decrease in amide absorption at 200 mμ as followed on a Cary 11 spectrophotometer and corrected for product absorption. The amide does not exhibit an absorption maximum until further out in the ultraviolet. Under our conditions molar extinction coefficients on the slope at 200 mμ for the amide were about 1000 in water, decreasing to about 200 in the concentrated acids, and for the product about 50. Since Zürn[1a] deduced his rates from an estimate of liberated ammonia, both studies are measuring the rate of disappearance of amide. His single rate value obtained at 30° in 1 M hydrochloric acid is consistent with this study. Under the conditions of both studies, hydrolysis of amides is virtually irreversible and appearance of a lactone as an intermediate is irrelevant to the rate analysis. In acid solutions γ-butyrolactone[2] is hydrolyzed more rapidly than γ-hydroxybutyramide, however. Values of Hammett acidity functions[3] and activity of water[4] were taken from the indicated references.

Results

Observed first-order rate constants for hydrolysis of γ-hydroxybutyramide in solutions 1 or 2 × 10^{-3} M in amide and several concentrations of perchloric acid are presented in Table I. When the observed first-order rate constants are plotted against $-H_0$, a maximum occurs at about $-H_0$ = 1.7 at 25° in perchloric acid. This result is similar to that previously obtained for other amide hydrolyses in acid solutions and suggests that the observed first-order rate constant k' be expressed as

$$k' = k a_{H_2O} h_0/(h_0 + K_a)$$

where k represents the first-order rate constant for hydrolysis of protonated amide at unit activity of water and $h_0/(h_0 + K_a)$ specifies the fraction of amide in the protonated form. Because protonation of amide is not complete in dilute acids, k may only be determined by studies over a range of acidity and water activity.

TABLE I

OBSERVED FIRST-ORDER RATE CONSTANTS FOR HYDROLYSIS OF γ-HYDROXYBUTYRAMIDE IN PERCHLORIC ACID SOLUTIONS AT 25°

$HClO_4$	$k' \times 10^3$ min.$^{-1}$
1.10 pH	0.50
0.20 pH	4.0
1.47 M	7.1
2.40	10.8
3.38	11.9
4.31	13.2
4.38	12.9
5.66	10.3
6.21	9.5
6.36	9.5
7.51	6.1
7.66	7.1
8.30	5.4
8.45	5.0
8.75	4.2

Plots[5] of log k' − log $h_0/(h_0 + K_a)$ *vs.* log α_{H_2O} for γ-hydroxybutyramide yield straight lines if a suitable value for K_a is chosen. In 0.1 to 9 M perchloric acid solutions at 25°, a straight line of slope ω = 0.65 is obtained when K_a = 4. These values of ω and K_a are consistent with the position of the maximum on the $-H_0$ scale according to a previously derived relationship relating these three quantities.[6] From the extrapolation to unit activity of water, we calculate that k = 1.7 × 10^{-2} min.$^{-1}$ in perchloric acid at 25°.

Results for experiments performed at three temperatures in 5 to 9.6 M sulfuric acid are shown in Fig. 1 where $-\log k'$ is plotted against $-\log \alpha_{H_2O}$. The plots are extrapolated to unit activity of water. Obtaining more experimental points at water activities nearer unity would not aid the extrapolation because a suitable value of K_a would have to be evaluated as the line passes into the region where the amide is not fully protonated. At 15.0°, 25.0°, and 35.0° we obtain ω = 0.37, 0.55, and 0.30, and k = 0.8, 1.8 and 4.3 × 10^{-2} min.$^{-1}$, respectively. These last three rate constants yield an activation energy of 14.6 kcal./mole, a pre-

(1) (a) L. Zürn, *Ann.*, **631**, 56 (1960); (b) T. C. Bruice and F. H. Marquardt, *J. Am. Chem. Soc.* **84**, 365 (1962).

(2) F. A. Long, F. B. Dunkle, and W. F. McDevit, *J. Phys. Colloid Chem.*, **55**, 829 (1951).

(3) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).

(4) Appendix of first paper of ref. 5.

(5) J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961).

(6) R. B. Martin, *ibid.*, **84**, 4130 (1962).

exponential log $A = 7.2$, and an activation entropy of about -28 entropy units. Agreement between the two k values in different acids at 25° is satisfactory. Our corresponding values of ω and activation entropy fall far off a plot relating these two quantities for many reactions.[5]

The acid-catalyzed hydrolysis of pyrrolidone or butyrolactam also was studied in sulfuric acid solutions. A plot similar to that of Fig. 1 at 25° yields two straight line portions. From $0.15 < -\log a_{H_2O} < 0.3$, $\omega \simeq 1.9$ and $k \simeq 21 \times 10^{-6}$ min.$^{-1}$, while from $0.4 < -\log a_{H_2O} < 0.75$, $\omega \simeq 0.45$ and the extrapolated value of $k \simeq 7 \times 10^{-6}$ min.$^{-1}$. These acid hydrolysis rates for the lactam are about 10^2 times slower than those for straight-chain amides.

Discussion

The kinetically inferred value of $K_a \simeq 4$ is less than the value estimated from a plot of absorption at 200 mμ *vs.* $-H_0$ for γ-hydroxybutyramide. This difference parallels that in other amides. The difficulties associated with equilibrium spectrophotometric determination of K_a in amides have been mentioned[6]; the kinetically determined value is preferable in this case. Evidently the protonation of amides does not follow precisely the Hammett acidity function.[7] None of the discussion that follows is dependent upon the precise K_a value.

Acid hydrolyses of straight-chain amides exhibit activation energies of about 20 kcal./mole, factors of log $A \simeq 9.5$, and activation entropies of about -15 e.u.[8] Thus the acid hydrolysis of γ-hydroxybutyramide is characterized by comparatively lower activation energies and pre-exponential factors, or a more negative entropy of activation. The greater rate of acid hydrolysis of γ-hydroxybutyramide compared with its straight-chain analog is evidently due to a pronounced lowering of the activation energy which more than offsets a relatively unfavorable pre-exponential or entropy of activation term.[9]

Since successive removal of the hydroxy group from γ- and δ-, to ε-positions from the amide function increases ratios of hydrolysis rates for hydroxy amides as compared with alkyl analogs,[1] simple inductive effects cannot account for the augmentation in rates. Some kind of ring formation consistent with a more negative entropy of activation for hydroxyamide hydrolysis is indicated. Nucleophilic attack of the hydroxy group at the carbonyl carbon of the amide protonated at the carbonyl oxygen is suggested because other combinations of reactive groupings would involve intermediate rings of greater than seven members in the case of ε-hydroxycapronamide hydrolysis. Considering the results for acid hydrolysis of other amides,[10] we also assume that once nucleophilic attack has occurred loss of amide

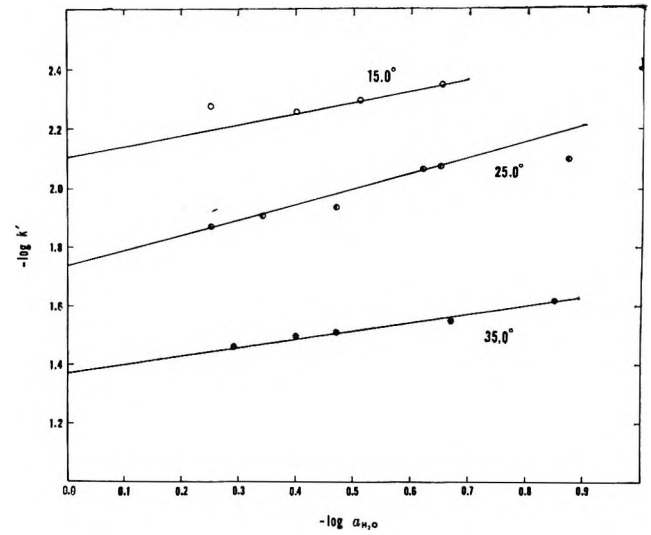


Fig. 1.—Plot of negative logarithm of first-order rate constant in min.$^{-1}$ *vs.* negative logarithm of activity of water for hydrolysis of γ-hydroxybutyramide in aqueous sulfuric acid solutions at three different temperatures.

function is inevitable; there is no appreciable reversion to reactant.

According to the Bunnett criterion for the role of water in the rate-determining step, $\omega < 0.0$ implies no involvement of water, $+1.2 < \omega < +3.3$ indicates water acting as a nucleophile, and $\omega > +3.3$ suggests water acting as a proton transfer agent.[5] In the acid hydrolysis of ordinary amides $\omega = 1.2$ to 2.6 indicative of water acting as a nucleophile.[5] In pyrrolidone hydrolysis the ω-value of about 2 at relatively high water activities is within the usual range for amides. We offer no explanation for the ω-value of about a half for the cyclic amide observed at low activities of water.

For γ-hydroxybutyramide the observed values of $\omega = 0.37$ to 0.65 fall into none of Bunnett's categories. The values are too high for no involvement of water, and in any case a role for water is indicated by the usual explanation given for a maximum in the observed rate constant *vs.* $-H_0$ plot. We have already concluded that the oxygen atom of the γ-hydroxy group functions as a nucleophile so that the only role remaining for water is that of a proton transfer agent. If this analysis is correct the acid hydrolysis of γ-hydroxybutyramide exhibits the lowest ω-value observed[5] for participation of water as a proton transfer agent with substrates protonated on oxygen or nitrogen. Can we rationalize ω-values at least 3 units lower than expected for water functioning as a proton transfer agent?

In perchloric acid solutions[5] hydrolysis of γ-butyrolactone exhibits a value of $\omega = 8.5$ while for the reverse reaction the lactonization of γ-hydroxybutyric acid $\omega = 2.2$. Since water is the nucleophile in hydrolysis while alcohol is the nucleophile in lactonization, there are reasons[6] for supposing that the difference in ω-values for hydrolysis and lactonization should be 1.2 to 3.3 units, corresponding to that for water functioning as a nucleophile. The observed difference, greater than expected by 3–5 units of ω, has been explained by unusual hydration changes brought about mainly by the already heavily hydrated γ-hydroxy group.[5] We might expect that a similarly hydrated hydroxy group in γ-hydroxybutyramide would yield observed ω-values 3–5 units lower in perchloric acid than normal

(7) J. T. Edward and I. C. Wang, *Can. J. Chem.*, **40**, 966 (1962).

(8) B. S. Rabinovitch and C. A. Winkler, *Can. J. Research*, **20B**, 73 (1942).

(9) We are comparing activation entropies of two pseudo first-order rate constants, and no problems concerning the choice of standard state arise. In comparing activation entropies for similar intramolecular and intermolecular reactions M. Bender [*Chem. Rev.*, **60**, 53 (1960)] has ignored a contribution of about -8 e.u. to activation entropies calculated from second-order rate constants due to the choice of standard state.

(10) M. L. Bender and R. D. Ginger, *J. Am. Chem. Soc.*, **77**, 348 (1955); C. A. Bunton, T. A. Lewis, and D. R. Llewellyn, *Chem. Ind.* (London), 1154 (1954).

for water acting as a proton transfer agent. Addition of 3–5 units of ω to our observed value in perchloric acid of 0.65 yields a derived ω = 3.6–5.7, well within the range suggested for water acting as a proton transfer agent. Thus we conclude that water is involved as a proton transfer agent in the rate-limiting step for acid hydrolysis of γ-hydroxybutyramide.

In a discussion of the results of Zürn,[1a] Witkop[11] suggested a nucleophilic attack of hydroxy oxygen on the carbonyl carbon of the protonated amide and direct transfer of hydroxy hydrogen proton to nitrogen. In order to accommodate a role for water as a proton transfer agent as indicated in this study, we suggest that the proton transfer from oxygen to nitrogen is mediated by one or more water molecules. Water removes the proton from the hydroxy oxygen and donates another proton to the nitrogen atom.

(11) B. Witkop, *Advan. Protein Chem.*, **16**, 221 (1961).

Acknowledgment.—This research was supported by grants from the National Institutes of Health and the National Science Foundation.

The Chemistry of 7-Substituted Norbornenes. The Reaction of Bicyclo[2.2.1]hept-2-en-7-one with Peracid[1,2]

P. G. GASSMAN AND P. G. PAPE[3]

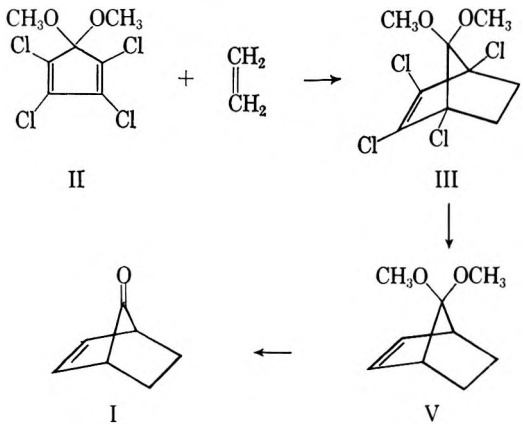
The Department of Chemistry, The Ohio State University, Columbus 10, Ohio

Received August 15, 1963

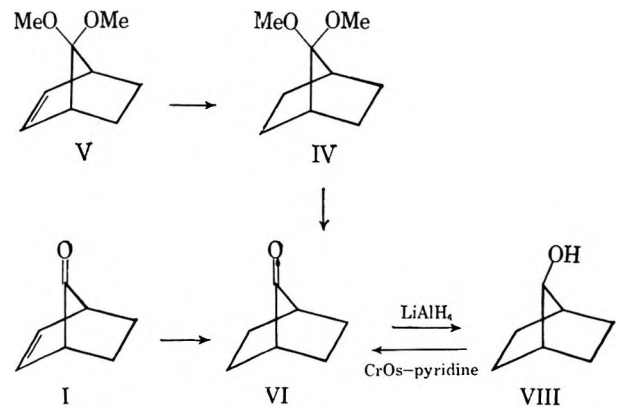
A short synthetic route to 7-substituted bicyclo[2.2.1]hept-2-enes has been developed. Bicyclo[2.2.1]hept-2-en-7-one has been prepared and was found to react with perbenzoic acid to give the epoxide (XI) rather than the Baeyer–Villiger product, indicating that there is very little interaction between the carbonyl and the nonconjugated double bond.

Although much is known about the chemistry of norbornenes, a relatively small amount of this recorded knowledge deals with the reactions of 7-substituted bicyclo[2.2.1]hept-2-enes. This paucity of information is due to the lack of a simple synthetic route to these relatively unknown compounds. We describe herein a simple four-step synthesis of bicyclo[2.2.1]-hept-2-en-7-one (I). Certain reactions of I are discussed. Of particular interest is the reaction of this unsaturated ketone with perbenzoic acid.

Ethylene reacts with 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (II) in an inert atmosphere at 180° to yield the expected Diels–Alder adduct (III).[4] Dechlorination of III according to the procedure of Winstein[5] gave partial reduction of the double bond resulting in a mixture of saturated and unsaturated ketals, IV and V, respectively. Although this mixture could be separated by extraction of the unsaturated ketal (V) with aqueous silver nitrate solution, this extra purification step was undesirable. Substitution of sodium for lithium in the dechlorination reaction gave pure 7,7-dimethoxybicyclo[2.2.1]hept-2-ene (V), which on hydrolysis under acidic conditions gave bicyclo[2.2.1]hept-2-en-7-one (I). The over-all yield of I from II was 45%.



The conversion of bicyclo[2.2.1]hept-2-en-7-one to well characterized compounds was considered to be an essential part of establishing the structure of I. Catalytic hydrogenation of I gave a 92% yield of bicyclo-[2.2.1]heptan-7-one (VI), a compound described in the literature as an oil[6] and as a solid.[7] Although our sample of the saturated ketone corresponded in melting point to that given in the literature,[7] the melting point of its 2,4-dinitrophenylhydrazone (VII) did not agree with the literature values.[6,7] Whereas both Walborsky and Norton list a melting point in the range 133–135°



(1) (a) Presented in part before the Division of Organic Chemistry, Abstracts of the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1963, p. 53M; (b) a preliminary communication of part of this work has appeared: P. G. Gassman and P. G. Pape, *Tetrahedron Letters*, **No. 1**, 9 (1963).

(2) We are indebted to the National Science Foundation, Grant 25221, for partial support of this research.

(3) National Science Foundation Summer Fellow, 1962.

(4) P. E. Hoch, *J. Org. Chem.*, **26**, 2066 (1961).

(5) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind.* (London), 405 (1960).

(6) H. M. Walborsky and D. F. Loncrini, *J. Org. Chem.*, **22**, 1117 (1957).

(7) C. Norton, thesis, Harvard University, 1955.

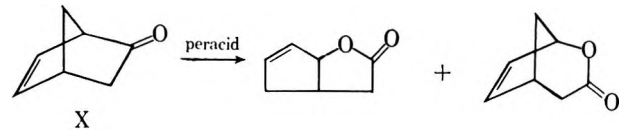
(8) Norton (ref. 7) reports 134–135° while we have found 137.2–137.8° for the melting point of the 2,4-dinitrophenylhydrazone of I.

for VII, we found a melting point of 158.2–158.8°. This was a confusing factor, especially since the 2,4-dinitrophenylhydrazone of bicyclo[2.2.1]hept-2-en-7-one melts in the 134–138° range.[8] Since the literature preparation of bicyclo[2.2.1]heptan-2-one made use of the oxidation of bicyclo[2.2.1]heptan-7-ol (VIII), we wondered if this oxidative approach was giving a mixture of ketones from which the 2,4-dinitrophenylhydrazone of something other than VI was being isolated. This idea was tested by preparing the well characterized bicyclo[2.2.1]heptan-7-ol and subjecting this alcohol to Sarett oxidation. The ketone formed in this reaction gave a crude 2,4-dinitrophenylhydrazone, m.p. 155–157° (157–158° after recrystallization), thus demonstrating that the oxidation of pure VIII was uncomplicated.[9]

One of the more interesting facets of bicyclo[2.2.1]-hept-2-en-7-one chemistry is the possible interaction of the carbonyl group and the nonconjugated double bond. In view of the large interaction between the carbonyl function and the nonconjugated olefinic linkage in dehydronorcamphor (X), as indicated by its ultraviolet charge transfer band at 225 mμ (ε 2800)[10] and by its behavior in its reaction with peracid,[11] we investigated the possible existence of nonconjugated interactions in I.

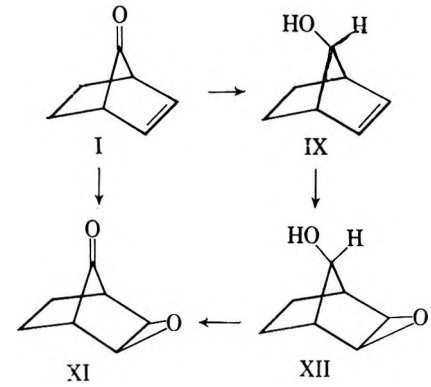
The ultraviolet spectrum of bicyclo[2.2.1]hept-2-en-7-one obtained under standard conditions showed no strong charge transfer band. This is in conflict with the much quoted spectrum of I described by Norton.[7] Whereas Norton reports $\lambda_{max}^{ethanol}$ 233 mμ (ε 1300), we found only strong end absorption in the 205-mμ region. Our observation of the absence of spectral evidence for a strong transannular interaction in strengthened by the recent report of Hurst and Whitham,[12] who obtained spectral data similar to ours for 1,5,5-trimethylbicyclo-[2.2.1]hept-2-en-7-one, *i.e.*, absorption rising to ε 3000 at *ca.* 200 mμ. Thus from a spectroscopic point of view there is little, if any, nonconjugated interaction of the two π-systems.[13]

A second indication that there is very little interaction between the carbonyl and the nonconjugated double bond resulted from the reaction of I with perbenzoic acid. As is commonly known, conjugated ketones react with peracid to give the Baeyer–Villiger product, whereas systems in which there is no interaction between the carbonyl and the double bond yield epoxides. Baeyer–Villiger reactions also occur in systems where there is no formal conjugation but where a strong nonconjugated interaction exists between the carbonyl and olefinic functions.[11,14] Dehydronorcamphor (X) has been shown by Meinwald and co-workers[11] to undergo only the Baeyer–Villiger reaction. They also have shown that this reaction is accompanied by skeletal rearrangement.



X

In the case of bicyclo[2.2.1]hept-2-en-7-one, we have been able to isolate only the epoxidation product, *exo*-2,3-epoxybicyclo[2.2.1]heptan-7-one (XI). This structural assignment was substantiated by infrared data (typical bicyclo[2.2.1]heptan-7-one carbonyl triplet at 5.39, 5.60, and 5.68; epoxide band at 11.92 μ) and by independent synthesis as follows. Lithium aluminum hydride reduction of I gave bicyclo[2.2.1]hept-2-en-*anti*-7-ol (IX). Treatment of IX with perbenzoic acid gave *exo*-2,3-epoxybicyclo[2.2.1]heptan-*anti*-7-ol (XII). On Sarett oxidation XII was converted to XI, identical in all respects to the product of the reaction of I with perbenzoic acid. Since the reaction of perbenzoic acid with I and IX yielded epoxides of similar stereochemistry it is assumed that the epoxidation occurred from the least hindered or *exo* side of the double bond.



Experimental[15]

Hexachlorocyclopentadiene.—The Hooker Chemical Company product was used without purification.[16]

5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (II).—Hexachlorocyclopentadiene was converted to II with methanolic potassium hydroxide according to the procedure of McBee.[17]

(9) An alternate explanation of the low melting points recorded by earlier workers is that the bicyclo[2.2.1]heptan-7-ol being oxidized was contaminated with a small amount of bicyclo[2.2.1]hept-2-en-7-ol (IX) resulting in a mixture of VI and I. Although this possibility could not be rigorously checked it was found that when I was mixed with VI and the mixture treated with 2,4-dinitrophenylhydrazine reagent, a derivative was obtained, m.p. 133–134°, after recrystallization from ethanol.

(10) (a) See S. Winstein, L. De Vries, and R. Orloski, *J. Am. Chem. Soc.*, **83**, 2020 (1961), for a leading reference; (b) R. C. Cookson and J. Hudec, *J. Chem. Soc.*, 429 (1962); (c) R. C. Cookson and N. S. Wariyar, *ibid.*, 2302 (1956); (d) P. D. Bartlett and B. E. Tate, *J. Am. Chem. Soc.*, **78**, 2473 (1956).

(11) J. Meinwald, M. C. Seidel, and B. C. Cadoff, *ibid.*, **80**, 6303 (1958).

(12) J. J. Hurst and G. H. Whitham, *J. Chem. Soc.*, 710 (1963).

(13) We have recently learned that Δ³-dihydro-dicyclopentadien-8-one, a substituted bicyclo[2.2.1]hept-2-en-7-one, shows $\lambda_{max}^{isooctane}$ 187.5 mμ (ε 6200) with shoulders at 190.0, 195.5, 203.0, and 215 mμ. This is reported to be in excellent agreement with a spectrum of bicyclo[2.2.1]hept-2-en-7-one determined by S. Winstein. This data indicates the possible existence of a *weak* charge transfer $\pi \rightarrow \pi^*$ transition. We wish to thank Dr. Kirby V. Scherer for making this information available prior to publication. See also K. V. Scherer, Abstracts of the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 61M. R. K. Bly and R. S. Bly recently have reported an ultraviolet spectrum for bicyclo-[2.2.1]hept-2-en-7-one similar to that which we found. See R. K. Bly and R. S. Bly, abstracts of the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 25M; also, R. K. Bly and R. S. Bly, *J. Org. Chem.*, **28**, 3165 (1963).

(14) S. Mori and F. Mukawa, *Bull. Chem. Soc. Japan*, **27**, 479 (1954).

(15) All melting points and boiling points are uncorrected. Microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herley, Denmark, or by Dr. Alfred Berhardt in the Max-Planck Institute, Mulheim (Ruhr) Hohenweg, Germany. Vapor phase chromatographic analyses were performed on an Aerograph Hy-Fi gas chromatograph. Preparative chromatography in the case of 7-ketonorbornane was carried out on an Aerograph Auto-Prep Model 700. Ultraviolet absorption spectra were run on a Cary Model 14 spectrophotometer. Infrared spectra were performed on a Perkin-Elmer Infracord except in the cases of 7-ketonorbornane and 7-ketonorbornene which were determined on a Perkin-Elmer Model 237 spectrophotometer.

(16) We wish to thank the Hooker Chemical Co. for a generous gift of this compound.

(17) J. S. Newcomer and E. T. McBee, *J. Am. Chem. Soc.*, **71**, 946 (1949).

7,7-Dimethoxy-1,2,3,4-tetrachlorobicyclo[2.2.1]hept-2-ene (III).[4]—A mixture of nitrogen and ethylene was bubbled into 200 g. of II which had been preheated to 185°. After maintaining these conditions for 6 hr. the reaction mixture was cooled and vacuum distilled to give 173.4 g. (78.5%) of III, b.p. 72–81° (0.10 mm.) [lit.[4] b.p. 56° (0.05 mm.)].

Lithium Dechlorination of 7,7-Dimethoxy-1,2,3,4-tetrachlorobicyclo[2.2.1]hept-2-ene (III).—To a stirred solution of 30 g. (0.102 mole) of III and 100 g. (1.35 moles) of *t*-butyl alcohol in 525 ml. of tetrahydrofuran under a nitrogen atmosphere was added 15 g. (2.55 g.-atoms) of finely chopped lithium wire. After 20 min. a vigorous exothermic reaction began which was controllable by attentive cooling with an ice bath. This exothermic reaction was maintained at steady reflux for 1 hr. As the exothermic reaction subsided the reaction mixture was heated externally to steady reflux for 1 hr. and then stirred at room temperature for an additional hour. The mixture was poured onto 3 l. of ice and extracted with three 250-ml. portions of ether. The ethereal solution was washed with three 500-ml. portions of water and one 200-ml. portion of saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the drying agent was removed by filtration. The solution was concentrated by distillation through a Vigreux column and then distilled *in vacuo* to give 10.10 g. (64%) of a colorless liquid, b.p. 70–81° (30 mm.). This product was shown by v.p.c., catalytic hydrogenation, and n.m.r. to be a mixture of *ca.* 65% 7,7-dimethoxybicyclo[2.2.1]hept-2-ene (V) and *ca.* 35% 7,7-dimethoxybicyclo[2.2.1]heptane (IV).

7,7-Dimethoxybicyclo[2.2.1]hept-2-ene (V). Method A. By Separation from the Mixture of 7,7-Dimethoxybicyclo[2.2.1]-hept-2-ene (V) and 7,7-Dimethoxybicyclo[2.2.1]heptane (IV) with Aqueous Silver Ion.[18]—A solution of 20.24 g. of a mixture of V and IV in 50 ml. of pentane was extracted with ten 25-ml. portions of a 20% aqueous silver nitrate solution. The reaction was followed by v.p.c., which showed a very pronounced decrease in the relative height of the unsaturated ketal peak in the mixture after each extraction. The combined silver nitrate extracts were poured into 100 ml. of concentrated ammonium hydroxide containing chipped ice. The ammonium hydroxide solution was extracted with pentane. The pentane extract was dried over anhydrous magnesium sulfate, and the drying agent was removed by filtration. The solution was concentrated by distillation and distilled *in vacuo* to give 10.26 g. (50.7% of the original mixture) of pure 7,7-dimethoxybicyclo[2.2.1]hept-2-ene (V), as shown by v.p.c., b.p. 74–78° (30 mm.). The clear liquid product was redistilled to give an analytical sample, b.p. 78° (30 mm.), $n^{28.6}$D 1.4584; infrared spectrum (neat), strong *cis* olefin absorption at 14.12 μ.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15; O, 20.75. Found: C, 70.10; H, 9.13; O, 20.91.

A 2,4-dinitrophenylhydrazone of bicyclo[2.2.1]hept-2-en-7-one was prepared from 0.22 g. (0.0014 mole) of 7,7-dimethoxybicyclo-[2.2.1]hept-2-ene by treating it with standard reagent[19] to give 0.35 g. (86%) of orange crystals, m.p. 133–134°. This derivative was recrystallized five times from 95% ethanol to give an analytical sample, m.p. 137.2–137.8°; ultraviolet absorption, $\lambda_{max}^{ethanol}$ 358 mμ (ε 22,800), 224 (18,700); $\lambda_{max}^{CHCl_3}$ 362 mμ (ε 23,800), [lit.[7] m.p. 134–135°, $\lambda_{max}^{CHCl_3}$ 360 mμ (ε 26,300)].

Anal. Calcd. for $C_{13}H_{12}N_4O_4$: C, 54.16; H, 4.20; N, 19.44. Found: C, 54.23; H, 4.36; N, 19.38.

Method B. By Direct Sodium Dechlorination of 7,7-Dimethoxy-1,2,3,4-tetrachlorobicyclo[2.2.1]hept-2-ene (III).—To a vigorously stirred solution of 31.92 g. (0.109 mole) of III, 90 g. (1.22 moles) of *t*-butyl alcohol, and 525 ml. of tetrahydrofuran under a nitrogen atmosphere was added 59 g. (2.57 g.-atoms) of finely chopped sodium metal. The mixture was heated to initiate the reaction, and a small amount of heat was applied during the reaction in order to maintain a steady reflux. No cooling was necessary in this reaction. After refluxing for 8 hr. the heating was stopped. The excess sodium reacted by slowly adding methanol (about 500 ml.) to the reaction mixture.

The reaction mixture was poured over 2 l. of ice and the reaction flask washed with about 700 ml. of water. The solution was extracted with four 250-ml. portions of ether. The combined ethereal solution was washed with three 500-ml. portions of water and one 250-ml. portion of a saturated sodium chloride solution. The ethereal solution was dried over anhydrous magnesium sulfate, and the drying agent was removed by filtration. After concentration by distillation the solution was distilled *in vacuo* to give 10.55 g. (62.8%) of 7,7-dimethoxybicyclo[2.2.1]-hept-2-ene (V), b.p. 70–77° (30 mm.). Its infrared spectrum and v.p.c. retention time were identical with those with the analytical sample of V. The latter instrumental method showed that V was uncontaminated by IV.

Bicyclo[2.2.1]hept-2-en-7-one (I).—7,7-Dimethoxybicyclo-[2.2.1]hept-2-ene (19.80 g.) was stirred vigorously with 25 ml. of 5% sulfuric acid for 20 hr. at 35° followed by extraction with two 10-ml. portions of pentane. The pentane solution was dried over anhydrous magnesium sulfate, and the drying agent was removed by filtration. The solution was concentrated by distillation at atmospheric pressure and the residue was distilled *in vacuo* to give 12.59 g. (91%) of bicyclo[2.2.1]hept-2-en-7-one (I), b.p. 66–70° (34 mm.). Redistillation gave an analytical sample, b.p. 63° (30 mm.), n^{25}D 1.4775. Infrared carbonyl absorption (neat) was 5.37 (medium), 5.58 (strong), 5.62 μ (medium); ultraviolet absorption, $\lambda_{max}^{ethanol}$ 273 mμ (ε 43), $\lambda_{max}^{CHCl_3}$ 273 mμ (ε 41), $\lambda_{max}^{isooctane}$ 274 mμ (ε 31) [lit.[7] b.p. 46–55° (13 mm.), $n^{26.5}$D 1.4780, infrared carbonyl absorption, 5.62 μ (strong)].

Anal. Calcd. for C_7H_8O: C, 77.75; H, 7.46. Found: C, 77.56; H, 7.69.

A 2,4-dinitrophenylhydrazone was prepared from 0.20 g. (0.00185 mole) of the unsaturated ketone (I) to give 0.52 g. (97%) of orange crystals, m.p. 123–130°. The product was recrystallized twice from 95% ethanol to give pure needles, m.p. 136–137°.

7,7-Dimethoxybicyclo[2.2.1]heptane (IV).—In a hydrogenation flask 10.91 g. of a mixture of V and IV and 0.200 g. of 5% palladium on carbon were stirred under hydrogen at room temperature and atmospheric pressure. After the hydrogen absorption had ceased, the catalyst was removed by filtration. The filtrate was vacuum distilled to give 9.53 g. (87%) of 7,7-dimethoxybicyclo[2.2.1]heptane (IV), b.p. 78–80° (30 mm.). The product was redistilled twice to give an analytical sample, b.p. 80° (30 mm.), n^{25}D 1.4533.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32; O, 20.49. Found: C, 69.46; H, 10.28; O, 20.45.

A 2,4-dinitrophenylhydrazone of bicyclo[2.2.1]heptan-7-one was prepared directly from 0.20 g. (0.0013 mole) of 7,7-dimethoxybicyclo[2.2.1]heptane to give 0.34 g. (91%) of crude orange crystals (VII), m.p. 152–153°. This derivative was recrystallized five times from 95% ethanol to give an analytical sample as orange needles, m.p. 158.2–158.8°. Ultraviolet absorption was $\lambda_{max}^{ethanol}$ 358 mμ (ε 20,400), 227 (16,700); $\lambda_{max}^{CHCl_3}$ 362 mμ (ε 22,500) [lit.[7] $\lambda_{max}^{CHCl_3}$ 367 mμ (ε 19,100)].

Anal. Calcd. for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.79; H, 4.87; N, 19.38.

Bicyclo[2.2.1]heptan-7-one (VI).—In a 25-ml. flask with distillation head, 2.06 g. (0.015 mole) of 7,7-dimethoxybicyclo-[2.2.1]heptane and 15 ml. (0.25 mole) of glacial acetic acid were heated to 115° for 10 hr. After cooling the solution was transferred to a separatory funnel with 30 ml. of petroleum ether (b.p. 35–45°). A solution of 12 g. (0.30 mole) of sodium hydroxide in 40 ml. of water was carefully added dropwise with cooling. An additional 40 ml. of water was added to dissolve the sodium acetate that had formed. The water layer was separated and washed twice more with 25-ml. portions of petroleum ether. The combined petroleum ether extracts were dried over anhydrous magnesium sulfate, and the drying agent was removed by filtration. The filtrate was concentrated to 15 ml. and transferred to a low temperature recrystallization apparatus in which a nitrogen atmosphere was maintained. The temperature was lowered slowly to Dry Ice temperature. At −20° a white crystalline solid began to precipitate. After crystallization was complete, the solvent was removed and the precipitate dried by passing nitrogen over the crystals to give 0.93 g. (64%) of extremely volatile bicyclo[2.2.1]heptan-7-one (VI), m.p. 77–79°.

Sublimation at 40° (7 mm.), two purifications by preparative v.p.c. (3/8 in. × 20 ft. aluminum column packed with 20% Dow 710 on 42/60 firebrick, helium as the carrier gas) and one further sublimation gave an analytical sample of VI as a clear waxy solid, m.p. 79.5–80.5°; infrared carbonyl absorption (Nujol), 5.42 (weak), 5.61 (strong), 5.73 μ (medium); ultraviolet absorption, $\lambda_{max}^{CHCl_3}$ 292 mμ (ε 22), $\lambda_{max}^{isooctane}$ 293 mμ (ε 18) [lit.[7] m.p. 80.2–

(18) S. Winstein and H. L. Lucas, *J. Am. Chem. Soc.*, **60**, 836 (1938).

(19) R. L. Shriver, R. C. Fuson, and D. Y. Custin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 219.

81.6°; infrared carbonyl absorption, 5.70 (strong), 5.62 μ (weak); ultraviolet absorption, $\lambda_{max}^{ethanol}$ 287 mμ (ε 32)].

Anal. Calcd. for $C_7H_{10}O$: C, 76.32; H, 9.15. Found: C, 76.40; H, 9.36.

A 2,4-dinitrophenylhydrazone derivative (VII) was prepared from 0.21 g. (0.0019 mole) of VI to give 0.50 g. (90%) of orange needles, m.p. 157.2–157.5°.

Hydrogenation of Bicyclo[2.2.1]hept-2-en-7-one (I).—In a hydrogenation flask 0.119 g. (0.00184 mole) of I with *ca.* 5 ml. of 95% ethanol and 50 mg. of 5% palladium on carbon was stirred under hydrogen at room temperature and atmospheric pressure. After 40 min. the ketone had taken up 98% of the theoretical volume of hydrogen. The catalyst was removed by filtration and the resulting filtrate was treated with 2,4-dinitrophenylhydrazone reagent to give 0.480 g. (92%) of the 2,4-dinitrophenylhydrazone of bicyclo[2.2.1]heptan-7-one, m.p. 152–154°. After recrystallization from ethanol, the orange needles melted at 156–157.5°.

Bicyclo[2.2.1]heptan-7-ol (VIII).—To a solution of 0.1029 g. (0.00093 mole) of bicyclo[2.2.1]heptan-7-one in 10 ml. of anhydrous ether was added dropwise with stirring a solution of 0.7412 g. (0.019 mole) of lithium aluminum hydride in 4 ml. of ether at 0°. After addition was complete the solution was stirred for 2 hr. whereupon 2.96 ml. of water was added dropwise to the stirring solution. The resulting slurry was stirred for 0.5 hr., filtered, and the precipitate washed with ether. The filtrate was dried over anhydrous magnesium sulfate, and the drying agent was removed by filtration. The ether was removed by flash evaporation to give 0.0897 g. (86%) of VIII, m.p. 151.5–153°. The white crystalline solid was recrystallized twice from petroleum ether (b.p. 65–75°) to give pure VIII, m.p. 152.4–153.6° (lit.[20] m.p. 152–153°).

Sarett Oxidation of Bicyclo[2.2.1]heptan-7-ol (VIII).—A solution of 0.73 g. of VIII in 20 ml. of pyridine was added to the complex formed from 2.0 g. of chromium trioxide and 20 ml. of pyridine.[21] After standing for 24 hr. the reaction mixture was poured into water and extracted with three portions of benzene–ether. The combined extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated. Treatment of the concentrate with 2,4-dinitrophenylhydrazine reagent gave 0.70 g. (37%) of VII, m.p. 155–157°, without purification.

***exo*-2,3-Epoxybicyclo[2.2.1]heptan-7-one (XI).**—Bicyclo[2.2.1]hept-2-en-7-one (1.50 g., 0.0139 mole) was added to 44.5 ml. of benzene containing 2.35 g. (0.0170 mole) of perbenzoic acid. The reaction mixture was kept at 2° for 64 hr. at which time iodometric titration indicated the reaction of 0.0129 mole of perbenzoic acid. The reaction mixture was extracted with two 25-ml. portions of a 10% sodium hydroxide solution followed by 25 ml. of water, and dried over anhydrous magnesium sulfate. Removal of the drying agent, followed by concentration of the solvent and dilution with pentane gave 0.99 g. (0.008 mole, 62%) of white crystalline XI. A combination of recrystallization from petroleum ether (b.p. 60–70°) and sublimation gave an analytical sample, m.p. 144–145°.

Anal. Calcd. for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.45; H, 6.46.

Bicyclo[2.2.1]hept-2-en-*anti*-7-ol (IX).—Bicyclo[2.2.1]hept-2-en-7-one (2.16 g.) was treated with excess lithium aluminum hydride in anhydrous ether at 0°. Hydrolysis with water, followed by filtration and removal of the solvent, gave an oily solid, which, after recrystallization from hexane and sublimation, yielded 1.20 g. (52%) of pure IX, m.p. 117.5–119.5° (lit. m.p. 117–118°).[7,22]

***exo*-2,3-Epoxybicyclo[2.2.1]heptan-*anti*-7-ol (XII).**—Bicyclo[2.2.1]hept-2-en-7-ol (0.55 g.) was added to a solution of 0.975 g. of perbenzoic acid in 25 ml. of methylene chloride. The reaction mixture was allowed to stand for 72 hr. at 2°, washed twice with 25 ml. of saturated sodium carbonate solution, washed once with 10 ml. of water, and dried over anhydrous magnesium sulfate. The solvent was stripped to yield 0.51 g. (82%) of white crystalline product, m.p. 150–155°. Two recrystallizations from hexane–benzene followed by sublimation gave an analytical sample of XII, m.p. 195.6–196.4°.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 67.00; H, 8.19.

***exo*-2,3-Epoxybicyclo[2.2.1]heptan-7-one (XI) *via* Oxidation of XII.**—A solution of 0.50 g. of pure XII in 15 ml. of pyridine was added to a stirred solution of the complex formed from 1.50 g. of chromium trioxide in 15 ml. of pyridine.[21] The reaction was stirred overnight, diluted with water, and extracted with ether. The ethereal solution was washed thoroughly with water, dried over anhydrous magnesium sulfate, filtered, and the ether evaporated to give 0.15 g. of semicrystalline keto epoxide. One recrystallization from petroleum ether (b.p. 60–70°) followed by sublimation gave pure XI, m.p. 142.5–143.5°. The infrared spectrum of this product was identical with XI obtained from the reaction of I with perbenzoic acid.

(20) S. Winstein and E. T. Stafford, *J. Am. Chem. Soc.*, **79**, 505 (1957).

(21) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *ibid.*, **75**, 422 (1953).

(22) (a) S. Winstein and M. Shatavsky, *ibid.*, **78**, 592 (1956); (b) P. R. Story, *J. Org. Chem.*, **26**, 287 (1961).

The Synthesis of 1α-Methylhydrocortisone and 1α-Methylcortisone Acetate[1]

W. J. WECHTER

Department of Chemistry, The Upjohn Company, Kalamazoo, Michigan

Received June 24, 1963

The synthesis of 1α-methylhydrocortisone, 1α-methylcortisone, and 1-methylprednisolone are described. The 1-methyl substituent is introduced by conjugate addition of methyl Grignard to the Δ[1]-3-keto steroid (I). The configuration of the 1-methyl is assigned by optical rotatory dispersion.

The introduction of methyl groups into the hydrocortisone molecule at positions 2,[2a] 6,[2b] 15,[3] and 16[4] has led to an enhancement of anti-inflammatory activity of the parent corticoid. Methylation at virtually all other positions in the hydrocortisone molecule, to give 4-,[5] 5-,[6] 7-,[7] 9-,[8,10] 11-,[9] 12-,[10] 14-, and 21-[11]methylhydrocortisones, has been reported to lead to diminution of anti-inflammatory activity. For the cases of enhanced cortical activity in which the substituent clearly can be designated as axial or equatorial (*i.e.*, exclusive of 15- and 16-methyl), methyl group orientation has been both α and equatorial. In order to

(1) Presented at the 145th National Meeting of the American Chemical Society, New York, N.Y., September, 1963.

(2) (a) J. A. Hogg, F. H. Lincoln, R. W. Jackson, and W. P. Schneider, *J. Am. Chem. Soc.*, **77**, 6401 (1955); (b) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek, and J. A. Hogg, *ibid.*, **78**, 5213 (1956).

(3) P. F. Beal and R. W. Jackson, private communication.

(4) S. L. Steelman, E. R. Morgan, and R. H. Silver, *Steroids*, **1**, 163 (1963).

(5) N. G. Steinberg, R. H. Hirschmann, and J. M. Chemerda, *Chem. Ind.* (London), 975 (1958).

(6) J. H. Fried, G. E. Arth, and L. H. Sarett, *J. Am. Chem. Soc.*, **82**, 1684 (1960).

(7) R. E. Beyler, A. E. Oberster, F. Hoffmann, and L. H. Sarett, *ibid.*, **82**, 170 (1960).

(8) F. Hoffman, R. E. Beyler, and M. Tishler, *ibid.*, **80**, 5322 (1958).

(9) G. S. Fonken and J. A. Hogg, *Tetrahedron*, **2**, 365 (1958).

(10) J. Fried, private communication.

(11) H. J. Hess, S. K. Figdor, G. M. K. Huges, R. Pinson, Jr., and W. T. Moreland, 138th National Meeting of the American Chemical Society, New York, N.Y., September, 1960, p. 39P.

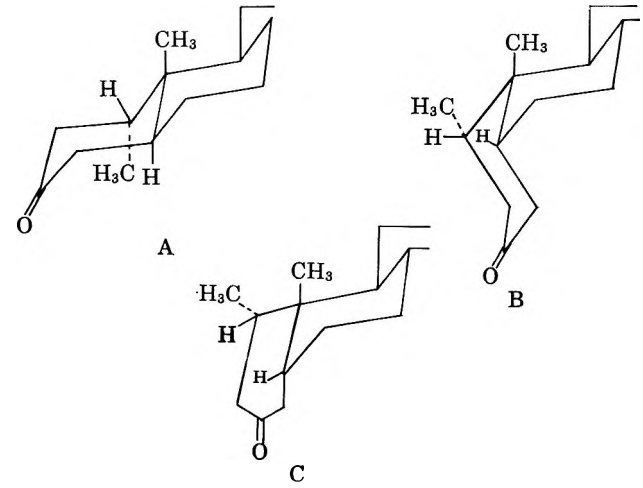
evaluate further this influence of α-methyl substitution and to provide steric protection from metabolism of ring A[12] we undertook the preparation of 1α-methylhydrocortisone (α and axial) and 1-methylprednisolone.

Earlier approaches to 1-methyl steroids have involved principally the dienone phenol rearrangement of $\Delta^{1,4}$-3-ketones followed by Birch reduction to give compounds which are probably 1β-methyl-19-nor steroids, although evidence for the conformation of the methyl group was not available. In this manner 1-methyl-19-nortestosterone,[13] 1-methyl-19-norprogesterone,[14] 1-methyl-17α-ethinyl-19-nortestosterone, and 1-methyl-19-norhydrocortisone[13] were synthesized. One might anticipate, however, that a 1-methyl-19-norcorticoid would be an unlikely prospect for enhanced cortical activity since 19-norhydrocortisone[15] itself is less active than hydrocortisone.

Weichert and Kaspar[16] have embarked on 1-methyl steroid syntheses by taking advantage of the Michael addition of diazomethane to a 5α-Δ^1-3-ketone, which gave a pyrazoline which was in turn pyrolyzed giving the 1-methyl-Δ^1 system. Reduction afforded principally 1β-methyl steroids which lack the desired α configuration needed to test the previous structural hypothesis. Until Djerassi recently published the short wave-length optical rotatory dispersion[17] curve of 1α- and 1β-methyl-19-norprogesterones, the configuration of the methyl group had been obscure.

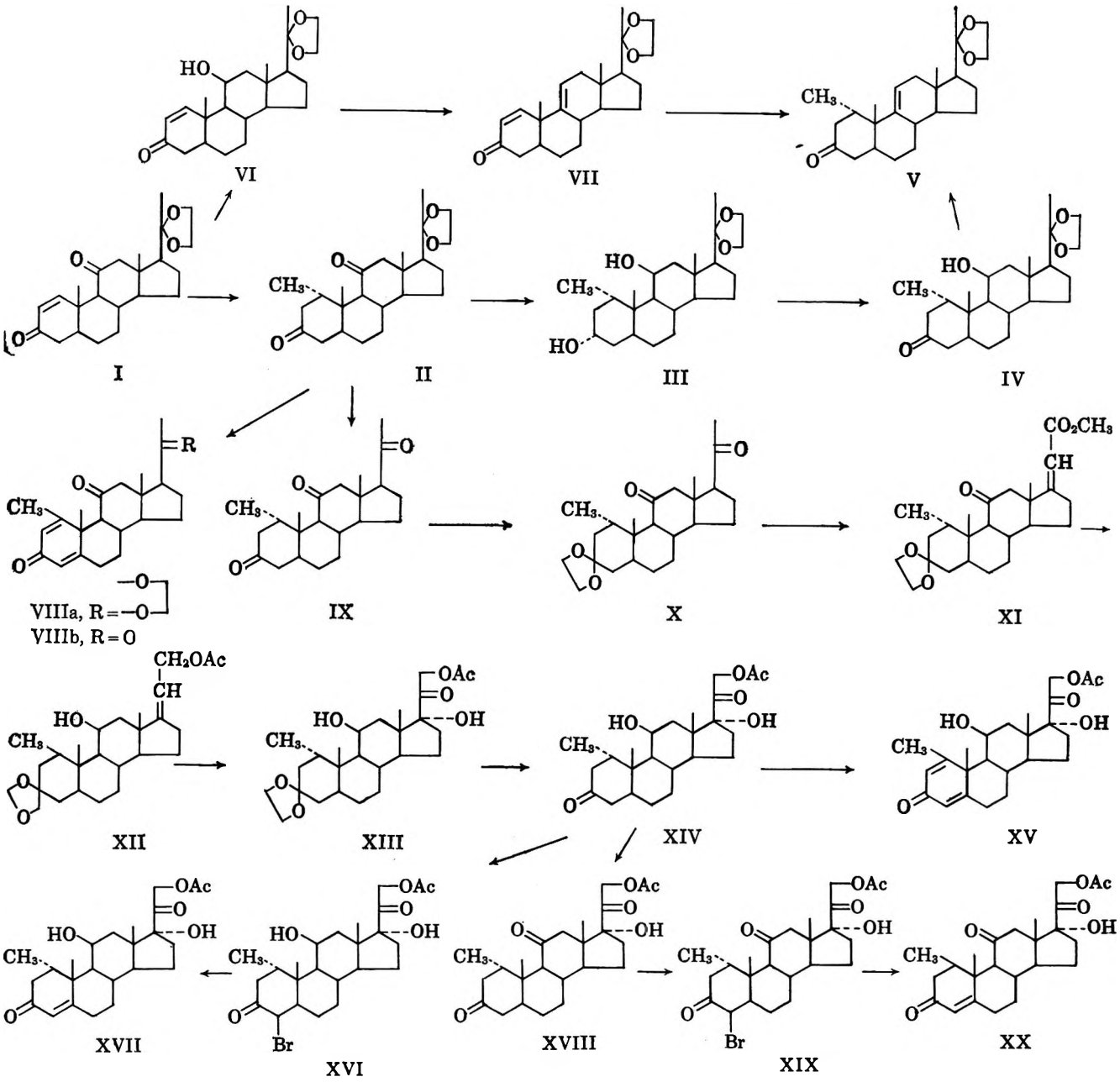
The most attractive route to 1α-methyl corticoids appeared to be *via* the 5β-Δ^1-ketone (I) which can be obtained from the incubation of 5β-pregnane-3,11,20-trione cyclic 20-(ethylene acetal) with *Septomixia affinis*.[18] Inverse addition of methyl Grignard to the α,β-unsaturated ketone (I) afforded the 1-methyl derivative (II) which gave, on ketal hydrolysis, 1-methylpregnanetrione (IX). Stereochemical considerations based on a study of molecular models suggested that alkylation need not take place preferentially from one side of the molecule. In this particular case, however, α attack might appear to be favored since the added substituent would be in the thermodynamically favorable equatorial configuration. Alkylations similar to this one have been reported[19] to yield exclusively the kinetic product; we found that the copper-catalyzed Grignard alkylation of I yielded stereoselectively the equatorial isomer. An explanation of the stereoselectivity and stereochemistry of our alkylation product has been sought. Subsequent to the completion of this work Mori[20] carried out the conjugate addition of methyl Grignard to Δ^1-dihydrotestosterone (A/B *trans*) and obtained 1α-methyltestosterone after introduction of the Δ^4-bond. Similarly 1α-methylcoprostan-3-one, 1α-methylcholest-4-en-3-one and its reduction product 1α-methylcholestan-3-one were prepared.

Mori[20] found that the 1α-methyl A/B-*trans* system (A) showed a typical positive Cotton effect curve whereas the 1α-methyl A/B *cis* system exhibited an abnormal weak positive Cotton curve. He observed from examination of molecular models of the 1α-methyl A/B *cis* system (abnormal Cotton curve) that in conformation B the 1α-methyl group violates the van der Waals radius of the 11-methylene. Since this appeared energetically unfavorable, he concluded that the A-ring actually existed in conformation C, which he suspected would give an abnormal O.R.D. curve. Subsequent publications by Djerassi[21] confirmed the hypothesis that such a boat or twist conformation might exhibit an abnormal exhalted O.R.D. curve. Similarly the 1-methyl-3-keto 20-ketals (IV and V) exhibited abnormal exhalted negative Cotton effect curves (molecular amplitudes $a = -55°$ and $-70°$, respectively) with respect to the normal negative Cotton curve of a closely related 3-keto 5β-steroid [calculated molecular amplitude = ($-8°$ for compound A, Fig. 1) $-$ ($25°$, for contribution for the β-equatorial methyl group) = $-33°$]. Consequently, we have concluded that our A/B *cis* 1-methyl steroid (II) possessed a 1α-methyl substituent and that A-ring exists in a boat or twist conformation.



In order to examine the possibility that the stereoselectivity of the 1-methylation might be directed *via* initial complexing of the Grignard reagent with the 11-ketone followed by alkylation internally at C-1,[22] the following experiments were carried out. The dione I was reduced with lithium aluminum hydride to the 3,11-diol and then oxidized selectively by means of the Oppenauer oxidation to the 11β-hydroxy 3-ketone (VI). This compound was in turn dehydrated to the diene VII. Upon alkylation the diene VII gave a single 1,4-addition product which was established to be the 1α-methyl steroid (V). The structure of V was related unequivocally to the original alkylation product (II) by reduction to the diol III, Oppenauer oxidation to the ketone IV, and finally dehydration which afforded the 1α-methyl $\Delta^{9(11)}$-steroid (V) identical in all regards with that obtained from the alkylation of the diene VII. Thus the stereochemical course of the 1,4-

(12) W. E. Dulin, L. E. Barnes, E. M. Glenn, S. C. Lyster, and E. J Collins, *Metab. Clin. Exptl.*, **7**, 398 (1958).
(13) H. J. Ringold, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, 2477 (1956).
(14) C. Djerassi, A. E. Lippman, and J. Grossman, *ibid.*, **78**, 2479 (1956).
(15) L. Sarett, "International Congress on Steroid Hormones," Milano, 1962.
(16) R. Weichert and E. Kaspar, *Ber.*, **93**, 1710 (1960).
(17) C. Djerassi, R. Records, E. Bummenberg, K. Mislow, and A. Moscovitz, *J. Am. Chem. Soc.*, **84**, 871 (1962).
(18) G. S. Fonken and H. C. Murray, *J. Org. Chem.*, **27**, 1102 (1962).
(19) H. D. House and H. W. Thompson, *ibid.*, **28**, 360 (1963).
(20) H. Mori, *Chem. Pharm. Bull.* (Tokyo), **10**, 386 (1962).
(21) (a) C. Djerassi and W. Klyne, *Proc. Natl. Acad. Sci. U. S.*, **48**, 1093 (1962); (b) C. Djerassi, E. Lund, and A. A. Akhrem, *J. Am. Chem. Soc.*, **84** 1249 (1962).
(22) J. A. Campbell and J. C. Babcock, *ibid.*, **81**, 4069 (1959).



Grignard step was the same whether a double bond or a ketone was present at C-11.

Selective halogenation at C-4 of the trione IX was unsuccessful under conditions[23] where 4-halo-5β-pregnane-3,11,20-triones are prepared in high yield from 5β-pregnane-3,11,20-trione.[24] Since selective halogenation at C-4 was not possible at this juncture, it was decided first to construct the dihydroxyacetone side chain and introduce the Δ^4-bond late in the synthesis. In order to establish that the A-ring would accommodate a Δ^4-bond a sample of the ketal II was dehydrogenated with selenium dioxide to the diene VIIIa, and the ketal hydrolyzed to yield the 1-methyl-$\Delta^{1,4}$-3,11,20-trione (VIIIb). Its structure was confirmed both by its infrared and ultraviolet spectra.

In order to protect the 3-ketone, the trione IX was selectively ketalized employing selenium dioxide and ethylene glycol in chloroform[25] to give the 3-monoketal (X). Employing the sequence of Hogg, *et al.*,[26] the side chain was glyoxylated, brominated, and the Favorskiĭ rearrangement carried out to give the ester XI in *ca.* 50% yield. Reduction with lithium aluminum hydride followed by acetylation in pyridine afforded the allylic ester (XII). Oxidation with N-methylmorpholine peroxide–hydrogen peroxide complex in the presence of osmium tetroxide gave the desired side-chain elaborated steroid (XIII). Acid hydrolysis of the ketal XIII afforded 1α-methyldihydrohydrocortisone acetate (XIV). Bromination with one mole of bromine in acetic acid containing a trace of hydrogen bromide followed by dehydrohalogenation *via* semicarbazone formation and pyruvate cleavage afforded 1α-methylhydrocortisone acetate (XVII). The structure of compound XIV and XVII were confirmed by their n.m.r. spectra which are summarized in Table I. The ultraviolet spectrum of the hydrocortisone derivative XVII was abnormal [λ_{max} 247 mμ (ε 13,150)].

(23) For summary of selective halogenations, see H. J. E. Lowenthal, *Tetrahedron*, **6**, 286 (1959).

(24) This fact lends further credence to the assumption that the A-rings of the 5β-3-ketones II–V possess a boat or twist conformation.

(25) E. P. Oliveto, H. I. Smith, C. Gerold, R. Rausser, E. B. Hershberg, *J. Am. Chem. Soc.*, **78**, 1414 (1956).

(26) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, *ibid.*, **77**, 4436 (1955).

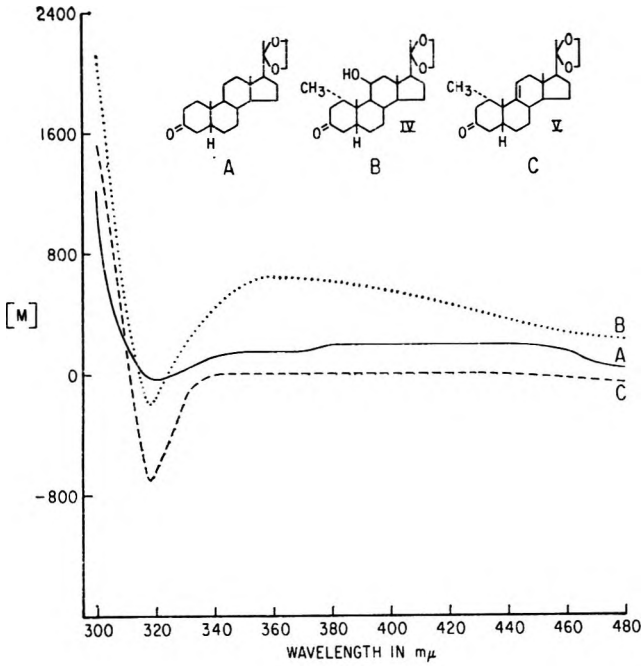


Figure 1.

A possible explanation of this fact may lie in the distortion of the A-ring by the 1α-methyl group which manifests itself also in the abnormal exalted O.R.D. curves (Fig. 1). Dreiding models do suggest, owing to the 11α-H–1α-methyl interaction, that the A-ring distortion in XVII is greater than in the 11-keto compound (XX) which has a normal ultraviolet spectrum.

If an excess of bromine is employed for the bromination of XIV, then the 11β-hydroxyl is oxidized to a ketone and 1α-methylcortisone acetate (XX) is the sole product isolated after dehydrohalogenation. 1α-Methylcortisone (XX) was prepared alternately by chromium trioxide oxidation of dihydrohydrocortisone acetate (XIV) to 1α-methyldihydrocortisone acetate (XVIII) followed by the bromination–dehydrohalogenation sequence. 1-Methylprednisolone acetate (XV) was prepared by selenium dioxide oxidation of the dihydrohydrocortisone (XIV). The structure of this product was confirmed by its infrared and ultraviolet spectra.

Compounds XVIII and XX exhibited very weak, if any, glucocorticoid activity.[27]

Experimental[28]

1α-Methyl-5β-pregnane-3,11,20-trione Cyclic 20-(Ethylene Acetal) (II).—To the Δ¹-5β-pregnene-3,11,20-trione 20-ketal (2.5 g., 6.7 mmoles) dissolved in 50 ml. of purified tetrahydrofuran containing 200 mg. of copper(I) bromide, chilled in an ice bath, was added dropwise a solution of 5 ml. of 3 *M* methylmagnesium bromide (15 mmoles) and 200 mg. of copper(I) bromide dissolved in 10 ml. of purified tetrahydrofuran with stirring. The stirred solution was allowed to come to room temperature during 2 hr. The reaction mixture was again chilled, treated with saturated ammonium chloride, and diluted with 150 ml. of ether. The organic layer was separated, washed with saturated ammonium chloride, twice with saturated sodium chloride solution, then dried over sodium sulfate. The solvent was removed on the rotary vacuum evaporator then absorbed onto a short Florisil[29] column (50 g.) and the product eluted with 5% acetone–Skellysolve B. This crystalline material was recrystallized from Skellysolve B–acetone giving 1.73 g. (69%) of a crystalline solid, m.p. 163–167°. A sample was recrystallized twice for analysis, m.p. 165.5–169°. Physical constants were ν_{max} 1700, 1330, 1070 and 1047 cm.$^{-1}$; O.R.D. (*c* 1.005, dioxane, 25°), $[M]_{290}$ +3130°, $[M]_{300}$ + 2320°, $[M]_{320}$ +1180°, $[M]_{355}$ +1005°, $[M]_{380}$ + 1080°, and $[M]_{589}$ + 595°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.46; H, 9.75.

1α-Methyl-5β-pregnane-3,11,20-trione (IX).—The 1α-methyl 20-ketal from the previous experiment (1.50 g., 3.88 mmoles) was dissolved in 25 ml. of alcohol (warm) and treated with 10 ml. of 3 *N* hydrochloric acid, then warmed on a steam bath for 3 hr. followed by dilution with hot water to the point of incipient crystallization. The product separated as white crystalline bars, 870 mg. (65%), m.p. 142–165°. Recrystallization twice from acetone–Skellysolve B afforded 510 mg. of product, m.p. 169–173°. A sample was recrystallized twice for analysis, m.p. 172–174°; ν_{max} 1697 and 1690 cm.$^{-1}$; O.R.D. (*c* 1.004, dioxane, 25°), $[M]_{302}$ +6210°, $[M]_{312.5}$ +7050°, $[M]_{340}$ +3815°, $[M]_{400}$ +1785°, $[M]_{480}$ 823°, and $[M]_{589}$ 377°.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.79; H, 9.52.

1α-Methyl-3α,11β-dihydroxy-5β-pregnan-20-one Cyclic (Ethylene Acetal) (III) and 1α-Methyl-11β-hydroxy-5β-pregnane-3,20-dione Cyclic 20-(Ethylene Acetal) (IV).—A 5.6-g. sample of the dione II was dissolved in 100 ml. of isopropyl alcohol and 2.5 g. of sodium borohydride dissolved in 50 ml. of water containing 0.5 ml. of 3 *M* sodium hydroxide solution was added. The mixture was heated at reflux for about 20 hr. After 7 hr. an additional 5 g. of sodium borohydride was added. The alcohol was then removed under reduced pressure and the solid isolated, washed with water, and dried (*in vacuo*, 60°). The infrared spectrum of this product was consistent with the expected structure, m.p. 171–186°; yield, 5.6 g. The crude diol was dissolved in 100 ml. of hot toluene containing 5.0 ml. of cyclohexanone and a small quantity of the solvent distilled so as to dry the reaction mixture. Aluminum tri-*t*-butoxide (5.6 g.) was then added and the suspension heated at reflux for 2 hr. The cooled suspension was extracted consecutively with *N* hydrochloric acid, water, saturated sodium chloride solution, dried with sodium sulfate, and evaporated to a small volume under reduced pressure. The residue was adsorbed onto 250 g. of Florisil and eluted over a gradient of from 2 to 15% acetone–Skellysolve B during twenty-five 400-ml. fractions. **Fractions 7–11** (2.67 g.) were combined and recrystallized from acetone to give 2.07 g. of the ketone (IV), m.p. 176–179°; ν_{max} 3400, 1690, and 1223 cm.$^{-1}$. A sample was recrystallized four times for analysis, m.p. 178.0–179.5°; O.R.D. (*c* 1.67, dioxane), $[M]_{48}$ +224°, $[M]^{max}_{360}$ +640°, $[M]^{min}_{317.5}$ −192°, and $[M]_{300}$ +2116°.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.96; H, 9.95.

Fractions 14–19 (1.61 g.) were combined and recrystallized from acetone to give 1.2 g. of the diol III, m.p. 188–194.5°. A sample was recrystallized four times for analysis, m.p. 197.0–199.5°; ν_{max} 3480, 1218 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73.43; H, 10.41.

11β-Hydroxy-5β-pregn-1-ene-3,20-dione Cyclic 20-(Ethylene Acetal) (VI).—5β-Pregn-1-ene-3,11,20-trione cyclic 20-(ethylene acetal) (10 g.) was treated as described previously. With removal of the toluene after oxidation a solid was isolated and recrystallized from ethyl acetate to give 3.48 g. of crude product, m.p. 202–208.5°. A sample was recrystallized four times from acetone, m.p. 217.5–218.5°; ν_{max} 3400, 1656, and 1613 cm.$^{-1}$; λ_{max} 227 mμ (ε 9300).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.99; H, 9.21.

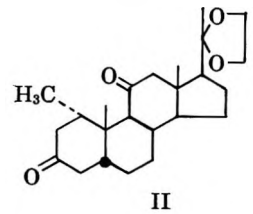
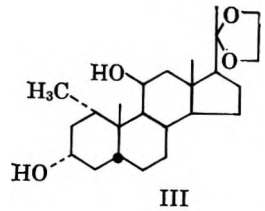
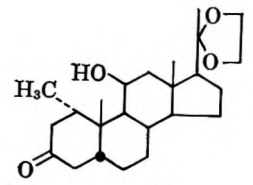
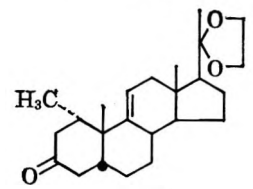
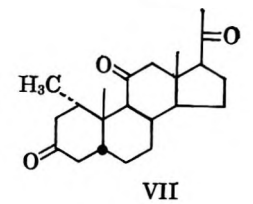
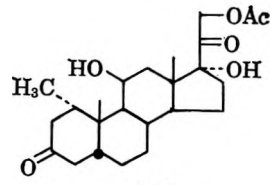
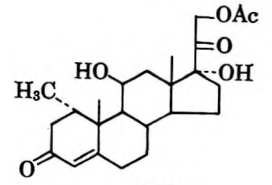
1α-Methyl-5β-pregn-9(11)-ene-3,20-dione Cyclic 20-(Ethylene Acetal) (V).—The alcohol (IV, 500 mg., 1.28 mmoles) was dissolved in 5 ml. of dry pyridine and treated under nitrogen with 193 mg. (1.4 moles) of N-bromoacetamide at room temperature for 15 min. The solution was then chilled in an ice bath and

(27) R. Stafford, L. Barnes, B. Bowman, and M. Meinzinger, *Proc. Soc. Exptl. Biol. Med.*, **89**, 371 (1955).

(28) Melting points were taken by capillary (except where noted) and are uncorrected. Infrared spectra were recorded as mineral oil mulls employing a Perkin Elmer Model 21 spectrometer. N.m.r. spectra were determined on 5–10% solutions in deuteriochloroform (except where noted) at 60 Mc. with a Varian 4320/2 spectrometer, employing tetramethylsilane as an internal reference. Frequencies are reported in cycles per second relative to tetramethylsilane as 0 c.p.s. Skellysolve B is a petroleum ether fraction, b.p. 50–70°.

(29) A synthetic magnesium silicate manufactured by the Floridin Co., Warren, Pa.

TABLE I

Compound	Function	Frequency, c.p.s.[a]	Multiplet	J	No. of H
 II	Ketal	234	m		4
	19-H[b]	74	s		3
	18-H	45	s		3
	21-H	75	s		3
	1α-CH_3[c]	54.7	d	6.5	3
 III	11α-H	258	m		1
	Ketal	241	m		4
	3β-H	*ca.* 240	m		1
	21-H	79	s		3
	19-H	70	s		3
	18-H	60	s		3
	1α-CH_3	61.5	d	8	3
 IV	11α-H	264	m		1
	Ketal	241	m		4
	21-H	79	s		3
	19-H	76	s		3
	18-H	63	s		3
	1α-CH_3	57.5	d	7	3
 V	Ketal	240	m		4
	11-H	338	m		1
	21-H	80	s		3
	19-H	69	s		3
	1α-CH_3	63.5	d	7	3
	18-H	44	s		3
 VII	21-H	125	s		3
	19-H	74	s		3
	18-H	34.5	s		3
	1α-CH_3	52.5	d	7	3
 XII	21-H[d]	296.5	AB	17	2
	11α-H	266	m		1
	19-H	72	s		3
	18-H	56	s		3
	1α-CH_3	56	d	6	3
 XVII	4-H	338	m		1
	21-H	292	AB	17	2
	11α-H	269	m		1
	19-H	82	s		3
	18-H	55.5	s		3
	1α-CH_3	63	d	6.5	3

[a] Downfield from tetramethylsilane. [b] R. F. Zurcher, *Helv. Chim. Acta*, **44**, 1380 (1961); G. Slomp and F. A. MacKellar, *J. Am. Chem. Soc.*, in press. [c] G. Slomp and R. B. McGarvey, *ibid.*, **81**, 2200 (1959). [d] N. R. Trenner, B. H. Arinson, D. Taub, and N. L. Wendler, *Proc. Chem. Soc.*, 214 (1961).

the excess oxidant destroyed with sulfur dioxide gas. The reaction mixture was then diluted with 25 ml. of water and refrigerated. The white crystalline product was filtered, washed thoroughly with water, and dried (*in vacuo*, 60°); yield, 400 mg. The solid was adsorbed onto 30 g. of Florisil and eluted over a gradient of from 2 to 7.5% acetone–Skellysolve B during twenty 50-ml. fractions. **Fractions 10–18** contained 131 mg. of material whose infrared spectrum was identical with that of the starting material. **Fractions 2–5** (276 mg.) were crystalline olefin, m.p. 159.0–159.5°. A sample was recrystallized for analysis, m.p. 159.0–159.5°; ν_{max} 3030, 1706, and 1600 cm.$^{-1}$; O.R.D. (*c* 1.09, dioxane), $[M]_{480}$ −67°, $[M]_{370}$ 00°, $[M]_{340}$ 00°, $[M]^{min}_{317.5}$ −707°, and $[M]_{305}$ +875°.

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.42; H 9.83.

5β-Pregna-1,9(11)-diene-3,20-dione Cyclic 20-(Ethylene Ace-

tal (VII).—The alcohol (VI, 3.1 g.) was treated as described previously with 1.0 g. of N-bromoacetamide in 20 ml. of pyridine. The crude product weighed 1.4 g., m.p. 110–144°. This material was adsorbed onto 75 g. of Florisil and eluted with twenty-four 100-ml. portions of acetone–Skellysolve B over a gradient of from 2 to 10% acetone. **Fraction 8–11** (365 mg.) proved to be the 11-ketone. **Fraction 4–5** (143 mg.) were combined and recrystallized from acetone two times, m.p. 164.5–166.5°; ν_{max} 3040, 1675, and 1612 cm.$^{-1}$; λ_{max}^{EtOH} 226 mμ (ε 20,200).

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.32; H, 9.43.

Grignard Alkylation of 5β,Pregna-1,9(11)-diene-3,20-dione Cyclic 20-(Ethylene Acetal).—The olefin (VII, 375 mg.) dissolved in 10 ml. of freshly purified tetrahydrofuran was chilled to 0° under nitrogen and 10 mg. of copper(I) bromide added. To this cold stirred solution was added, dropwise, 1 ml. of 3 *N* methylmagnesium bromide (in ether) and 10 ml. of copper(I) bromide in 5 ml. of tetrahydrofuran after which the reaction mixture was allowed to warm to room temperature during 1 hr. The suspension was again chilled and 5 ml. of saturated ammonium chloride solution added dropwise. The organic layer was separated and the aqueous phase extracted three times with ether. The combined extracts were washed consecutively with saturated ammonium chloride solution, saturated sodium chloride solution, dried with sodium sulfate, and evaporated to dryness. The residue was adsorbed onto 50 g. of Florisil and eluted over a gradient of from 0–5% acetone–Skellysolve B. Fraction 10 was the 1α-methyl olefin (V). One spot was observed by t.l.c. (silica gel G, 35% ethyl acetate–65% cyclohexane). The structure was confirmed by the infrared spectrum of this fraction, m.p. 158.8–159.5°. **Fractions 11–16** (mixture of three components) were recombined and rechromatographed on 32 g. of Florisil taking twenty-five 50-ml. fractions over a gradient of from 0.5 to 2% acetone–Skellysolve B, plus ten fractions of 5% acetone. **Fractions 13–24** were combined and recrystallized to give 127 mg. of 1α-methyl-5β-pregn-9(11)-ene-3,20-dione 20-cyclic (ethylene acetal) (V), m.p. 156.5–157.5°, identical by infrared with an authentic sample, admixture with an authentic sample exhibited no melting point depression. **Fractions 26–27** contained a gum whose infrared spectrum was consistent with 1,2-addition to give 3ξ-hydroxy-5β-pregna-1,9(11)-dien-20-one cyclic (ethylene acetal). The mother liquor solids (29 mg.) from the crystallization of combined fractions 13–24 by t.l.c. (*vide infra*) are a mixture of the 1α-methyl product (V) and a second slower moving substance. These solids dissolved in acetone were applied to a preparative t.l.c. (silica gel G, 20 cm. × 20 cm. × 1 mm.) and the chromatogram developed with ethyl acetate–cyclohexane (1:1). The position of the products was determined by strip spraying with 50% aqueous sulfuric acid followed by heat. The slower moving product was isolated in the usual manner[30] (extracted into acetone), but there was insufficient material for characterization.

1-Methyl-1,4-pregnadiene-3,11,20-trione Cyclic 20-(Ethylene Acetal) (VIIIa).—A stirred mixture of 1α-methyl-5β-pregnane-3,11,20-trione cyclic 20-(ethylene acetal) (3.0 g.), selenium dioxide (1.8 g., Fairmount Chemical Co.), pyridine (0.6 ml.), and *t*-butyl alcohol (200 ml.) was heated to reflux under nitrogen for about 30 hr. The cooled solution was filtered (Super-Cel filter aid) then taken to dryness under reduced pressure. The residue was taken up in ethyl acetate (100 ml.), treated with Norit, and washed consecutively with water, freshly prepared ammonium sulfide, cold 17% ammonium hydroxide, water, dilute hydrochloric acid, water, saturated sodium chloride solution, dried with sodium sulfate, and evaporated to dryness under reduced pressure giving a brown gum. The gum was dissolved in methylene chloride and adsorbed onto 125 g. of Florisil. The product was eluted over a gradient of from 7 to 18% acetone in Skellysolve B. Fractions 7–10 were combined and recrystallized from Skellysolve B–acetone to give 410 mg. of light yellow crystals, m.p. 165.0–172.5°. A sample was recrystallized once for analysis, m.p. 176.0–177.8°; ν_{max} 3020, 2990, 1710, 1668, 1662 and 1603 cm.$^{-1}$; λ_{max} 244 mμ (ε 16,950) *R* (244 mμ/264 mμ) = 2.01 ($\Delta^{1,4}$).

Anal. Calcd. for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.77; H, 8.33.

1-Methyl-1,4-pregnadiene-3,11,20-trione (VIIIb).—The dione (VIIIa, 340 mg.) dissolved in acetone (20 ml.) was treated with 3 *N* hydrochloric acid (1 ml.) overnight. The solution was diluted with an equal volume of water and the acetone removed under reduced pressure to give a partially crystalline solid. The solid was adsorbed onto a short Florisil column (10 g.) and eluted with 10% acetone–Skellysolve B to give 170 mg. of crystalline material, m.p. 194.0–195.5°. A sample of this material was recrystallized for analysis, m.p. 194.5–195.2°; ν_{max} 3060, 3020, 2990, 1710, 1668, 1622, and 1603 cm.$^{-1}$; λ_{max} 244 mμ (ε 17,650).

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.22; H, 8.38.

1α-Methyl-5β-pregnane-3,11,20-trione Cyclic 3-(Ethylene Acetal) (X).—1α-Methyl-5β-pregnane-3,11,20-trione (10.5 g.), selenium dioxide (10.5 g., Fairmount Chemical Co.), ethylene glycol (150 ml.), and alcohol-free chloroform (100 ml.) was stirred for 4 days at room temperature. The reaction mixture was then poured into water (1.25 l.) containing potassium carbonate (17 g.). The chloroform layer was separated and the aqueous extracted twice with methylene chloride. The combined extracts were dried with sodium sulfate, taken to a small volume under reduced pressure, then adsorbed onto 200 g. of Florisil. The product was eluted with eight 400-ml. fractions of 10% acetone–Skellysolve B and the combined solids were crystallized from acetone–Skellysolve B to give 4.42 g. of colorless cubes, m.p. 161.0–164.5°. A sample was recrystallized for analysis, m.p. 163.0–164.0°; ν_{max} 1700, 1225, 1185, 1150, 1060, and 1030 cm.$^{-1}$; O.R.D. (*c* 1.022, dioxane, 25°), $[M]_{295}$ +6600°, $[M]_{302.5}$ +6700°, $[M]_{335}$ +2955°, $[M]_{500}$ +428°, and $[M]_{589}$ +326°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.28; H, 9.26.

Methyl 3,11-diketo-5β-pregn-17(20)-en-21-oate Cyclic 3-(Ethylene Acetal) (XI).—A sample of the dione (X, 4.42 g., 11.86 mmoles) dissolved in *t*-butyl alcohol (75 ml.) and warmed to 55° under a cover of nitrogen was treated with ethyl oxalate (5.1 g., 35 mmoles, 4.7 ml.), heating was stopped and 25% sodium methoxide in methanol (23.72 mmoles, 5.06 g.) was added rapidly, then the solution allowed to come to room temperature during 1 hr. Glacial acetic acid (1.42 g., 23.72 mmoles) was added followed by sodium acetate (23.72 mmoles, 1.95 g.) in methanol (50 ml.). The solution was chilled to −2° and treated with bromine (24 mmoles, 3.04 g. in 40 ml. of cold methanol) dropwise over 10 min. Stirring was continued and after 5 min. 25% sodium methoxide (64 mmoles, 13.65 g., 14.0 ml.) added and the solution stirred at room temperature overnight. A small amount of insoluble material (*ca.* 10–100 mg.) was removed by filtration, the solution diluted with water (200 ml.), and the solvent distilled under reduced pressure. The product was extracted into methylene chloride, washed with water, dried with sodium sulfate, and adsorbed onto 125 g. of Florisil. The product was eluted in twenty 250-ml. fractions over a gradient of from one to 10% acetone in Skellysolve B. Fractions 2–7 contained 4.1 g. of crystalline material. These fractions were combined and crystallized from Skellysolve B to give 2.43 g., m.p. 137.0–143.0°. Two recrystallizations from Skellysolve B afforded an analytical sample, m.p. 148.5–150.0°; ν_{max} 1718, 1703, and 1655 cm.$^{-1}$; λ_{max} 233 mμ (ε 11,750).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.03; H, 8.89.

1α-Methyl-11β,21-dihydroxy-5β-preg-17(20)-en-3-one Cyclic 3-(Ethylene Acetal) 21-Acetate (XII).—The Favorskiĭ ester (XI) (2.3 g., 5.5 mmoles) dissolved in ether (25 ml.) was added to a suspension of lithium aluminum hydride (760 mg., 20 mmoles) in ether (25 ml.) at room temperature and stirred for 1 hr. The excess hydride was decomposed with ethyl acetate (0.5 ml.) followed by water (1.5 ml., 80 mmoles) with stirring. The ether solution was decanted, washed with saturated sodium chloride solution, dried with sodium sulfate, and evaporated to dryness under reduced pressure. The residue was taken up in a mixture of pyridine (10 ml.) and acetic anhydride (2 ml.) and allowed to stand at room temperature overnight. The solution was diluted to 100 ml. of water and the gummy precipitate washed with water by decantation. The residue was partitioned between ether–water and the ether solution washed twice with water, once with sodium chloride solution, dried with sodium sulfate, and evaporated to dryness. The residual pyridine was distilled azeotropically (*in vacuo*) by the addition of toluene to give a crystalline solid. This material was taken up in acetone and crystallized from Skellysolve B to give short colorless needles, m.p. 141.2–143.0°; yield, 1.04 g. (45%). A sample was recrystallized from Skellysolve B for analysis, m.p. 144.0–145.0°; ν_{max} 3560, 1725, 1673, and 1265 cm.$^{-1}$

(30) C. G. Honegger, *Helv. Chim. Acta*, **45**, 1409 (1962).

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 71.86; H, 9.18.

1α-Methyl-11β,17α,21-trihydroxy-5β-pregnane-3,20-dione Cyclic 3-(Ethylene Acetal) 21-Acetate (XIII).—The ketal (XII, 880 mg., 20 mmoles) dissolved in *t*-butyl alcohol (40 ml.) was treated with pyridine (1 drop), N-methylmorpholine oxide peroxide (2.4 ml.), and osmium tetroxide (4.8 mg. in 1.9 ml. of *t*-butyl alcohol). The resulting solution was allowed to stand under nitrogen overnight, after which sodium hydrosulfite (80 mg.) in water was added, and the solution stirred for 0.5 hr. The solution was then taken to dryness *in vacuo* and the residue taken up in methylene chloride. After washing (water) the methylene chloride solution was dried with sodium sulfate, and adsorbed onto 50 g. of Florisil. The product was eluted during fifteen 100-ml. fractions over a gradient of from 10 to 25% acetone–Skellysolve B. Fractions 3–5 contained 673 mg. of crystalline material which was recrystallized to give 430 mg. of colorless prisms, m.p. 192.5–204°, infrared consistent with structure; ν_{max} 3420, 1735, 1720 cm.$^{-1}$. A sample was recrystallized three times from acetone–Skellysolve B for analysis, m.p. 202.5–205.0°, ν_{max} 3640, 1736, 1715, and 1265 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{40}O_7$: C, 67.21; H, 8.68. Found: C, 67.01; H, 8.70.

1α-Methyl-11β,17α,21-trihydroxy-5β-pregnane-3,20-dione 21-Acetate (XIV).—To the ketal (XIII) (2.05 g.) in acetone (15 ml.) was added *N* hydrochloric acid (1 ml.) and the solution allowed to stand overnight at room temperature. Water (15 ml.) was added and the acetone removed under reduced pressure to give a white solid. This material was washed, dried (*in vacuo*, 60°), and crystallized from acetone to give two crops: crop 1, 980 mg., m.p. 196.5–198°; crop 2, 430 mg., m.p. 192.5–196.5°. A sample was recrystallized for analysis, m.p. 194.5–195.5°; ν_{max} 3460, 3400, 1743, 1626, 1683, and 1272 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.63; H, 8.55.

1α-Methyl-17α,21-dihydroxy-5β-pregnane-3,11,20-trione 21-Acetate (XVIII).—A sample of the dione (XIV, 250 mg.) was dissolved in acetone (5 ml.) and oxidized with Jones reagent[31] (0.125 ml. of 2.67 *N* reagent, 1.5 mmoles) at room temperature for 10 min. The reaction mixture was then diluted with water to a volume of 20 ml. and refrigerated. The product was isolated by filtration, washed, and dried giving 210 mg. of solid. Recrystallization from acetone afforded 150 mg., m.p. 239.5–242°. The infrared of this material was consistent with the expected structure. A second crop was isolated, 31 mg., m.p. 237.0–240.5°. A sample of crop 1 material was submitted for analysis.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.03; H, 8.65.

1α-Methylhydrocortisone Acetate (XVII).—1α-Methyl-5β-dihydro F acetate (XIV, 420 mg., 1.0 mmoles) was dissolved with stirring in glacial acetic acid (10 ml.), a microdrop of 33% HBr–HOAc added followed by the dropwise addition of 4.72 ml. of freshly prepared 0.212 *M* bromine in acetic acid (1.1 mmoles) at such a rate that the bromine was consumed between the addition of each drop. The reaction was then poured into saturated sodium chloride solution (200 ml.) and refrigerated (bromination time *ca.* 3–4 min.). The product was filtered, washed with water, and dried giving 390 mg. of a yellow gum. The product was then taken up in dimethylformamide (5 ml.) and treated under nitrogen at 60° with 400 mg. of semicarbazide hydrochloride and 300 mg. of sodium acetate in 2 ml. of water for >2 hr. The solution was then treated with 1 ml. of 50% aqueous pyruvic acid at 60° for 2 hr. The resulting solution was poured into 50 ml. of saturated sodium chloride solution and the product filtered after refrigeration to give a light tan solid; it was dried at 60° *in vacuo*; yield, 210 mg. This material was chromatographed on 25 g. of Florisil taking 50-ml. fractions (twenty-five) over a gradient of from 5 to 25% acetone–Skellysolve B. Fractions 12–18 containing 115 mg. of crystalline material were combined and recrystallized for analysis from acetone–Skellysolve B to give colorless needles (crop 1) and cubes crop 2 (at 4°). Crop 1 exhibited m.p. 210.8–212° (Kofler); yield, 51 mg. Crop 2 exhibited m.p. 203–210.5° (Kofler); yield, 35 mg. The yield was 20.5% over-all from 5β-dihydro derivative, λ_{max} 247 mμ (ε 13,150).

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.59; H, 7.89.

1α-Methylcortisone Acetate (XX).—1α-Methyl-5β-dihydrocortisone acetate (XI) (180 mg., 0.43 mmole) was dissolved with stirring in 20 ml. of glacial acetic acid and treated with a microdrop of 33% HBr–HOAc followed by 0.45 mole of bromine in acetic acid (2.14 ml. of 0.21 *M* solution). The reaction was allowed to proceed for *ca.* 3 min., after which the solution was poured into *ca.* 200 ml. of saturated sodium chloride solution and refrigerated. The white solid precipitate was filtered, washed with water, and dried briefly at 60° in the vacuum oven, then crystallized from acetone–Skellysolve B. The crystalline solid was taken up in dimethylformamide (5 ml.) and treated under nitrogen with 400 mg. of semicarbazide hydrochloride and 300 ml. of sodium acetate in 2 ml. of water for about 1 hr. at 60°. The solution was then treated with 1.5 ml. of 50% aqueous pyruvic acid at 60° for 2 hr. The solution was then poured into 50 ml. of saturated sodium chloride solution and the product recovered, after refrigeration, by filtration. The solid was then adsorbed onto 10 g. of Florisil (in methylene chloride) and eluted with 20-ml. fractions of 15% acetone–Skellysolve B. Fractions 7–10 were combined and crystallized for analysis from acetone–Skellysolve B to give 24.7 mg., m.p. 208.5–217.5° dec. (Kofler, subl. 199°); λ_{max}^{EtOH} 242.0 mμ (ε 14,100), essentially a single spot by benzene–formamide paper chromatogram. The infrared of this material was consistent with that of the expected structure as an acetone solvate. A sample was recrystallized for analysis, m.p. 212.5–214.5° (Kofler).

Anal. Calcd. for $C_{24}H_{32}O_6 \cdot CH_3COCH_3$: C, 68.33; H, 7.74. Found: C, 68.40; H, 7.59.

1-Methylprednisolone Acetate (XV).—1α-Methyl-5β-dihydrocortisone acetate (XIV, 780 mg.) and selenium dioxide (600 mg.) in 50 cc. of *t*-butyl alcohol containing 0.5 ml. of acetic acid was heated at reflux for 7 hr., an additional 600 mg. of selenium dioxide was added, and reflux continued 2 days under a cover of nitrogen. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate (100 ml.) and treated with Norit. The ethyl acetate solution was washed consecutively with water, freshly prepared cold ammonium sulfide solution (three times with one back wash), dilute cold ammonium hydroxide solution (twice), water, dilute hydrochloric acid, water, saturated sodium chloride solution and dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was taken up in methylene chloride and chromatographed on Florisil (50 g.) taking 100-ml. fractions over a gradient of from 10 to 25% acetone–Skellysolve B (20 fractions). Semisolid fractions 9–19 contained 88 mg. and were combined. Paper chromatogram on the benzene–formamide system indicated a mixture of seven substances. These materials were separated by preparative paper chromatography employing the benzene–formamide system. The products were eluted with methanol from the paper and the product (fraction group 2) separated from high-boiling solvents by chromatography over a short Florisil column and eluting with 20% acetone–Skellysolve B to give a small amount of a white crystalline solid. Recrystallization from ethanol–water afforded *ca.* 8 mg. of crystalline material, m.p. 231–239°, remelting at 248° (Kofler); λ_{max}^{EtOH} 253 mμ (ε 16,800), *R* (*a*253 mμ/*a*273 mμ) = 2.20 ($\Delta^{1,4}$); ν_{max} 3425, 1750, 1725, 1659, 1619 and 1265, and 1230 cm.$^{-1}$.

Acknowledgment.—The author wishes to express his appreciation to Fred Kagan and John C. Babcock for critical evaluation of the manuscript, R. W. Reinhart and associates for infrared and microanalyses, G. Slomp and associates for n.m.r. spectra, Arlen J. Taylor for technical assistance, and Ronald Houtman for optical rotatory dispersion spectra.

(31) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

On the Stereochemistry of Conjugate Addition. II. Hydrocyanation of 1-Acetyl-$\Delta^{1,8}$-hydrindene[1,2a]

WALTER L. MEYER AND JAMES F. WOLFE[2b]

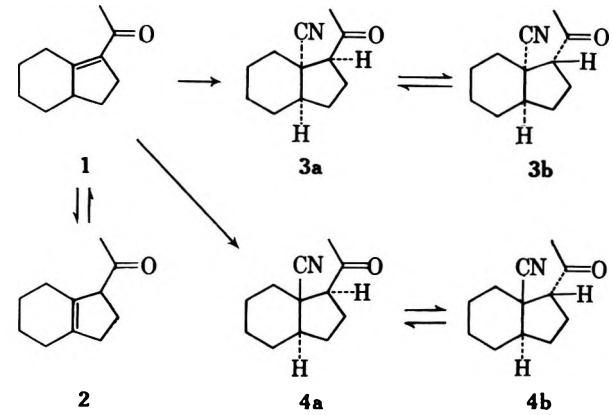
Department of Chemistry, Indiana University, Bloomington, Indiana[2c]

Received July 29, 1963

Reaction of 1-acetyl-$\Delta^{1,8}$-hydrindene (**1**) with potassium cyanide and ammonium chloride in aqueous dimethylformamide produces a mixture of the four racemic 1-acetyl-8-cyanohydrindanes. The *cis*-fused products (**3**) of this kinetically controlled addition predominate over the *trans* isomers (**4**) in a 63:37 ratio. Relative configurations of these products at the ring-junction positions were determined by degradation of two of them to the known *cis*- and *trans*-hydrindane-8-carboxamides, respectively, the degradative sequence involving conversion of the cyano ketones to their C-1 enol acetates, ozonolysis to the 8-cyano-1-hydrindanones, hydrolysis to the corresponding ketoamides, formation of the ethylene thioketals, and Raney nickel desulfurization of the latter. The significance of the observed stereoselectivity of the conjugate addition reaction with respect to steroid synthesis and the mechanism of 1,4-addition of hydrogen cyanide is discussed.

As part of a study of the stereoselectivity of conjugate nucleophilic additions to α,β-unsaturated carbonyl compounds and the utility of such reactions for introduction of angular functional groups in natural product total synthesis,[1] we examined addition of hydrogen cyanide to 1-acetyl-$\Delta^{1,8}$-hydrindene (**1**). This ketone provides an excellent model for the C/D ring system of the 20-keto steroids. Consequently, if it proved possible in this way to introduce an angular cyano group with the correct (*trans*) configuration, due to the synthetic versatility of the nitrile function the technique promised to be of considerable significance in affording a new route to synthesis of various important 18-functional steroids (aldosterone, conessine, etc.) as well as the angularly methylated hormones (progesterone, etc.). The crucial question, of course, was whether the reaction would result in the necessary stereoselectivity at the angular position.

Exposure of the enone[3] **1** to potassium cyanide in aqueous dimethylformamide containing ammonium chloride[4] smoothly produced a mixture of the four racemates[5] of the desired 1-acetyl-8-cyanohydrindane (**3** and **4**).[6] Two of these, a liquid *trans*-fused cyano ketone (**4a** or **4b**) and a crystalline *cis* isomer, m.p. 65–65.5° (**3a** or **3b**), were isolated in pure form by chromatography over Florisil, and a small amount of a third isomer was obtained in approximately 70% purity according to gas–liquid chromatographic (g.l.c.) analysis. The functionality of each cyano ketone was attested by its infrared spectrum, which like that of the crude mixture contained absorption characteristic of nitrile (4.5 μ) and saturated ketone (5.85 μ) but no other functional groups. Further, the n.m.r. spectrum of each pure isomer showed the sharp singlet resonance of an acetyl group (7.83 τ for the oil **4** and 7.72 τ for the solid **3**).



Formation of more than two cyano ketone adducts was not unanticipated, for during conjugate addition a new asymmetric center is introduced not only at the angular C-8 position but also at C-1, and thus there is a possibility of producing a total of four 1-acetyl-8-cyanohydrindanes, two *cis*-fused (**3a** and **3b**) and two *trans*-fused C-1 epimers (**4a** and **4b**). From the standpoint of assessing the stereoselectivity of the conjugate addition reaction, the configurations at C-1 are unimportant, for configurations at that center are determined by protonation of the C-1 enolates (or ketonization of the corresponding enols) and this step follows determination of the angular configuration by attachment of cyanide at C-8. While the cyanide addition step is irreversible under the reaction conditions used, C-1 protonation is reversible, and thus the relative proportions of the two C-1 epimers in each series are determined subsequent to and independent of the cyanide addition.

Gas chromatography of the total reaction product was the method of choice for determination of the ratio of *cis*-fused (**3**) and *trans*-fused (**4**) products from the addition, but before this could be successfully applied it was necessary to relate the two pure isomers, whose ring-fusion configurations were determined by degradation, to the remaining two isomers, which were not readily isolable in pure form. Furthermore, only *three* cyano ketone peaks were present in gas chromatograms of the crude mixture. These represented 6%, 37%, and 56% (±2%) of the total material, and corre-

(1) Part I, W. L. Meyer and N. G. Schnautz, *J. Org. Chem.*, **27**, 2011 (1962).

(2) (a) Abstracted from the Ph.D. dissertation of James F. Wolfe, Indiana University, 1963; (b) U. S. Public Health Service Predoctoral Fellow, 1961–1963; (c) Communication no. 1158.

(3) W. L. Meyer and J. F. Wolfe, *J. Org. Chem.*, **27**, 3263 (1962).

(4) W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *ibid.*, **26**, 2411 (1961); W. Nagata, T. Terasawa, T. Aoki, and K. Takeda, *Chem. Pharm. Bull.* (Tokyo), **9**, 783 (1961).

(5) All synthetic compounds discussed are *racemic*, although the prefix *dl* is omitted and only one enantiomer of each is depicted in the structural formulas.

(6) Use of aqueous-methanolic potassium cyanide for the hydrocyanation was a considerably less efficient alternative. Under these more basic conditions partial hydrolysis of the nitrile, tautomerization of the starting enone, and other side reactions also occurred, and in addition to cyano ketones the product mixture contained significant amounts of the corresponding ketoamides, the $\Delta^{8,9}$-double bond tautomer (**2**) of the starting ketone, and high-melting products apparently similar to those previously encountered from cyanide additions under analogous conditions: *cf.* ref. 1, 4, and A. Bowers, *J. Org. Chem.*, **26**, 2043 (1961).

sponded in retention times to the cyano ketone obtained in 70% purity by chromatography, the pure crystalline *cis* isomer, and the pure liquid *trans* isomer, respectively. However, to the extent that angular cyanation led to both C-8 configurations, production of all four rather than only three isomers was expected, since inspection of molecular (Dreiding) models did not reveal any apparent steric reason for absence of either C-1 epimer from a C-1 equilibrium mixture in either the *cis* or the *trans* series. Indeed, although the n.m.r. spectrum contained three sharp singlets in the acetyl region (7.72, 7.75, and 7.83 τ), each of them was much more intense than could be accounted for by a 6% component of the mixture. This suggested that all four racemates were in fact present and that the gas chromatographic technique failed to reveal the presence of one of them because its retention time was coincident with that of another on all columns examined.

In order to interrelate the two *cis* and the two *trans* C-1 epimers and also to confirm that the fourth racemate had been present in the initial mixture but was concealed to g.l.c. assay, the two pure isomers were converted to their corresponding C-1 epimeric equilibrium mixtures by treatment with *p*-toluenesulfonic acid in diethylene glycol dimethyl ether at room temperature. Under these conditions each cyano ketone produced a different mixture of only two components according to gas–liquid chromatography, and after 72 hr. the ratios of components became constant. The liquid *trans*-cyano ketone (56% original g.l.c. component) afforded itself and the 6% initial component in a ratio of 86:14 ± 2%, with no trace of the 37% initial component appearing in the chromatogram. The solid *cis*-cyano ketone (the 37% initial component), on the other hand, was converted to a 61:39 ± 2% mixture of itself and a substance with the same retention time as the 56% initial component, no trace of the 6% original component being visible in the chromatogram. These results established three crucial points. First, such acid-catalyzed equilibration does not alter the ring-fusion configuration in addition to that of the side chain, for if it had, both the solid (*cis*) and the liquid (*trans*) cyano ketones would have produced the same equilibrium mixture. Secondly, the minor (6%) cyano ketone in the reaction mixture, like the liquid cyano ketone with which it equilibrates, corresponds to a *trans*-fused structure. Thirdly, the *cis*-fused C-1 epimer of the 65° cyano ketone has the same g.l.c. retention time as does the major *trans*-cyano ketone, and it is distinctly possible that the 56% peak in the crude cyano ketone mixture represents both of these products.

With these results in hand, the ratio of *cis*-fused and *trans*-fused products could be ascertained by subjecting the crude conjugate addition product mixture to acid-catalyzed side-chain equilibration followed by g.l.c. analysis, for it had been established that under these conditions no interconversion of ring-fusion isomers occurred. After such treatment the ratio of areas of the three g.l.c. peaks due to the four cyano ketones was 9:40:51% ± 2%. Combination of this result with the previously determined equilibrium ratios of the *cis*- and the *trans*-fused epimers shows that the ratio of total *cis*- to total *trans*-locked compounds is 63:37 ± 4%. Consideration of the relative intensities of the 4 acetyl proton resonances in the n.m.r. spectrum of the crude product leads to exactly the same result.

This ratio is clearly the result of kinetically controlled attack of cyanide ion on the enone **1** rather than a subsequent equilibration of the ring-fusion stereoisomers by reversal of the addition reaction,[4] for treatment of either the pure *cis*- or the pure *trans*-cyano ketone with potassium cyanide and ammonium chloride under conditions of the reaction produces C-1 epimerization but *no* interconversion of *cis* and *trans* isomers. Whether the selectivity results from "steric approach control" or "product development control"[7] is not clear, however, for it is difficult to assess the structural factors involved in terms of the small energy difference (0.5 kcal.) between the two transition states. It does appear that approach of cyanide ion from that side of the enone **1** which leads to a *trans*-fused product is somewhat more hindered (particularly by the axial hydrogens at C-4 and C-6) than is approach from the other side. It seems that stereoelectronic effects resulting from efficient overlap between the developing carbon–cyanide bond and the enolate π-system[1,4] might not be so significant in this instance as they probably are with endocyclic enones like $\Delta^{1,9}$-2-octalone, for the exocyclic location of the developing enolate allows nearly as efficient overlap in the transition state leading to the *cis*-fused product as in that leading to the *trans* isomer, so far as one can judge from models. Neither transition state appears to suffer exceptional crowding in order to attain such orbital overlap, but that leading to the *trans* adduct may be of slightly higher energy due to deformation of the five-membered ring and eclipsing of the acetyl group with the equatorial C-7 hydrogen.

From the standpoint of steroid synthesis, the stereochemical result of this cyanide addition is of considerable interest, for although the *trans*-fused isomer is the minor product of the reaction, it is formed in sufficient quantity to make the process synthetically practical. Indeed, since this work was initiated, two laboratories have utilized such an approach to steroid total synthesis, syntheses of 3-hydrox-19-norpregna-1,3,5(10)-trien-20-one,[8a] conessine,[8b,9] progesterone,[10] 5α-pregnan-3β-ol-20-one,[8b] and latifoline[8b] having thus far appeared. The steric results of addition of cyanide to the tetracyclic analogs of **1** used in those programs were quite similar to those we have observed, yields of *cis*-fused products exceeding[8] or approximately equalling[9] those of the *trans* forms when similar reaction conditions were used.[11] However, at least in the bicyclic series the reaction can in practice be made completely stereospecific in either desired sense, for we have found that exposure of either cyano ketone (**3** or **4**) to sodium methoxide reverses the addition, giving a mixture of the starting enone **1** and its

(7) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

(8) (a) W. Nagata, I. Kikkawa, and K. Takeda, *Chem. Pharm. Bull.* (Tokyo), **9**, 79 (1961); (b) W. Nagata, T. Terasawa, and T. Aoki, *Tetrahedron Letters*, 865, 869 (1963).

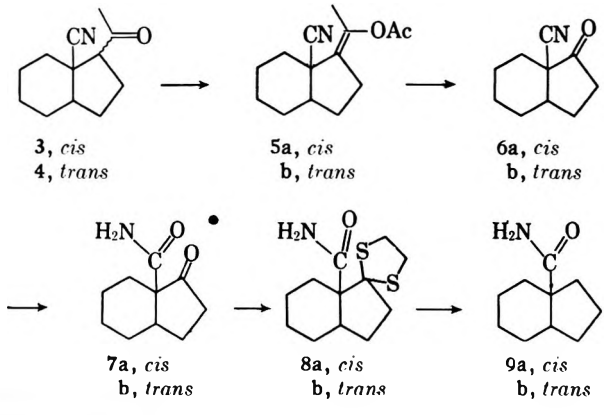
(9) J. A. Marshall and W. S. Johnson, *J. Am. Chem. Soc.*, **84**, 1485 (1962).

(10) W. S. Johnson, J. F. W. Keana, and J. A. Marshall, *Tetrahedron Letters*, 193 (1963).

(11) See W. Nagata, M. Yoshioka, and S. Hirai, *ibid.*, 461 (1962), and ref. 8b for quite different conditions which lead predominantly to a *trans* product.

$\Delta^{8,9}$ tautomer 2. Elimination of hydrogen cyanide to form the conjugated ketone is more rapid under these conditions than is the equilibration of the acetylhydrindenes (**1** and **2**), because after 12 hr. at room temperature no cyano ketone remained but the two enones were present in a 43:57 ratio (conjugated–nonjugated) compared with the equilibrium ratio of 20:80.[3] Presumably suitable conditions of basicity could thus be found for conversion of the undesired *cis* adduct (corresponding to **3**) only to the starting enone (corresponding to **1**) and this could be recycled. Marshall and Johnson[9] achieved a similar regeneration of enone in a tetracyclic series by heating the corresponding *cis*-fused adduct.

Configurations of the 1-Acetyl-8-cyanohydrindanes.—In order to ascertain which 1-acetyl-8-cyanohydrindane possessed the *trans* fusion and which the *cis*, both were degraded to the corresponding hydrindane-8-carboxamides of known configuration. On treatment with acetic anhydride and *p*-toluenesulfonic acid,[12] each cyano ketone (**3** and **4**) was converted to a corresponding enol acetate (**5a** and **5b**, respectively). That these were indeed tetrasubstituted olefinic derivatives was apparent from the absence of vinyl proton resonance from their n.m.r. spectra, but to which of the geometric isomers about the double bond they correspond is not known. In each case, however, g.l.c. showed only one product peak, and the n.m.r. spectrum had only one strong acetyl proton resonance and one strong allylic methyl proton resonance, suggesting the presence of a significant amount of only one isomer. The conditions of enol acetylation were rather vigorous, but the original ring-junction configuration must have been retained in each instance, for when each isomeric cyano ketone was heated at 140–150° in diethylene glycol dimethyl ether with *p*-toluenesulfonic acid, conditions of temperature and acidity equivalent to those of enol acetylation, only side-chain epimerization occurred. Further, although the two enol acetates were but poorly resolved by gas chromatography and had similar infrared spectra, ozonolysis of each provided a distinctly different 8-cyano-1-hydrindanone, the solid 1-acetyl-8-cyanohydrindane (**3**) leading to a crystalline cyanohydrindanone (**6a**), m.p. 75–76°, and the liquid acetylcyanohydrindane (**4**) affording an oily derivative (**6b**). These two cyanohydrindanones were well resolved by gas chromatography, and neither was contaminated by its isomer, even in the crude ozonolysis product.



3, *cis*
4, *trans*
5a, *cis*
b, *trans*
6a, *cis*
b, *trans*
7a, *cis*
b, *trans*
8a, *cis*
b, *trans*
9a, *cis*
b, *trans*

With the intent of removing the nuclear carbonyl group, the solid (**6a**) and liquid (**6b**) cyanohydrindanones were converted to the corresponding thioketals, m.p. 137–139° and 88–90°, respectively. Attempted desulfurizations with W-2 Raney nickel were hampered by concomitant reduction of the nitrile function, however, and use of deactivated nickel[13] produced considerable amounts of carbonyl-containing by-products. Attempted Clemmensen reduction[14] of the crystalline cyano hydrindanone resulted in formation of a complex mixture, and the method was not explored in the other series.

Since the strongly basic conditions of the Wolff–Kishner reduction rendered its use inadvisable because the angular nitrile might have been saponified and decarboxylatively lost or the β-ketonitrile system might have undergone reverse Claisen ring opening, further efforts to remove the ketone were preceded by conversion of the nitrile to a group more stable toward reduction. The cyano groups of the cyanothioketals were unaltered by attempted alkaline hydrolysis, no doubt for steric reasons, but the cyanohydrindanones (**6a** and **6b**) themselves were readily converted by concentrated sulfuric acid at 80° [15] to the corresponding 1-hydrindanone-8-carboxamides, **7a** (m.p. 129–130.5°) and **7b** (m.p. 178–179.5°), respectively. Infrared spectra and thin layer chromatograms of these derivatives showed them to be different and uncontaminated by one another. The keto amides (**7a** and **7b**) were readily transformed[16] into their thioketals, **8a** (m.p. 223–224°) and **8b** (m.p. 148–149°), which were smoothly desulfurized by Raney nickel to the respective hydrindane-8-carboxamides, **9a** and **9b**. Like the other intermediates in the degradation, these products were clearly different and uncontaminated by each other as demonstrated by infrared spectroscopy and gas and thin layer chromatography.

The hydrindane-8-carboxamide with m.p. 114–115° (**9a**) was identical in all respects with a sample of the authentic *cis* amide.[17] Infrared spectra (chloroform solution) of the two samples were superimposable, and a mixture melting point was undepressed, although admixture with the *trans* amide produced a depression of some 20° in melting point. Since this amide was derived from the crystalline 1-acetyl-8-cyanohydrindane (**3**) and no step in the degradation altered the ring-fusion configuration, that cyano ketone and all of its progeny (**5**–**9a**) have the *cis* configuration. The liquid 1-acetyl-8-cyanohydrindane (**4**) and its derivatives (**5**–**9b**) accordingly are in the *trans*-fused series. The latter conclusion is substantiated by identity of the thence-derived hydrindane-8-carboxamide (**9b**), m.p. 123.5–125°, with the authentic *trans* isomer.[18]

(12) C. W. Marshall, T. H. Kritchevsky, S. Lieberman, and T. F. Gallagher, *J. Am. Chem. Soc.*, **70**, 1837 (1948).

(13) G. B. Spero and A. W. McIntosh, *ibid.*, **70**, 1907 (1948).

(14) R. D. Haworth, B. G. Hutley, R. G. Leach, and G. Rogers, *J. Chem. Soc.*, 2720 (1962).

(15) L. T. Tsai, T. Miva, and M. S. Newman, *J. Am. Chem. Soc.*, **79**, 2530 (1957).

(16) L. F. Fieser, *ibid.*, **76**, 1945 (1954).

(17) W. G. Dauben, J. W. MacFarland, and J. B. Rogan, *J. Org. Chem.*, **26**, 297 (1961). We are grateful to Professor Dauben for samples of the two amides with which ours were compared.

(18) W. G. Dauben, unpublished work.

Experimental[19]

Addition of Potassium Cyanide to 1-Acetyl-$\Delta^{1,8}$-hydrindene.—To a 3.99-g. (0.0243 mole) sample of 1-acetyl-$\Delta^{1,8}$-hydrindene (**1**),[3] b.p. 102° at 8 mm. (90% pure by g.l.c., contaminated only by the β,γ-unsaturated isomer **2**), in 60 ml. of dimethylformamide was added a solution of 3.20 g. (0.0492 mole) of potassium cyanide and 1.98 g. (0.0370 mole) of ammonium chloride in 20 ml. of water.[4] The resulting cloudy solution was stirred at 100° for 6 hr.,[20] during which time aliquots were analyzed by gas chromatography. The reaction mixture was concentrated *in vacuo* to approximately one-fourth of its original volume and poured into 200 ml. of water which was extracted with methylene chloride. The extracts were dried over sodium sulfate and concentrated to afford 4.30 g. (92% as $C_{12}H_{17}NO$) of crude products as a dark red oil; λ_{max}^{film} 4.5 and 5.85 μ; n.m.r. (CCl_4), 7.72 (s), 7.75 (s), 7.78 (s, very small), and 7.83 τ (s). The intensities of the acetyl resonances were in the ratio 37:30:32 if the 7.78-τ peak is excluded and 36:29:4:31 if it is included.

Gas chromatograms (Z, 200°) of the crude product mixture showed three peaks which represented, in order of elution from the column, 6% (peak A), 37% (peak B), and 56% (peak C) ± 2% of the total material (average of four preparations). The entire unrefined sample was chromatographed on 120 g. of Florisil. Elution with 1 l. of benzene–cyclohexane (7:3 through 4:1) furnished 1.216 g. (26%) of crude 1-acetyl-8-cyano-*cis*-hydrindane (**3**), m.p. 60–65°, the 35% component (g.l.c. peak B). Further elution with 1.4 l. of pure benzene afforded 1.053 g. (23%) of intermediate (mixed) fractions, g.l.c. of which showed approximately 40% of peak B and 60% of peak C (these fractions appear to be mainly a mixture of the two *cis* adducts **3a** and **3b**). Elution with 1.6 l. of benzene–ether (9:1) yielded 1.375 g. (30%) of 1-acetyl-8-cyano-*trans*-hydrindane (**4**, g.l.c. peak C) as a colorless oil; $\lambda_{max}^{CHCl_3}$ 4.5 and 5.85 μ; b.p. 120° (oil bath) at 1.5 mm.; $n^{27}D$ 1.4919; n.m.r. ($CDCl_3$), 7.83 τ (s).

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.0; H, 8.8; N, 7.4.

Recrystallization of the combined fractions of the solid isomer from petroleum ether (b.p. 30–60°) afforded 1.150 g. (25%) of the pure *cis* adduct (**3**) as stout prisms, m.p. 65–65.5°; $\lambda_{max}^{CHCl_3}$ 4.5 and 5.85 μ; n.m.r. ($CDCl_3$), 7.72 τ (s).

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.4; H, 8.8; N, 7.6.

Rechromatography of the mother liquors from recrystallization of **3** and the mixed fractions obtained from the first chromatogram resulted in isolation of 55 mg. of an oily fraction rich (70% by g.l.c.) in the 7% component (g.l.c. peak A) which had λ_{max}^{film} 4.5 and 5.85 μ. However, for the most part the intermediate fractions from the first chromatography were not resolved but were eluted from the column together in approximately the same 1.5:1 ratio. Chromatography on neutral activity I alumina resulted in no better separation of components.

The total isolated yield of *cis* ketonitrile (**3**) was 25% while the yield of *trans* product (**4**) was 30%. The intermediate fractions, consisting primarily of the two *cis* isomers **3a** and **3b**, amounted to 1.119 g. (24%). The total yield of adducts amounted to 3.644 g. (79%).

Acid-Catalyzed Equilibration of Cyano Ketones 3, 4, and a Crude Cyanation Reaction Mixture. Determination of the Ratio of Total *cis* and *trans* Adducts. **A.**—A mixture of 26.0 mg. (0.136 mmole) of *cis* ketone **3**, m.p. 64–65° (g.l.c. peak B) and 23 mg. (0.136 mmole) of *p*-toluenesulfonic acid in 2 ml. of diethylene glycol dimethyl ether was allowed to stand at room temperature under a nitrogen atmosphere. Aliquots were examined by gas chromatography at 6-hr. intervals for the first 24 hr. and at 12-hr. intervals thereafter for a period of 192 hr. After 72 hr. the mixture had come to equilibrium, g.l.c. showing 61 ± 2% of peak B and 39 ± 2% of peak C.

B.—A 24-mg. sample of the oily *trans* ketone **4** (chromatographed and pure by g.l.c., peak C) was added to a solution of 22 mg. (0.125 mmole) of *p*-toluenesulfonic acid in 2 ml. of diethylene glycol dimethyl ether. Aliquots were analyzed as in A and after 72 hr. equilibrium had been attained, g.l.c. showing 86 ± 2% of peak C and 14 ± 2% of peak A.

C.—A 172-mg. sample of the crude conjugate addition product mixture, g.l.c. of which showed 6 ± 2% of peak A, 37 ± 2% of peak B, and 57 ± 2% of peak C, was added to 8 ml. of diethylene glycol dimethyl ether containing 155 mg. of *p*-toluenesulfonic acid. After 72 hr. at room temperature the ratios of isomers ceased to change and equilibrium was attained with g.l.c. showing 9 ± 2% of peak A, 40 ± 2% of peak B, and 51 ± 2% of peak C. On the basis of this equilibria the ratio of total *cis*-(**3a** and **3b**) to total *trans*-1-acetyl-8-cyanohydrindanes (**4a** and **4b**) in the crude reaction mixture was calculated to be 1.7 ± 0.3 to 1.

Treatment of Acetylcyanohydrindanes 3 and 4 with Sodium Methoxide. **A.**—A 36-mg. sample of *cis*-cyano ketone **3** was allowed to stand at room temperature with 3 ml. of 1 *N* methanolic sodium methoxide. After 24 hr. a gas chromatogram (Z, 200°) of the reaction mixture showed the presence of two peaks corresponding to 43% of 1-acetyl-$\Delta^{1,8}$-hydrindene (**1**) and 57% of 1-acetyl-$\Delta^{8,9}$-hydrindene (**2**) but no residual cyano ketone. After 48 hr. the 4 to 1 equilibrium mixture of enones **2** and **1** was obtained.

B.—A 44-mg. sample of pure (g.l.c.) *trans*-cyano ketone **4** was treated with 4 ml. of 1 *N* sodium methoxide solution as in A. After 24 hr. an identical mixture of enones **1** (43%) and **2** (57%) was obtained, and after 48 hr. the equilibrium mixture of the enones **1** and **2** was observed by g.l.c.

Treatment of Acetylcyanohydrindanes 3 and 4 with Potassium Cyanide and Ammonium Chloride. **A.**—A 27.7-mg. (0.145 mmole) sample of the pure *cis* adduct (**3**), m.p. 64–65° (g.l.c. peak B), 9.0 mg. (0.145 mmole) of potassium cyanide, and 4.0 mg. (0.075 mmole) of ammonium chloride in 0.5 ml. of dimethylformamide and 0.2 ml. of water was heated at 100° for 24 hr. Gas chromatographic analysis (Z, 200°) of the crude reaction mixture showed the presence of both *cis*-fused C-1 epimers in a 65:35 ratio (peak B–peak C) but no *trans* isomer (peak A).

B.—A mixture consisting of 42.6 mg. (0.22 mmole) of the pure (g.l.c. peak C) *trans*-cyano ketone (**4**), 14 mg. (0.21 mmole) of potassium cyanide, and 6.0 mg. (0.11 mmole) of ammonium chloride in 0.5 ml. of dimethylformamide and 0.2 ml. of water was heated at 100° under a nitrogen atmosphere for a total of 24 hr. A gas chromatogram (Z, 200°) of an aliquot of the reaction mixture after this time showed the presence of both *trans*-fused C-1 epimers in a 10:90 ratio (peak A–peak C) but no *cis* isomer (peak B).

Enol Acetate of 1-Acetyl-8-cyano-*cis*-hydrindane (5a).—A solution of 880 mg. (0.0046 mole) of 1-acetyl-8-cyano-*cis*-hydrindane (**3**), m.p. 65–66°, and 790 mg. (0.0046 mole) of *p*-toluenesulfonic acid in 155 ml. of acetic anhydride[12] was distilled over a period of 7 hr. The residue was diluted with water and extracted into ether. Concentration of the ether extracts yielded 1.07 g. of the crude *cis*-enol acetate as a dark viscous oil; $\lambda_{max}^{CHCl_3}$ 4.5, 5.7, 5.85 (weak) and 6.0 μ; n.m.r. ($CDCl_3$), 7.87 (s), 8.16 τ (poorly resolved triplet, $J < 1$ c.p.s., probably long range). The unrefined product had a gas chromatogram (Z, 225°) similar to that of the *trans*-enol acetate, and a mixture of *cis*- and *trans*-enol acetates was poorly resolved. Subsequent experiments demonstrated their nonidentity.

Enol Acetate of 1-Acetyl-8-cyano-*trans*-hydrindane (5b).—A solution of 870 mg. (0.00455 mole) of 1-acetyl-8-cyano-*trans*-hydrindane (**4**, pure by g.l.c.) and 780 mg. (0.00455 mole) of *p*-toluenesulfonic acid in 90 ml. of acetic anhydride was distilled slowly[12] at 150–160° until approximately 10 ml. of acetic anhydride remained (11 hr.). The residue was cooled, poured into 100 ml. of ice–water, and the resulting solution was extracted with ether. The extracts were washed with 5% sodium hydroxide solution and water and dried over sodium sulfate. Removal of

(19) Infrared spectra were obtained on Perkin-Elmer Models 21, 137, and 137G spectrophotometers, ultraviolet spectra were taken using a Cary Model 14 ultraviolet spectrophotometer, and n.m.r. spectra were obtained from dilute solutions with tetramethylsilane as internal standard using a Varian A-60 spectrometer or a Varian DP-60 spectrometer operating at 60 Mc. and equipped with a Model 3506 flux stabilizer. Band positions in DP-60 spectra were determined by the audio sideband technique. Chemical shifts are expressed in τ-units, the designation (s) indicating a singlet resonance. Gas–liquid chromatograms (g.l.c.) were run on a Perkin-Elmer Model 154D vapor fractometer with helium as the carrier gas and a thermal conductivity detector or on an F & M Model 609 chromatograph using nitrogen as the carrier gas with a hydrogen flame ionization detector. A 2-m. 20% Apiezon L grease column, designated Q or a 2-m. 9% silicone gum (SE30) on Chromosorb W column, designated Z, was employed. Compositions of mixtures were estimated as the ratios of peak areas, *cf.* M. Dimbat, P. E. Porter, and F. H. Stross, *Anal. Chem.*, **28**, 290 (1956). That the isomeric acetylcyanohydrindanes indeed gave identical detector responses was confirmed with known mixtures. Melting points (microscope hot stage) are corrected for stem exposure. Boiling points are uncorrected. Microanalyses were by Alfred Bernhardt, Mulheim (Ruhr), Germany.

(20) Reaction times up to 14 hr. at 100° did not change the ratio of products appreciably but resulted in formation of some polymeric material which was not characterized.

the ether afforded 929 mg. of crude *trans*-enol acetate as a dark red oil; $\lambda_{max}^{CHCl_3}$ 4.5, 5.7, 5.8 (weak) and 6.0 μ; n.m.r. ($CDCl_3$), 7.87 (s), 8.13 τ (poorly resolved triplet, $J < 1$ c.p.s., probably long range). The gas chromatogram (Z, 225°) had a single major peak less volatile than starting material which was also present as a minor contaminant.

8-Cyano-*cis*-1-hydrindanone (6a).—The 1.07-g. sample of crude *cis*-enol acetate (**5a**) prepared before was dissolved in 75 ml. of methylene chloride and treated with excess ozone at −75°. The reaction mixture was allowed to warm to room temperature, 10 ml. of acetic acid, 5 ml. of water, and 1.5 g. of powdered zinc were added, and the resulting heterogeneous mixture was refluxed for 4 hr. The zinc was removed by filtration and the methylene chloride was washed with sodium bicarbonate solution and water. Evaporation of the solvent after drying over sodium sulfate afforded an orange oil which was chromatographed on 30 g. of Florisil. Elution with benzene–cyclohexane (4:1), benzene, and benzene–ether (9:1) afforded 286 mg. of crystalline material, m.p. 70–73°. After repeated recrystallization from hexane, 200 mg. (38% from **3**) of the *cis* ketone (**6a**) was obtained as colorless needles, m.p. 75–76°, $\lambda_{max}^{CHCl_3}$ 4.5 and 5.75 μ.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.7; H, 7.8; N, 8.6.

The gas chromatogram of the crude material showed it to be completely without contamination by the *trans* isomer.

The *cis* ketone was converted to its thioketal as in the case of the *trans* isomer. Recrystallization from methanol afforded the analytical sample, m.p. 137–139°, $\lambda_{max}^{CHCl_3}$ 4.5 μ.

Anal. Calcd. for $C_{12}H_{17}NS_2$: C, 60.24; H, 7.16; N, 5.85; S, 26.75. Found: C, 60.1; H, 7.0; N, 6.3; S, 26.4.

8-Cyano-*trans*-1-hydrindanone (6b).—The entire 929-mg. sample of crude *trans*-enol acetate (**5b**) prepared as described before was dissolved in 60 ml. of methylene chloride and treated with excess ozone at −75°. The ozonide was decomposed as in the preceding experiment with 10 ml. of acetic acid, 5 ml. of water, and 1.5 g. of powdered zinc. Filtration and concentration of the methylene chloride resulted in isolation of a dark viscous oil which was chromatographed on 20 g. of Florisil. Elution with benzene–cyclohexane (7:3) and benzene furnished 176 mg. (24% from **4**) of the desired *trans* ketone (**6b**) as a colorless oil, $\lambda_{max}^{CHCl_3}$ 4.5 and 5.75 μ. The gas chromatogram (Z, 225°) was indicative of a single product.

Reaction of **6b** with 1,2-ethanedithiol and boron trifluoride etherate in acetic acid[16] afforded the expected 8-cyano-1,1-ethylenedithio-*trans*-hydrindane as colorless prisms from methanol, m.p. 88–90°, $\lambda_{max}^{CHCl_3}$ 4.5 μ.

Anal. Calcd. for $C_{12}H_{17}NS_2$: C, 60.21; H, 7.16; N, 5.85; S, 26.75. Found: C, 60.4; H, 7.3; N, 5.95; S, 26.5.

***cis*-1-Hydrindanone-8-carboxamide (7a).**—A solution of 146 mg. (0.895 mmole) of 8-cyano-*cis*-1-hydrindanone (**6a**), m.p. 74–76°, in 0.4 ml. of concentrated sulfuric acid was heated at 80–90° for 2 hr. under nitrogen.[15] The resulting dark red solution was poured into 5 ml. of cold water and the crude keto amide was extracted with methylene chloride. The extracts were washed with sodium bicarbonate and water, dried over sodium sulfate, and concentrated to furnish 128 mg. of crude yellow crystals, m.p. 129–130°. Repeated recrystallization from cyclohexane–ethyl acetate yielded 108 mg. (67%) of *cis*-keto amide (**7a**), m.p. 129–130.5°; $\lambda_{max}^{CHCl_3}$ 2.85, 2.95, 5.8, 6.0, and 6.3 μ.

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.3; H, 8.4; N, 8.0.

***trans*-1-Hydrindanone-8-carboxamide (7b).**—A 123-mg. (0.755 mmole) sample of the liquid 8-cyano-*trans*-1-hydrindanone (**6b**) was heated with 0.4 ml. of concentrated sulfuric acid at 80° for 2 hr. under a nitrogen atmosphere.[15] The acid solution was poured into 5 ml. of cold water and the resulting cloudy solution was extracted with methylene chloride. Washing of the extracts with sodium bicarbonate solution and water was followed by drying over sodium sulfate and removal of the solvent. The 95 mg. of light yellow crystals, m.p. 167–175°, thus obtained was recrystallized from cyclohexane–ethyl acetate to afford 68 mg. (50%) of the desired *trans*-keto amide (**7b**), m.p. 178–179.5°; $\lambda_{max}^{CHCl_3}$ 2.85, 2.95, 5.80, 6.0, and 6.3 μ.

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.2; H, 8.4; N, 8.2.

Gas chromatographic analysis (Z, 225°) of the *cis*- and *trans*-keto amides failed. However, they were well resolved by thin layer chromatography which with solution infrared spectra established their nonidentity. The same methods showed neither isomer to be contaminated by the other even in the crude state.

8-Carboxamido-1,1-ethylenedithio-*cis*-hydrindane (8a).—A solution consisting of 86.9 mg. (0.480 mmole) of *cis*-1-hydrindanone-8-carboxamide (**7a**), m.p. 148–150°, 0.75 ml. of glacial acetic acid, 0.2 ml. of 1,2-ethanedithiol, and 0.2 ml. of boron fluoride etherate[16] was allowed to stand at room temperature for 25 hr. The reaction mixture was poured into 5 ml. of water and the thioketal was extracted with methylene chloride. The extracts were washed with sodium bicarbonate solution and water, and dried over sodium sulfate. Evaporation of the solvent resulted in isolation of 130 mg. of a colorless solid, m.p. 222–223°. Recrystallization from methanol gave 93 mg. (72%) of the *cis* thioketal (**8a**) as colorless prisms, m.p. 223–224°; λ_{max}^{KBr} 2.92, 3.04 (weak), 3.16, 6.0, and 6.24 μ.

Anal. Calcd. for $C_{12}H_{19}NOS_2$: C, 56.02; H, 7.44; N, 5.44; S, 24.88. Found: C, 55.8; H, 7.3; N, 5.5; S, 24.7.

8-Carboxamido-1,1-ethylenedithio-*trans*-hydrindane (8b).—Reaction conditions and isolation were similar to those used with the *cis*-keto amide. Reaction of a 38.6 mg. (0.213 mmole) sample of *trans*-1-hydrindanone-8-carboxamide (**7a**), m.p. 178–179°, in 0.4 ml. of glacial acetic acid with 0.1 ml. of 1,2-ethanedithiol and 0.1 ml. of boron fluoride etherate yielded 48 mg. of crude thioketal, m.p. 146–155°. Recrystallization from cyclohexane afforded 36 mg. (65%) of pure *trans* thioketal (**8b**) as colorless prisms, m.p. 148–149°; $\lambda_{max}^{CHCl_3}$ 2.82, 2.92, 6.0, and 6.31 μ.

Anal. Calcd. for $C_{12}H_{19}NOS_2$: C, 56.02; H, 7.44; N, 5.44; S, 24.88. Found: C, 56.1; H, 7.3; N, 5.5; S, 24.7.

Nonsuperimposable infrared spectra (KBr mull) and thin layer chromatography established the nonidentity of the isomeric thioketals.

***cis*-Hydrindane-8-carboxamide (9a).**—A mixture of 53 mg. (0.206 mmole) of 8-carboxamido-1,1-ethylenedithio-*cis*-hydrindane, m.p. 222–223°, and 0.75 g. of Raney nickel in 10 ml. of absolute ethanol was refluxed gently for 20 hr. Evaporation of the ethanol after repeated washing of the nickel resulted in isolation of 30 mg. of crude white crystalline solid, m.p. 110–112°. Repeated recrystallization from *n*-hexane afforded 21.6 mg. (63%) of pure *cis* amide (**9a**) as colorless needles, m.p. 114–115° (lit.[17] 111–112°); $\lambda_{max}^{CHCl_3}$ 2.82, 2.92, 6.0, and 6.32 μ. A mixture melting point with an authentic sample of *cis* amide[17] was undepressed. However, on admixture with the *trans* amide (**9b**), the melting point was depressed more than 20°. The solution infrared spectrum of **9a** was identical with that of the authentic sample of *cis* amide. A mixture of the crude *cis* and *trans* amides was resolved by gas chromatography (Z, 225°) and thin layer chromatography on silica gel. Examination of each amide in the crude state by the same methods provided their nonintercontamination.

***trans*-Hydrindane-8-carboxamide (9b).**—A mixture consisting of 25 mg. (0.097 mmole) of 8-carboxamido-1,1-ethylenedithio-*trans*-hydrindane, m.p. 148–149°, 0.5 g. of Raney nickel, and 3 ml. of absolute ethanol was refluxed for 17 hr. The reaction mixture was cooled and the Raney nickel was removed by centrifugation and washed with 50 ml. of hot absolute ethanol. The ethanol was evaporated *in vacuo* and the solid residue was dissolved in ether. The ether solution was centrifuged to remove turbidity and evaporated to dryness to afford 13.6 mg. of crude *trans* amide (**9b**), m.p. 118–126°. Four recrystallizations from *n*-hexane yielded 7.0 mg. (43%) of pure amide as colorless prisms, m.p. 123.5–125°[21] (reported[18] 123–124°); $\lambda_{max}^{CHCl_3}$ 2.82, 2.92, 6.0, and 6.32 μ. The gas chromatogram (Z, 225°) had a single peak and a thin layer chromatogram on silica gel G showed a single spot when developed with iodine. No melting point depression was observed on admixture with an authentic sample.[18] The infrared spectrum of a chloroform solution was identical in every respect with that of the authentic amide.

Acknowledgment.—We thank the National Science Foundation for a grant (G-18744) which supported this work and the Division of General Medical Sciences, U. S. Public Health Service, for a predoctoral fellowship for J. F. W.

(21) Melting of this material, as well as Professor Dauben's sample, was characterized by softening of the original rather poorly defined crystals at 114–115° with the rapid formation of sharp prisms which then melted at 123.5–125°.

The Cyanoethylation of Indene and Related Reactions

HANS DRESSLER[1a] AND ROBERT J. KURLAND[1b]

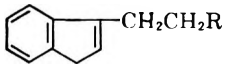
Contribution No. RP-63-11 from the Research Department of Koppers Company, Inc., Monroeville, Pennsylvania, and the Department of Chemistry, Carnegie Institute of Technology, Pittsburgh, Pennsylvania

Received July 17, 1963

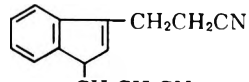
The cyanoethylation of indene was reinvestigated. Improved preparations, physical constants, and unambiguous proofs of structure for the products *via* proton magnetic resonance spectra are described. The related base-catalyzed additions to indene of vinylpyridine and acrylates also were studied. In all cases the mono-, di-, and trisubstitution products were indenes substituted in the 3-, 1,1-, and 1,1,3-positions, respectively. The cyanoethylation products were selectively hydrogenated to give the corresponding (aminopropyl)-indenes rather than the expected substituted indans.

The base-catalyzed addition of acylonitrile to indene was described by Bruson[2] to yield a product mixture which upon distillation gave an unidentified liquid, indenedipropionitrile (II and/or IIIa) in 13.5% yield, plus 1,1,3-indenetripropionitrile (IVa), m.p. 65°, in 35.1% yield. In a more recent paper,[3] the monocyanoethylation of indene in 13.5% yield was described; the liquid product was believed to be 3-indenepropionitrile (Ia), but it was stated that the structure of the product remained uncertain. Indeed, in the past the position of substituents in the alicyclic ring of indene has been frequently problematic since structure proofs were possible only by laborious methods.

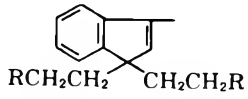
The purpose of this paper is to report supplemental data on the cyanoethylation and related reactions of indene, including the preparation of new indene derivatives, improved preparations of known compounds, and the use of proton magnetic resonance spectroscopy for the structure proof of indenes substituted in the alicyclic ring.



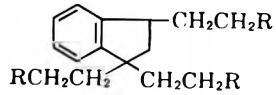
Ia, R = CN
b, R = COOH
c, R = $COOCH_3$
d, R = $COOC_2H_5$
e, R = COO*n*-C_4H_9
f, R = CH_2NH_2



II



IIIa, R = CN
b, R = COOH
c, R = CH_2NH_2



IVa, R = CN
b, R = COOH
c, R = $COOC_2H_5$
d, R = CH_2NH_2

Cyanoethylation of Indene.—The yield of 3-indenes propionitrile (Ia) was raised to 38% by using an excess of indene and benzyltrimethylammonium chloride plupotassium hydroxide as the catalyst. This product previously was described to be a liquid[3] but we obtained Ia as stout prisms, m.p. 31.0–31.5°. Hydrolysis of this nitrile gave the corresponding carboxylic acid Ib, m.p. 127–128°, whose structure previously had been uncertain (as discussed in ref. 3 with older literature citations). The methyl ester (Ic) of Ib was prepared in the usual manner for further structural identification.

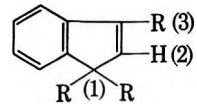
A reinvestigation of the polycyanoethylation of indene showed that the crude reaction product consisted of 20–25% of 1,1-indenedipropionitrile (IIIa) and about 70% of 1,1,3-indenetripropionitrile (IVa). This was inferred from the fact that the distilled dicyanoethylation product (25% yield) underwent almost no further reaction with acrylonitrile; therefore, the major or only indenedipropionitrile formed was IIIa which is incapable of anion formation with base while II, never prepared, would be convertible to indenetripropionitrile. Alkaline hydrolysis of the crude reaction product followed by an extraction-selective reprecipitation process gave a 69% yield of 1,1,3-indenetripropionic acid (IVb) plus a 14% yield of 1,1-indenedipropionic acid (IIIb). The dinitrile (IIIa) had m.p. 40.0–40.5° and the trinitrile (IVa) had m.p. 91.0–91.5° (*vs.* m.p. 65° reported by Bruson[2]). Alkaline hydrolysis of IIIa and IVa gave the corresponding carboxylic acids of m.p. 154–155° (IIIb) and m.p. 167–169° (IVb, Bruson[2] gave m.p. 161–162°), respectively.

Bergmann[4] reviewed the cyanoethylation reaction as a special case of the Michael reaction. He states: "An interesting point emerges from the behavior of compounds such as indene which gives a tris(cyanoethyl) derivative. One has to assume that the primary products rearrange to give a new reactive methylene group." (The primary product is shown to be 1-indenepropionitrile which rearranges to 3-indenepropionitrile, etc.). In a more detailed discussion, other Michael- and aldol-type reactions of indene and fluorene were said to proceed either by a concerted or a two-step mechanism.[5] It is still not possible to decide which mechanism operates here. However, the initial acrylonitrile addition product (anionic) must have the 1-indenepropionitrile structure in either case. The fact that the only monocyanoethylation product isolated is 3-indenepropionitrile then means that it must have been formed by rearrangement; this would be possible only if it were thermodynamically more stable. Perhaps 3-indene propionitrile is stabilized both by conjugation of the 2,3-double bond with the benzene ring and also by hyperconjugation of the methylene group adjacent to the 2,3-double bond with it (similar triad systems are discussed by Ingold[6]). It appears that 1,3-dicyanoethylated indene is not isolated because it is quickly cyanoethylated further. On the other hand, 1,1-dicyanoethylated indene does not have an active hydrogen on the ring and is not capable of rearrangement.

(1) (a) Koppers Co., Inc.; (b) Carnegie Institute of Technology.
(2) H. A. Bruson, *J. Am. Chem. Soc.*, **64**, 2457 (1942); U. S. Patent 2,280,058 (1942).
(3) F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 3011 (1957).
(4) E. D. Bergmann, *Org. Reactions*, **10**, 179 (1959).
(5) M. Avramoff and Y. Sprinzak, *J. Am. Chem. Soc.*, **82**, 4953 (1960).
(6) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 563 ff.

TABLE I

N.M.R. SPECTRA. CHEMICAL SHIFTS OF INDENE AND DERIVATIVES[a]



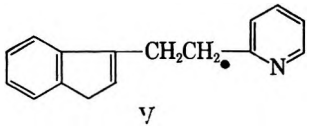
Compound	Substituent(s) R(1)	Substituent(s) R(3)	Chemical shift (τ-value) H(1)	H(2)	H(3)	Protons on benzene ring and on substituents
Indene[b]	H	H	7.01	3.86	3.34	
Ia	H	CH_2CH_2CN	6.84	3.88		2.86 (benzene ring); 7.5, 7.6 (—CH_2CH_2CN)
Ic	H	$CH_2CH_2COOCH_3$	6.83	3.92		2.81 (benzene ring); 6.44 (—OCH_3); 7.4 (—CH_2CH_2—)
If	H	$CH_2CH_2CH_2NH_2$	6.78	3.91		2.84 (benzene ring); 7.0, 7.4, 7.9 (—$CH_2CH_2CH_2$—); 9.15 (—NH_2)
VI	H	CH_2CH_2-4-pyridyl	6.74	3.88		1.65 (α-H, pyridyl); 2.81 (benzene ring); 2.98 (β-H, pyridyl); 7.1 (—CH_2CH_2—)
IIIa	CH_2CH_2CN	H		3.81	3.18	2.77 (benzene ring); 7.8, 8.3 (—CH_2CH_2CN)
IIIa[c]	CH_2CH_2CN	H		3.71	3.14	
IIIc	$CH_2CH_2CH_2NH_2$	H		3.82	3.35	2.84 (benzene ring); 7.6, 8.3–9.0 (—$CH_2CH_2CH_2$—); 9.16 (—NH_2)
IVa[c]	CH_2CH_2CN	CH_2CH_2CN		3.85		2.70 (benzene ring); 7.16 (—CH_2CH_2CN)
IVc	$CH_2CH_2COOC_2H_5$	$CH_2CH_2COOC_2H_5$		4.16		2.81 (benzene ring); 6.0 (—OCH_2—); 7.3, 7.8, 8.2 (—CH_2CH_2—); 8.8 (—CH_3)
IVd	$CH_2CH_2CH_2NH_2$	$CH_2CH_2CH_2NH_2$		4.13		2.88 (benzene ring); 7.3, 7.6, 8.3–9.0 (—$CH_2CH_2CH_2$—); 9.19 (—NH_2)

[a] Measured as 10% solutions in carbon tetrachloride except where noted otherwise. [b] Ref. 10. Samples of pure indene were run as the neat liquid. [c] Measured as 10% solution in acetone.

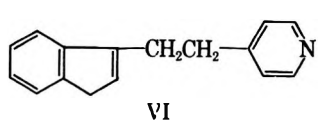
Other Michael-Type Additions to Indene.—Howell and Taylor[3] obtained a 47% yield of ethyl 3-indenepropionate (Id) by the reaction of indene with ethyl acrylate in the presence of sodium methoxide as the catalyst. We obtained a 57% yield of *n*-butyl 3-indenepropionate (Ie) plus a 7.6% yield of di-*n*-butyl indenedipropionate (not identified) by treating excess indene with *n*-butyl acrylate using potassium *t*-butoxide as the catalyst.

Similarly, the reaction of excess indene with 2- and 4-vinylpyridine using potassium *t*-butoxide as the catalyst gave a 47% yield of 3-[2-(2-pyridyl)ethyl]-indene (V), b.p. 161–163° (2 mm.), plus an 11% yield of di[2-(2-pyridyl)ethyl]indene; and a 60% yield of 3-[2-(4-pyridyl)ethyl]indene (VI), m.p. 102–103°, plus an 8.4% yield of di[2-(4-pyridyl)ethyl]indene, respectively. The dipyridylethylation products were not further investigated.

In a recent patent[7] these reactions were reported to give a 25% yield of 4-(1-indenylethyl)pyridine, m.p. 96–97°, and a 30% yield of 2-(1-indenylethyl)pyridine, b.p. 145–155° (0.5 mm.), under fairly similar conditions. Structural analyses were not given, making the position of the substituents on the indene nucleus ambiguous. Presumably, the products obtained as described in this patent are identical with those obtained by us.



V



VI

Derivatives of the monoadduct (V) of 2-vinylpyridine to indene were prepared by reaction with bromine to give 2,3-dibromo-3-[2-(2-pyridyl)ethyl]indan and by base-catalyzed reaction with anisaldehyde to give 1-anisylidene-3-[2-(2-pyridyl)ethyl]indene.

(7) Irwin, Neisler and Co., British Patent 842,996 (1930).

Amines from Cyanoethylated Indenes.—There are numerous reports[8] in the literature which show that the catalytic hydrogenation of the alicyclic double bond of indene takes place under relatively mild conditions. It was, therefore, surprising to find that the catalytic hydrogenation of indene cyanoethylation products in the presence of ammonia, using a nickel catalyst and 1000-p.s.i.g. total pressure at 170°, resulted only in the reduction of the nitrile group, leaving the alicyclic double bond intact. In this manner, 3-indenepropylamine (If), 1,1-indenedipropylamine (IIIc), and 1,1,3-indenetripropylamine (IVd) were obtained.

Structure Proof of Products *via* N.m.r. Spectra.—The chemical shifts of indene and the indene derivatives are given in Table I. Certain regularities are apparent: olefinic protons in the 3-position show lines in the neighborhood of $\tau \cong 3.2$–3.3; olefinic protons in the 2-position show lines in the neighborhood of $\tau \cong 3.8$–4.2; and protons at the 1-position show lines in the neighborhood of $\tau \cong 6.8$. It should be noted that the chemical shifts of indene itself, obtained by Elleman and Manatt,[9] are not to be compared too closely with those of the indene derivatives, since the indene sample was run as the neat liquid while the indene derivatives were run as 10% solutions in carbon tetrachloride. It should also be noted that, in general, the chemical shift of the proton in the 2-position shows a progressive upward shift with increasing alkyl group substitution. The 1,1-disubstituted compounds showed an AB quartet for the protons in the 2,3-positions with a coupling constant between the 2,3-protons of about 5.7 c.p.s., in agreement with the coupling constant of 5.58 c.p.s. observed for indene.[9] The coupling between the protons in the 1,2-positions, of the order of 2 c.p.s., was not resolved, presumably because of broadening by the allylic coupling. Other groups of lines, as listed in

(8) *E.g.*, K. Alder and O. Wolff, *Ann.*, **576**, 182 (1952); W. M. Kutz, J. E. Nickels, J. J. McGovern, and B. B. Corson, *J. Am. Chem. Soc.*, **70**, 4026 (1948); "Chemistry of Carbon Compounds," Vol. IIIB, E. H. Rodd, Ed., Elsevier Publishing Co., Amsterdam, 1956, p. 1253.

(9) D. D. Elleman and S. Manatt, *J. Chem. Phys.*, **36**, 2346 (1962).

Table I, were identified with protons on the benzene ring or on substituent groups; only their centers, in the case of unresolved peaks, are given.

The structure proofs for indene derivatives *via* their n.m.r. spectra are unambiguous. In the case of the monosubstituted indenes, substitution at the 3-position is demonstrated by the lines at $\tau \sim 3.9$ (which implies the olefinic proton is at the 2-position), the absence of AB patterns which would arise from olefinic protons at both the 2- and 3-positions, and the presence of lines at $\tau \sim 6.8$ (arising from protons at the 1-position). The disubstituted indenes are substituted at the 1,1-position as shown by the AB coupling pattern from the olefinic protons at the 2,3-positions and the presence of lines at $\tau \sim 3.1$–3.4 (arising from protons at the 3-positions). The trisubstituted indenes are substituted at the 1,1,3-positions, as indicated by lines at $\tau \sim 3.9$–4.2, corresponding to a proton at the 2-position.

Experimental

All melting points are corrected, all boiling points are uncorrected.

3-Indenepropionitrile (Ia).—To a stirred mixture of 348 g. (3.0 moles) of indene, 6.0 g. (0.019 mole) of 60% aqueous benzyltrimethylammonium chloride, 1.5 g. (0.023 mole) of potassium hydroxide, and 2.0 g. of methanol was added 53 g. (1.0 mole) of acrylonitrile dropwise during 5 hr. at 20–27°. The mix was stirred for an additional 0.5 hr. at 25°, then treated with 5.0 ml. of concentrated hydrochloric acid in 100 ml. of water. The organic layer was separated, washed with 100 ml. of 20% aqueous sodium chloride, then distilled through a 4-in. Vigreux column to give 64.0 g. (38% yield) of 3-indenepropionitrile as a pale yellow oil, b.p. 125–130° (3 mm.) [54.3 g. of a higher boiling residue also was produced]. The monocyanoethylation product was diluted with 75 ml. of isopropyl alcohol, cooled to 0°, and filtered to give 62.1 g. of colorless prisms, m.p. 31.0–31.5°.

Anal. Calcd. for $C_{12}H_{11}N$: N, 8.28. Found: N, 8.20.

1,1-Indenedipropionitrile (IIIa) **and 1,1,3-Indenetripropionitrile** (IVa).—To a stirred mixture of 119 g. (1.0 mole) of 97% indene, 150 ml. of benzene, and a premix of 7.0 g. (0.023 mole) of 60% aqueous benzyltrimethylammonium chloride, 1.7 g. (0.026 mole) of potassium hydroxide, and 2.4 g. of methanol was added 175 g. (3.3 moles) of acrylonitrile dropwise during 4 hr. at 25–27° (the reaction temperature range was maintained by a cold water bath). After stirring for an additional 0.5 hr., the mixture was neutralized by adding a solution of 4.9 ml. of concentrated hydrochloric acid in 100 ml. of 20% aqueous sodium chloride, and filtered. The filtrate was transferred to a separatory funnel, the organic layer was separated and washed acid-free with two 125-ml. portions of 20% sodium chloride solution. The organic product was then flash-distilled to 150° (pot) at 10 mm. to give 261 g. of crude polycyanoethylated indene as a dark oily residue. This crude was distilled through a 4-in. Vigreux column to give 55 g. (24.8% yield) of crude indenedipropionitrile, b.p. 196–202° (1 mm.), a viscous amber oil, and 148 g. (53.8% yield) of 1,1,3-tripropionitrile, b.p. 270–298° (1 mm.), a reddish oil. The latter was crystallized from 300 ml. of 95% ethanol to give 122 g. of pale yellow platelets, m.p. 89–90°; after one recrystallization from benzene–hexane, m.p. 91.0–91.5°.

Anal. Calcd. for $C_{15}H_{17}N_3$ (IVa): N, 15.27. Found: N, 15.0.

To a stirred mixture of 77 g. (0.35 mole) of the above indenedipropionitrile of b.p. 196–202° at 1 mm. (from two runs), 100 ml. of benzene, and a premix of 2.5 g. (0.013 mole) of 60% aqueous benzyltrimethylammonium chloride, 0.61 g. (0.013 mole) of potassium hydroxide, and 0.86 g. of methanol was added 20 g. (0.38 mole) of acrylonitrile dropwise during 1 hr. at 22–29°. After stirring for an additional 0.5 hr., the mixture was neutralized with a solution of 1.8 ml. of concentrated hydrochloric acid in 80 ml. of 20% sodium chloride solution, treated with 4.0 g. of Norit, and filtered. The organic layer was separated, washed free of acid with two 90-ml. portions of 20% sodium chloride solution, and concentrated to 117° (pot) at 5 mm. to give 80 g. of residue. This was distilled through a 4-in. Vigreux column to give 58 g. (79% recovery) of a heart cut of b.p. 186–190° (0.5 mm.) yielding a pale yellow solid, m.p. 39–40°, which after recrystallization from toluene had m.p. 40.0–40.5°.

Anal. Calcd. for $C_{15}H_{14}N_2$ (IIIa): N, 12.66; Found: N, 12.5.

Methyl 3-Indenepropionate (Ic).—A mixture of 64 g. (0.34 mole) of 3-indenepropionic acid (Ib, m.p. 127–128°, obtained by alkaline hydrolysis of the corresponding nitrile), 400 ml. of methanol and 2.5 g. of *p*-toluenesulfonic acid monohydrate was refluxed for 17 hr. The methanol was then evaporated on the steam bath, the residue was taken up in 150 ml. of toluene, and washed successively with 100 ml. of water, 100 ml. of 5% sodium bicarbonate, and two 100-ml. portions of water. The organic layer was dried over Drierite and filtered. The filtrate was stripped of toluene in a Rinco rotating evaporator. The residue was distilled through a 4-in. Vigreux column to give 61.5 g. (90% yield) of methyl 3-indenepropionate (Ic), b.p. 115–121° (1 mm.), a pale yellow oil.

Anal. Calcd. for $C_{13}H_{14}O_2$: sapon. equiv., 205. Found: sapon. equiv., 202.

1,1-Indenedipropionic Acid (IIIb).—A mixture of 22.2 g. (0.1 mole) of 1,1-indenedipropionitrile (m.p. 40.0–40.5°), 9.0 g. (0.22 mole) of sodium hydroxide, and 200 ml. of water was stirred and refluxed for 20 hr., after which no further ammonia was evolved. The clear yellow solution was treated with Norit and filtered hot. The pale yellow filtrate was acidified with dilute hydrochloric acid. The colorless precipitate was filtered off, washed with water, and dried to give 25.4 g. (98% yield) of colorless 1,1-indenedipropionic acid (IIIb), m.p. 155–156°, after recrystallization from 25% aqueous ethanol, m.p. 157–157.5°.

Anal. Calcd. for $C_{15}H_{16}O_4$: neut. equiv., 130.0. Found: neut. equiv., 130.0.

***n*-Butyl 3-Indenepropionate** (Ie).—To a stirred mixture of 232 g. (2.0 moles) of indene and 2.0 g. (0.018 mole) of solid potassium *t*-butoxide was added 128 g. (1.0 mole) of *n*-butyl acrylate dropwise during 1 hr at 100–120°. The mixture was stirred for an additional hour at 120–150°, then neutralized with 1.5 ml. of glacial acetic acid, filtered, and flash-distilled to 138° (pot) at 2 mm. The residue was distilled through a 4-in. Vigreux column to give 136 g. (57% yield) of *n*-butyl 3-indenepropionate as an almost colorless oil, b.p. 138–150° (2 mm.).

Anal. Calcd. for $C_{16}H_{20}O_2$: sapon. equiv., 244. Found: sapon. equiv., 241.

In addition there was obtained 28.2 g. (7.6% yield) of di-*n*-butylindenedipropionate as a yellow oil, b.p. 210–230° (2 mm.).

Anal. Calcd. for $C_{23}H_{32}O_4$: sapon. equiv., 188. Found: sapon. equiv., 186.

The high boiling residue weighed 24.0 g. and may have represented a 4.8% yield of tri-*n*-butyl indenetripropionate.

Triethyl 1,1,3-Indenetripropionate (IVc).—A mixture of 56 g. (0.17 mole) of 1,1,3-indenetripropionic acid (IVb, m.p. 167–169°, obtained by alkaline hydrolysis of the corresponding trinitrile), 3.0 g. of *p*-toluenesulfonic acid monohydrate, and 350 ml. of absolute ethanol was stirred and refluxed for 6 hr. The excess alcohol was then removed on the steam bath. The residue was taken up in 200 ml. of toluene and washed successively with 100 ml. of 5% sodium carbonate and three 50-ml. portions of water. The organic phase was dried over Drierite, filtered, and concentrated to 150° (pot) at 5 mm. to give 42 g. (59.3% yield) of triethyl 1,1,3-indenetripropionate, a pale yellow oil.

Anal. Calcd. for $C_{24}H_{32}O_6$: sapon. equiv., 139. Found: sapon. equiv., 141.

The low yield was due to losses during the washing step and some foamover during the final devolatilization.

3-[2-(2-Pyridyl)ethyl]indene (V).—To a stirred mixture of 119 g. (1.0 mole) of 97.5% indene, 100 ml. of toluene, and 2.0 g. (0.018 mole) of solid potassium *t*-butoxide was added 110 g. (1.05 moles) of 2-vinylpyridine during 1 hr. at 57–90°. The mixture was stirred for an additional 15 min. at 90–100°, then neutralized with 1.0 ml. of glacial acetic acid, and filtered. The clear filtrate was distilled through a 4-in. Vigreux column to give 103 g. (47% yield) of pale yellow liquid 3-[2-(2-pyridyl)ethyl]indene (V), b.p. 161–163° (2 mm.).

Anal. Calcd. for $C_{16}H_{15}N$ (V): N, 6.33; Found: N, 6.0.

In addition, there was obtained 36.5 g. (11% yield) of a red oil, b.p. 220–250° (2 mm.), with correct analysis for di[2-(2-pyridyl)-ethyl]indene.

Anal. Calcd. for $C_{23}H_{22}N_2$: N, 8.59. Found: N, 8.4.

1-[2-2-Pyridyl)ethyl]-1,2-dibromoindan (VII).—To a stirred solution of 44.2 g. (0.2 mole) of 3-[2-(2-pyridyl)ethyl]indene in 100 ml. of chloroform was added a solution of 32.0 g. (0.2 mole) of bromine in 100 ml. of chloroform during 30 min. at 0–5°. The mixture was stirred for an additional hour, then evaporated to dryness. The brown residue was recrystallized from *n*-butyl alcohol to give 42 g. (55% yield) of light tan crystals, m.p. 204° dec.

Anal. Calcd. for $C_{16}H_{15}Br_2N$ (VII): N, 3.68; Br, 42.0. Found: N, 3.70; Br, 41.2.

1-Anisylidene-3-[2-(2-pyridyl)ethyl]indene (VIII).—Into a mixture of 22.1 g. (0.1 mole) of 3-[2-(2-pyridyl)ethyl]indene, 50 ml. of toluene, and 1.0 g. (0.01 mole) of potassium *t*-butoxide was stirred a solution of 27.2 g. (0.2 mole) of anisaldehyde in 50 ml. of toluene dropwise during 1 hr. at 30–35°. The mixture was then stirred for 2 hr. at 75°, finally neutralized with 1.0 ml. of glacial acetic acid, and filtered. The filtrate was concentrated to 150° (2 mm.) and the brownish residue (48 g.) was recrystallized from 95% ethanol to give 13 g. (38% yield) of a yellow solid, m.p. 88–90°.

Anal. Calcd. for $C_{24}H_{21}NO$ (VIII): N, 4.33. Found: N, 4.10.

3-[2-(4-Pyridyl)ethyl]indene (VI).—To a stirred mixture of 238 g. (2.0 moles) of indene and 2.0 g. (0.018 mole) of potassium *t*-butoxide was added dropwise 110 g. (1.05 moles) of 4-vinylpyridine during 1 hr. at 80–140°. The mixture was stirred for an additional hour at 90–130°, then neutralized with 1.5 ml. of glacial acetic acid, and filtered. The filtrate was concentrated to 162° (pot) at 2 mm. The residue was distilled through a 4-in. Vigreux column to give 133 g. (60% yield) of 3-[2-(4-pyridyl)-ethyl]indene, b.p. 162–165° (2 mm.), a yellow oil which solidified on standing, m.p. 97–101°; after recrystallization from ethyl acetate, large colorless prisms, m.p. 102–103°.

Anal. Calcd. for $C_{16}H_{15}N$: N, 6.33. Found: N, 6.3.

3-Indenepropylamine (If).—A 1-gal. stainless steel, stirring-type autoclave was charged with 338 g. of 3-indenepropionitrile, 500 ml. of benzene, 50 g. of ammonia, 30 g. of nickel-on-kieselguhr catalyst, and a solution of 0.6 g. sodium hydroxide in 30 ml. of 1:1 water–methanol, pressured to 500 p.s.i.g. with hydrogen, and heated to 140° (maximum pressure of 850 p.s.i.g. was reached). The autoclave was repressured with hydrogen to 850 p.s.i.g. whenever the pressure fell to 600 p.s.i.g., until no further pressure drop took place after 2 hr. The autoclave was cooled and vented. The charge was filtered, the cake washed with a little benzene, and the combined filtrates were concentrated to 10° (pot) at 35 mm. The residue was distilled through a 4-in. Vigreux column to give a heart cut of b.p. 146–149° (10 mm.), 273 g. (78% yield) of 3-indenepropylamine, a pale yellow oil.

Anal. Calcd. for $C_{12}H_{15}N$: neut. equiv., 173.0. Found: neut. equiv., 174.1.

1,1-Indenedipropylamine and 1,1,3-Indenetripropylamine.—A 1-gal. stainless steel, stirring-type autoclave was charged with 532 g. of crude polycyanoethylated indene (preparation described before), 500 ml. of benzene, 25 ml. of water, 25 ml. of methanol, 1.0 g. of sodium hydroxide, 142 g. of ammonia, and 50 g. of a stabilized nickel-on-kieselguhr catalyst. The autoclave was pressured to 500 p.s.i.g. with hydrogen and heated to 170°. The autoclave was repressured to 1000-p.s.i.g. total pressure whenever the pressure fell to 600 p.s.i.g. After 2.5 hr. at 172–175° and 1000-p.s.i.g. pressure, no further pressure drop took place. The autoclave was cooled, vented, and discharged. The product was filtered and the filtrate concentrated to 100° (pot) at 9 mm. to give 502 g. of a brown oil. This residue was distilled through a 4-in. Vigreux column to give 55.3 g. of a fraction of b.p. 143–153° (1 mm.) with correct analysis for 1,1-indenedipropylamine.

Anal. Calcd. for $C_{15}H_{22}N_2$: neut. equiv., 115.0. Found: neut. equiv., 116.6.

In addition, there was obtained 253 g. of a fraction of b.p. 220–232° (2 mm.), which corresponded to 1,1,3-indenetripropylamine.

Anal. Calcd. for $C_{18}H_{29}N_3$: neut. equiv. 95.7. Found: neut. equiv., 96.9.

N.m.r. spectra were run at room temperature (22 ± 2°) at 60.00 Mc. on a Varian 4302 DP-60 spectrometer. Line positions were obtained with respect to tetramethylsilane as an internal reference by calibration between side bands of set frequency.[10] Line positions are given in terms of τ-values (chemical shifts in parts per million with respect to tetramethylsilane, tetramethylsilane being set at 10). All samples were run as 10% (by weight) solutions in carbon tetrachloride (except where noted as otherwise in Table I).

Acknowledgment.—The authors wish to thank Dr. J. O'Brochta and Dr. R. B. Carlin for their interest in this work and Mr. H. W. Hampson for his laboratory assistance.

(10) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959.

Reaction of Indole Derivatives with Thionyl and Sulfuryl Chlorides

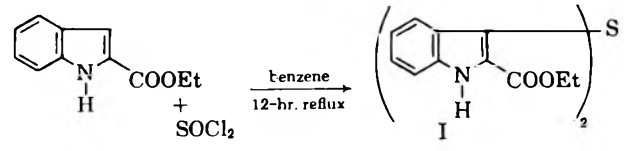
JACOB SZMUSZKOVICZ

Research Laboratories of The Upjohn Company, Kalamazoo, Michigan

Received July 22, 1963

Reaction of 1-methylindole-2-carboxylic acid (II), the corresponding methyl ester V, and of ethyl indole-2-carboxylate with thionyl chloride afforded sulfinyl chlorides III, VI, and XXIII, respectively. Thionyl chloride and N,1-dimethylindole-2-carboxamide (XIX) led to sulfide XX and imide sulfoxide XXI. Sulfinyl chloride VI was converted to several sulfinamides (XI) on treatment with amines. Sulfinamides XI were oxidized with permanganate to sulfonamides XII. Treatment of VI with hydrazine in the cold gave disulfide IV, which was transformed to XXVII on heating with hydrazine. Monosulfide VIII, disulfide IV, and trisulfide X were obtained from the reaction of V with sulfur monochloride. Reaction of 1-methylindole-2-carboxylic acid hydrazide (XXX) with sulfuryl chloride led to the dichloro compound (XXXI), and V with sulfuryl chloride afforded the tetrachloro compound (XXXI) and the hexachloro compound (XXXII).

Kunori[1] has reported recently on the reaction of ethyl indole-2-carboxylate with thionyl chloride and isolation of sulfide I from the reaction mixture. We would like to describe at this time our experiments on the condensation of several indole derivatives with the same reagent.[2]



I

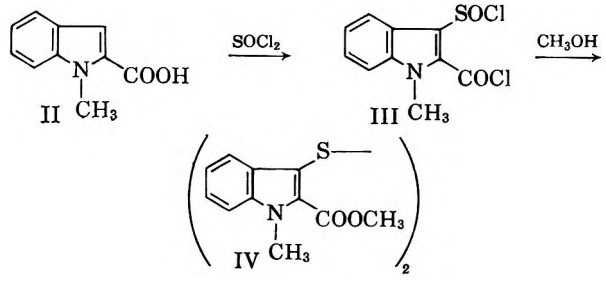
During an attempted preparation of 1-methylindole-2-carbonyl chloride[3] from the corresponding acid (II)

(1) M. Kunori, *Nippon Kagaku Zasshi*, **80**, 407 (1959); *Chem. Abstr.*, **55**, 5457 (1961).

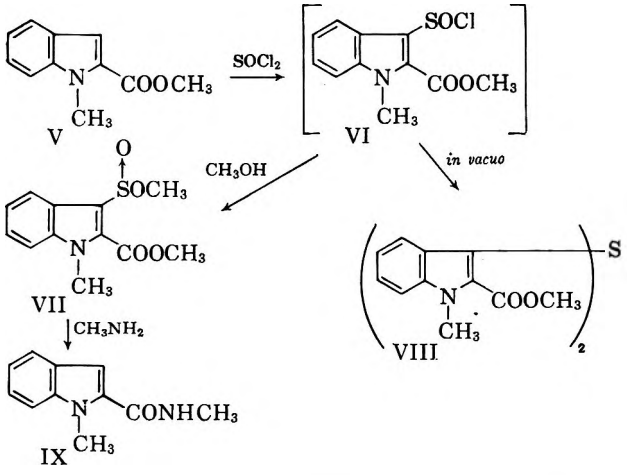
(2) This work was complete prior to the appearance of Kunori's paper[1] in *Chemical Abstracts*.

(3) This acid chloride is best prepared from the acid with phosphorus pentachloride in ether according to J. R. Johnson, R. B. Hasbrouck, J. D. Dutcher, and W. F. Bruce, *J. Am. Chem. Soc.*, **67**, 423 (1945).

and thionyl chloride we observed that under certain conditions (see the Experimental) a sulfur-containing compound was produced for which structure III is proposed.[4a] Treatment of III with methanol brought about a disproportionation[4b] and led to disulfide IV which was identical with an authentic sample.

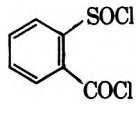


Extension of the thionyl chloride reaction to methyl 1-methylindole-2-carboxylate (V) gave the sulfinyl chloride (VI) in excellent yield. Unlike III, treatment of VI with methanol afforded the dimethyl ester (VII). On the other hand, VI underwent disproportionation *in vacuo* to give the monosulfide VIII which was identical with an authentic sample. The authentic



monosulfide (VIII) and disulfide IV along with trisulfide X were obtained from the reaction of V with sulfur monochloride.[5a] No reaction occurred between the dimethyl ester (V) and methanolic ammonia or dimethylamine. On the other hand, methylamine under the same conditions produced N,1-dimethylindole-2-carboxamide (IX).[5b]

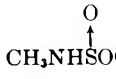
(4)(a) Three structures have been proposed for the product obtained from the reaction of anhydrous chlorine on *o*-thiolbenzoic acid. Recently I. B. Douglass and B. S. Farah [*J. Org. Chem.*, **26**, 351 (1961)] indicated a preference for structure i.

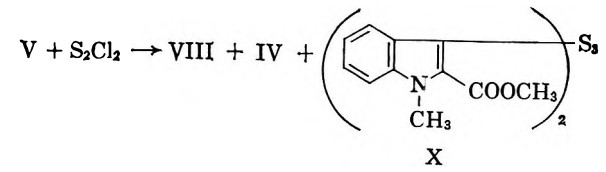


i

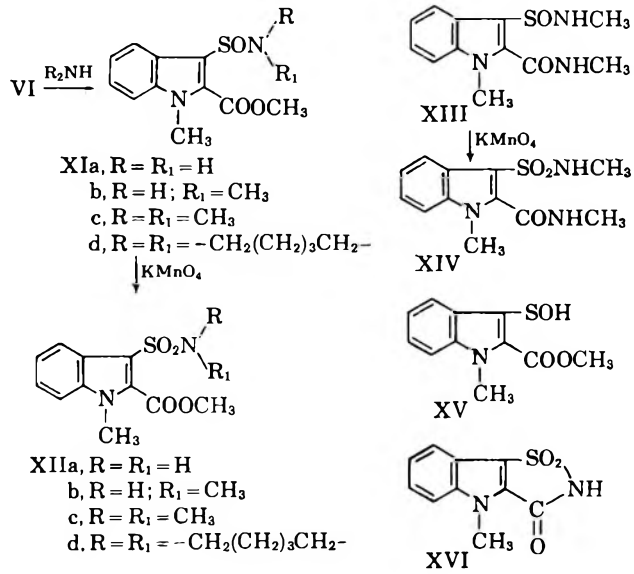
(b) *Cf.* F. Muth, "Methoden der Organischen Chemie" (Houben-Weyl), Vol. 9, E. Muller, Ed., Georg Thieme Verlag, Stuttgart, 1955, p. 299.

(5)(a) *Cf.* T. Wieland, O. Weiberg, E. Fischer, and G. Horlein, *Ann.*, **587**, 146 (1954); M. Kunori, *Nippon Kagaku Zasshi*, **80**, 409 (1959); *Chem. Abstr.*, **55**, 5458 (1961). (b) The mechanism of this reaction was not investigated. This reaction may proceed either by displacement at the O–CH_3 bond to give dimethylamine and SO_2 as by-products, or by displacement at the C–S bond to give the following.

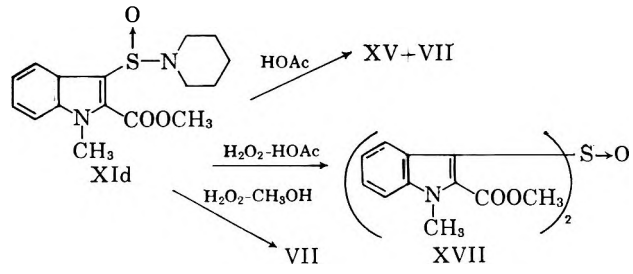




Reaction of sulfinyl chloride VI under anhydrous conditions with ammonia, methylamine, dimethylamine, and piperidine afforded sulfinamides XIa, XIb, XIc, and XId, respectively. In the case of methylamine some conversion to the bismethyl amide (XIII) also occurred. Reaction of VI with aqueous dimethylamine afforded 1-methyl-2-carbomethoxyindole-3-sulfenic acid (XV) along with sulfinamide XIc. Sulfenic acid XV also was isolated from an attempted condensation of VI with acetamide in pyridine.

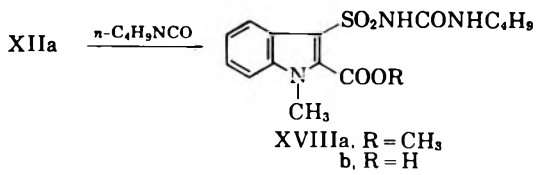


Several additional reactions were carried out with sulfinamide XId. In acetic acid solution XId underwent disproportionation to give sulfenic acid XV and monosulfide VII. Conversion of XId to sulfoxide XVII occurred with hydrogen peroxide in acetic acid, and with hydrogen peroxide in methanol, XId afforded diester VII.

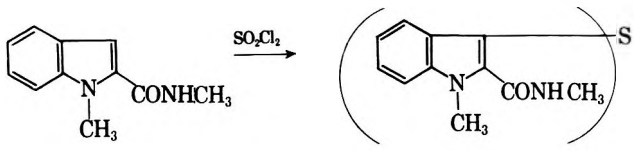


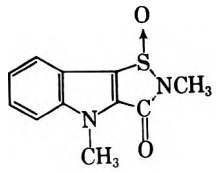
Oxidation of sulfinamides XIa, XIb, XIc, XId, and XIII with potassium permanganate in aqueous acetone afforded sulfonamides XIIa, XIIb, XIIc, XIId, and XIV, respectively. In the case of sulfinamide XIa, imide XVI also was isolated from the oxidation reaction by acidification of the alkaline filtrate.

Sulfonamide XIIa reacted with butyl isocyanate to give the urea derivative (XVIIIa), which was hydrolyzed with aqueous base to the corresponding acid (XVIIIb).



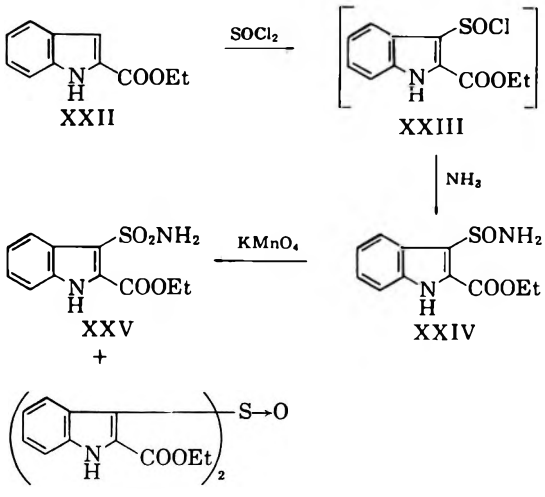
Extension of the thionyl chloride reaction to N,1-dimethylindole-2-carboxamide (XIX) led to sulfide XX and imide sulfoxide XXI. Thionyl chloride also reacted with ethyl indole-2-carboxylate (XXII)[6] and





XXI

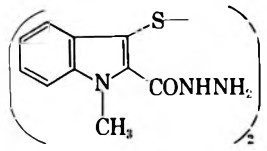
afforded the corresponding sulfinyl chloride XXIII which was converted to sulfinamide XXIV in 87% over-all yield. Oxidation of XXIV with permanganate led to sulfonamide XXV, accompanied by a small quantity of sulfoxide XXVI.



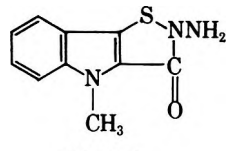
Sulfinyl chloride VI was very smoothly converted with hydrazine in the cold to the disulfide IV in 70% yield. On refluxing with hydrazine hydrate, IV was transformed to a new compound for which structure XXVII is postulated. Compound XXVII formed a bisbenzylidene derivative, a tetraacetyl derivative, and a bisisopropylidene derivative. The n.m.r. spectrum[7] of the tetraacetyl derivative showed $COCH_3$ hydrogens at 127 c.p.s. (area 6), NCH_3 at 230 (area 3), aromatic hydrogen at 415 to 462 (area 4), and NH at 645 (area 0.9). The presence of hydrogen, typical of the NH

(6) Kunori isolated from this reaction only disproportionation products and not XXIII, since he employed more drastic conditions.

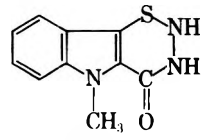
(7) The spectrum was run with a Varian H.R. 60 spectrometer and deuterated dimethyl sulfoxide as solvent. Frequencies are reported in cycles per second downfield from internal tetramethylsilane. We thank Dr. G. Slomp and F. A. MacKellar for the spectrum and its interpretation.



XXVII



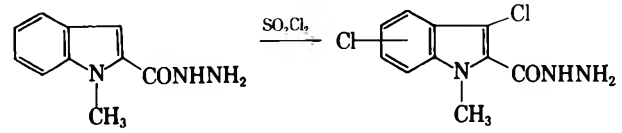
XXVIII

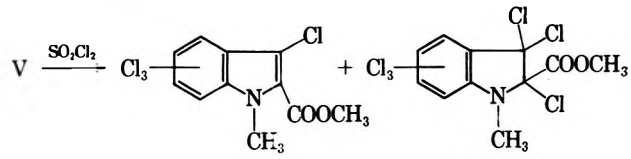


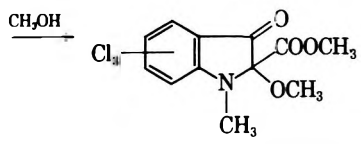
XXIX

grouping, provides strong support for structure XXVII in preference to the tricyclic structures (XXVIII and XXIX), assuming that no skeletal change occurred during the mild acetylation reaction.

Two reactions were carried out with sulfuryl chloride. Treatment of 1-methylindole-2-carboxylic acid hydrazide (XXX) with sulfuryl chloride afforded the dichloro derivative (XXXIa). Reaction of V with sulfuryl chloride led to a mixture of the tetrachloro compound







XXXIII

(XXXIb) and the hexachloro compound (XXXII). On refluxing with methanol, XXXII afforded the trichloro derivative (XXXIII). The structures of the last three compounds are postulated on the basis of analytical data, and ultraviolet and infrared spectra.

Experimental[8,9]

Condensation of 1-Methylindole-2-carboxylic Acid (II) with Thionyl Chloride.—Thionyl chloride (7 ml.) was added to acid II[10] (m.p. 212–214°, 3.50 g., 0.02 mole). The resulting solid mass was heated on the steam bath for a short time and, since solution did not occur, 25 ml. of benzene was added and the mixture was refluxed for 75 min. The resulting brown solution was evaporated to dryness on the steam bath *in vacuo*; the residue was flushed twice with benzene and crystallized from benzene–Skellysolve B to give 1.85 g., m.p. 141–143°. Two recrystallizations from benzene with considerable loss of material afforded

(8) Melting points were taken in a capillary tube and are uncorrected. Ultraviolet spectra (recorded in mμ) were determined in 95% ethanol using a Cary spectrophotometer Model 14. Infrared spectra (recorded in $cm.^{-1}$) were determined in Nujol using a Perkin-Elmer recording infrared spectrophotometer, Model 21. Skellysolve B is commercial hexane, b.p. 60–70°, made by Skelly Oil Co., Kansas City, Mo.

(9) The author is indebted to Dr. R. W. Rinehart and his associates for microanalyses, to Betty F. Zimmer and Miss L. M. Pschizoda for ultraviolet and infrared spectra, and to Mr. L. G. Laurian for laboratory assistance.

(10) H. R. Snyder and P. L. Cook, *J. Am. Chem. Soc.*, **78**, 969 (1956).

yellow needles of III, m.p. 151–152°. Ultraviolet spectrum (in dimethylacetamide) showed λ_{max} 295 mμ (ε 12,400), sh 312 (10,000), sh 324 (8700), sh 372 (2500). Infrared spectrum showed 1750; 1604 (C=O); 1563, 1487 (C=C) cm.$^{-1}$. This compound decomposes on standing at room temperature.

Anal. Calcd. for $C_{10}H_7Cl_2NO_2S$: C, 43.49; H, 2.56; Cl, 25.68; N, 5.07; S, 11.61. Found: C, 44.15; H, 2.15; Cl, 24.98; N, 5.41; S, 11.93.

Conversion of III with Methanol to IV.—The dichloride (200 mg., m.p. 148–150°) was dissolved in 5 ml. of boiling methanol and allowed to crystallize overnight, to give 47 mg., m.p. 185–187° (fast). Recrystallization from methanol afforded plates, m.p. 183.5–184.5°. Sublimation at 160–170° (0.01 mm.) followed by crystallization from acetone gave disulfide IV, m.p. 191–192°, which was identical (ultraviolet and infrared spectra, mixture melting point) with the product obtained by the reaction of V with sulfur monochloride.

Condensation of Methyl 1-Methylindole-2-carboxylate (V) with Thionyl Chloride.—Thionyl chloride (5 ml.) was added to V[11] (m.p. 96.5–97.5°, 1.89 g., 0.01 mole). Solution occurred, followed by vigorous evolution of gas, and then solidification. The mixture was allowed to stand for 5 min., 15 ml. of anhydrous ether was added, the solid was triturated, filtered, and washed with ether. The infrared spectrum of this yellow product VI showed a strong band at 1745 cm.$^{-1}$. The solid was dried *in vacuo* for 10 min. and amounted to 2.45 g., m.p. 85–88° dec. It was not sufficiently stable for analysis. This reaction could be run using 0.8 mole of the ester.

Methyl 1-Methyl-2-carbomethoxyindole-3-sulfinate (VII).—A suspension of VI (0.5 g.) in 15 ml. of methanol was refluxed until solution resulted (*ca.* 5 min.). It was evaporated to a small volume and allowed to crystallize to colorless prisms, 0.45 g. (64%), m.p. 104–110° dec., discolors at 80°. Recrystallization from methanol afforded VII melting at 108–110° dec., discolors at 93°. Ultraviolet spectrum showed λ_{max} 215 mμ (ε 25,600), 237 (24,000), 304 (15,500). Infrared spectrum showed 1715 (C=O); 1603, 1564, 1490 (C=C); 1240, 1120, 1110, 1100 (C–O/S→O) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{13}NO_4S$: C, 53.92; H, 4.90; N, 5.24; S, 12.00; OCH_3, 23.22. Found: C, 53.79; H, 4.52; N, 5.21; S, 12.13; OCH_3, 22.40.

This compound was stable for a period of only a few days, but could be kept indefinitely *in vacuo*.

Disproportionation of VII *in Vacuo*.—The sulfinyl chloride (VII, 1.4 g.) was left *in vacuo* at room temperature overnight. The resulting oily mixture was boiled with 20 ml. of methanol and the solution was evaporated to *ca.* 5 ml. and allowed to crystallize; needles (380 mg.), m.p. 147–150°. Recrystallization from methanol raised the melting point to 152–152.5°. This material was identical (ultraviolet and infrared spectra, mixture melting point) with the monosulfide VIII obtained from the reaction of V with sulfur monochloride.

Reaction of V with Sulfur Monochloride.—Sulfur monochloride (13.5 g., 0.1 mole) was added during 20 min. to a solution of V (38 g., 0.2 mole) in 250 ml. of benzene with stirring under nitrogen and cooling so that the temperature was below 5°. The mixture was stirred for 3 hr. The suspension was filtered and the solid was washed with benzene to give 7.3 g. of A, m.p. 157–161°. The filtrate was diluted with 1 l. of petroleum ether (b.p. 30–60°) and cooled in ice for 0.5 hr. It was filtered and the solid washed with petroleum ether to give 11 g. of B, m.p. 127–160°. The filtrate was evaporated to dryness and the residue was crystallized from 100 ml. of benzene and 100 ml. of petroleum ether to give 18.5 g., m.p. 128–141°. Recrystallization from acetone afforded 3 g. of trisulfide X, m.p. 155–157°, and filtrate C. The analytical sample melted at 158.5–159.5° (from acetone). Ultraviolet spectrum showed λ_{max} 222 mμ (ε 38,100), sh 276 (17,000), 299 (21,200), sh 344 (9300). Infrared spectrum showed 1705 (C=O); 1615, 1575, 1490 (C=C); 1235 (C–O) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{20}N_2O_4S_3$: C, 55.91; H, 4.27; N, 5.93; S, 20.36; OCH_3, 13.13. Found: C, 55.85; H, 4.05; N, 5.84; S, 20.28; OCH_3, 13.66.

Solid A was crystallized from 300 ml. of acetone to give 2.71 g. of disulfide IV as yellow rods, m.p. 199–200°, unchanged on further purification. Ultraviolet spectrum showed λ_{max} 216 mμ (ε 41,000), 234 (33,200), 279 (21,200), 302 (22,200), sh 356 (5850). Infrared spectrum showed 3050, 3020 (=CH); 1708 (C=O); 1610, 1573, 1488 (C=C); 1255 (C–O) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{20}N_2O_4S_2$: C, 59.98; H, 4.58; N, 6.36; S, 14.56; OCH_3, 14.09. Found: C, 60.11; H, 4.41; N, 6.47; S, 14.71; OCH_3, 13.07.

Solid B was crystallized from acetone as before and afforded 2.53 g. of disulfide IV, m.p. 198–199.5° (identified by mixture melting point determination). The filtrate from the acetone crystallization of solid B was concentrated to about one-half volume and allowed to crystallize to give 2.3 g. of monosulfide VIII, m.p. 149.5–150.5°. Recrystallization from benzene–petroleum ether raised the melting point to 150.5–152°. Ultraviolet spectrum showed λ_{max} 237 mμ (ε 41,250), 299.5 (24,000), 352 (9650). Infrared spectrum showed 1705 (C=O); 1610, 1492 (C=C) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{20}N_2O_4S$: C, 64.69; H, 4.94; N, 6.86; S, 7.85; OCH_3, 15.20. Found: C, 65.00; H, 4.76; N, 6.74; S, 7.82; OCH_3, 14.03.

Filtrate C was evaporated to dryness to give 13.7 g. of solid. It was dissolved in minimum of benzene and chromatographed on Woelm neutral alumina (411 g.). Elution with 0.5% methanol–benzene (4800 ml.) gave 10.13 g. which was allowed to crystallize from 25 ml. of benzene. A mixture resulted which was separated mechanically to give 0.3 g. of colorless rods of monosulfide VIII, m.p. 150.5–152°, and 1.2 g. of yellow prisms of disulfide IV, m.p. 190–195°, raised on recrystallization from acetone to 197–200°. The benzene filtrate was diluted with 10 ml. of petroleum–ether (b.p. 30–60°) to give an additional 3.1 g. of monosulfide VIII, m.p. 149–152°.

Reaction of VII with Amines. A. With Methylamine.—Sulfinate VII (4.0 g., 0.015 mole) was dissolved in 150 ml. of methanol and methylamine was added until 32 g. was absorbed. The solution was allowed to stand for 70 hr. It was then evaporated to dryness to give a colorless crystalline product melting at 108–111°. It was dissolved in ether, filtered from a small amount of a brown amorphous solid, and allowed to crystallize to give 2.2 g., m.p. 110–112°. The second crop amounted to 0.55 g., m.p. 109–111°. The ultraviolet [λ_{max} 217 mμ (ε 29,350), 291 (16,150)] and infrared spectra were identical with those of authentic N,1-dimethylindole-2-carboxamide[11] and the mixture melting point showed no depression.

B. With Anhydrous Ammonia.—The reaction was run as under A using 13 g. of ammonia. The solution was evaporated to dryness to give recovered starting material in quantitative yield, m.p. 95–97° (polymorph of the previously encountered form as shown by infrared spectra in chloroform and mixture melting point).

C. With Dimethylamine.—The reaction was run as under A using 50 g. of dimethylamine. The solid residue was crystallized from methanol and afforded 2.84 g. of recovered starting material.

Methyl 1-Methyl-3-(aminosulfinyl)indole-2-carboxylate (XIa).—Sulfinyl chloride VI (prepared from 0.2 mole of V) was added during 3 min. to a solution of 150 ml. of liquid ammonia in 300 ml. of ether with stirring and cooling in a Dry Ice bath. The suspension was then stirred for an additional 5 min. and the Dry Ice bath was replaced with tap water to evaporate the ammonia. Ether was then evaporated *in vacuo*, 200 ml. of water was added, and the solid was filtered and washed well with three 100-ml. portions of water. Crystallization from 100 ml. of methanol and 100 ml. of water afforded 47.5 g. (94.5%), m.p. 111–116.5° unchanged on further recrystallization. Ultraviolet spectrum showed λ_{max} 216 mμ (ε 24,000), 234 (24,000), 301 (14,600). Infrared spectrum showed 3580, 3340, 3200 (NH/OH); 1698 (C=O); 1635, 1565, 1500 (C=C); 1250 (C–O) cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{12}N_2O_3S \cdot 1/4H_2O$: C, 51.44; H, 4.73; N, 11.17; S, 12.49; OCH_3, 12.08. Found: C, 51.27; H, 4.47; N, 11.43; S, 13.01; OCH_3, 11.36.

Methyl 1-Methyl-3-sulfamoylindole-2-carboxylate (XIIa) and XVI.—A solution of potassium permanganate[12] (5.25 g., 0.0332 mole) in 110 ml. of water (in all the other experiments the amount of water was reduced to half this volume) was added during 15 min. with stirring to a solution of sulfinamide XIa (12.6 g., 0.05 mole) in 500 ml. of purified acetone (boiled with potassium permanganate, dried over potassium carbonate, and distilled) keeping the temperature at 22–25° by occasional cooling. The mixture was then stirred for 1.5 hr. A saturated solution of

(11) Prepared according to reference quoted in ref. 3.

(12) This experiment will serve as the general procedure for oxidation of sulfinamides with potassium permanganate.

sodium sulfite (3 ml.) was added (in all the other experiments reaction times were longer and addition of reducing agent was omitted), the mixture was filtered, and the precipitate washed with acetone. The filtrate was evaporated *in vacuo* at 35°, the resulting aqueous suspension was filtered, and the resulting XIIa was washed with water to yield 8.3 g. (62%), m.p. 167–170°. Recrystallization from methanol afforded plates, m.p. 168.5–170°. Ultraviolet spectrum showed λ_{max} 210 mμ (ε 31,750), sh 234 (14,000), 297 (12,600). Infrared spectrum showed 3370, 3280 (NH); 3090, 3060, 3020 (=CH); 1710, 1700 (C=O); 1615, 1607, 1600, 1550, 1520 (C=C) cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{12}N_2O_4S$: C, 49.24; H, 4.51; N, 10.44; S, 11.95. Found: C, 49.11; H, 4.51; N, 10.36; S, 12.11.

The aqueous filtrate was cooled in ice, acidified with concentrated hydrochloric acid, and the mixture was extracted with ether. The extracts were washed with saturated salt solution, dried through sodium sulfate, and evaporated to give 3.1 g. of crude 4-methyl-4*H*-isothiazolo[4,5-*b*]indol-3(2*H*)-one 1,1-dioxide (XVI), m.p. 200–220°. Crystallization from acetone–water afforded 1.7 g. (14.4%), m.p. 265–267° dec. One further recrystallization gave needles, m.p. 278–279° dec., discolors at 240°. Ultraviolet spectrum showed λ_{max} 229 mμ (ε 27,900), sh 252 (4600), 262 (3350), 305 (10,000). Infrared spectrum showed 3220 (NH); 1745 (C=O); 1540, 1505, 1485 (C=C) cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_8N_2O_3S$: C, 50.83; H, 3.41; N, 11.86; S, 13.57. Found: C, 50.73; H, 2.98; N, 11.50; S, 13.47 (no methoxyl).

Methyl 1-Methyl-3-(methylaminosulfinyl)indole-2-carboxylate (XIb) and 1-Methyl-3-(methylaminosulfinyl)indole-2-methylcarboxamide (XIII).—Sulfinyl chloride, VI (prepared from 0.2 mole of V) was added during 5 min. to a solution of methylamine (173 ml.) in 660 ml. of ether with stirring and cooling at −9°. The temperature rose to 5° during the addition and the mixture was maintained at this temperature for 15 min. It was then evaporated to dryness *in vacuo*, 125 ml. of water was added, and the solid was filtered and washed with water. It was crystallized from ethyl acetate to give 23.5 g. (44% yield) of XIII as clusters of colorless prisms, m.p. 165–168°, raised to 171–172° on recrystallization from methanol. Ultraviolet spectrum showed λ_{max} 217 mμ (ε 30,500), sh 225 (28,600), 291 (16,400). Infrared spectrum showed 3250 (NH); 3100, 3050 (=CH); 1660, 1653 (amide I); 1570 (amide II); 1610, 1500 (C=C) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{15}N_3O_2S$: C, 54.32; H, 5.70; N, 15.83; S, 12.08. Found: C, 54.52; H, 5.79; N, 15.32; S, 11.97 (no methoxyl).

The ethyl acetate filtrate was allowed to stand overnight to give 8.72 g. (16%) of XIb as prisms, m.p. 137–138°, unchanged on recrystallization from ethyl acetate. Ultraviolet spectrum showed λ_{max} 216 mμ (ε 23,650), 234 (26,050), 302 (15,050), sh 328 (6100), sh 336 (4200). Infrared spectrum showed 3280, 3240 (NH); 1712 (C=O); 1610, 1570, 1505 (C=C); 1250 (C—O) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{14}N_2O_3S$: C, 54.12; H, 5.30; N, 10.52; S, 12.04; OCH_3, 11.65. Found: C, 54.16; H, 5.19; N, 10.32; S, 11.82; OCH_3, 10.85.

Methyl 1-Methyl-3-(methylsulfamoyl)indole-2-carboxylate (XIIb).—Sulfinamide XIb (8.72 g., 0.033 mole) was oxidized[12] during 17.5 hr. The resulting solid melted at 119–120°. Crystallization from benzene–petroleum ether (b.p. 30–60°) gave 5.1 g. (55%), m.p. 121–122°. This product was a polymorph of XIIb obtained from a similar experiment (as determined by infrared in Nujol and in chloroform solution) and which melted at 114.5–115.5°. Ultraviolet spectrum showed λ_{max} 211 mμ (ε 33,100), sh 236 (10,350), 291 (10,950). Infrared spectrum showed 3320 (NH); 1695 (C=O); 1650, 1610, 1565, 1505 (C=C); 1265 (C—O) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{14}N_2O_4S$: C, 51.05; H, 5.00; N, 9.92; S, 11.36; OCH_3, 10.99. Found: C, 51.47; H, 4.98; N, 9.72; S, 11.53; OCH_3, 10.65.

1-Methyl-3-(methylaminosulfinyl)indole-2-methylcarboxamide (XIV).—Sulfinamide XIII (11.3 g., 0.043 mole) was oxidized[12] during 4 hr. The resulting solid was crystallized from 35 ml. of methanol and afforded 7.7 g. (64%), m.p. 186–187°, unchanged on recrystallization. Ultraviolet spectrum showed λ_{max} 215 mμ (ε 40,850), 282 (10,900). Infrared spectrum showed 3330, 3170 (NH); 1660 (amide I); 1575 (amide II); 1500 (C=C) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{15}N_3O_3S$: C, 51.23; H, 5.37; N, 14.94; S, 11.40. Found: C, 51.19; H, 5.09; N, 14.93; S, 11.97 (no methoxyl).

Preparation of Methyl 1-Methyl-3-(dimethylaminosulfinyl)indole-2-carboxylate (XIc). A. With Anhydrous Dimethylamine.—Sulfinyl chloride VI (prepared from 0.2 mole of V) was added during 5 min. to a solution of dimethylamine (180 g.) in 660 ml. of ether with stirring and cooling at 3°. The mixture was then stirred for 15 min. and evaporated *in vacuo*. Water (150 ml.) was added and the solid XIc was filtered, washed with water, and crystallized from methanol to give 46.5 g. (83%), m.p. 132–134°, raised to 134–135° on recrystallization. Ultraviolet spectrum showed λ_{max} 215 mμ (ε 24,000), 235 (26,150), 303 (15,300), sh 324, sh 326 (4,700). Infrared spectrum showed 3070 (=CH); 1720 (C=O); 1610, 1567, 1495 (C=C); 1240 (C—O) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{16}N_2O_3S$: C, 55.69; H, 5.75; N, 9.99; S, 11.44; OCH_3, 11.06. Found: C, 55.71; H, 5.80; N, 9.60; S, 11.20; OCH_3, 10.65.

B. With Aqueous Dimethylamine.—Sulfinyl chloride VI (prepared from 0.03 mole of V) was added to a solution of dimethylamine (6.8 ml. of 40% aqueous solution, 0.06 mole) and 50 ml. of ether with stirring and ice cooling. The mixture was stirred in the cold for 2 hr. It was then filtered and the yellow solid (m.p. 95–147°) crystallized from acetone–water to give 2.4 g., m.p. 193–194° dec., unchanged on recrystallization. This compound was identical with sulfenic acid XV obtained below (mixture melting point and infrared spectrum).

The aqueous acetone filtrate was evaporated to get rid of acetone and the solid (2.37 g., m.p. 128–130°) was crystallized from benzene–petroleum ether (b.p. 30–60°); m.p. 132–133°. This compound was identical with XIc (C, H, N, S, OCH_3 analyses, ultraviolet and infrared spectra).

Methyl 1-Methyl-3-(dimethylsulfamoyl)indole-2-carboxylate (XIIc).—Sulfinamide XIc (33.37 g., 0.119 mole) was oxidized[12] during 23 hr. The residue was extracted with four 200-ml. portions of benzene, the extract was washed with saturated salt solution, dried over sodium sulfate, and evaporated. The residue (25 g.) was dissolved in benzene and chromatographed on 750 g. of acid-washed alumina. Elution with four 400-ml. portions of benzene gave 1.91 g. (m.p. range 60–69°) which could not be crystallized. Further elution with fourteen 400-ml. portions of benzene gave a total of 5.09 g. which was crystallized from benzene–petroleum ether (b.p. 30–60°) to give 2.4 g., m.p. 113–115°, raised to 114–115.5° on recrystallization. Ultraviolet spectrum showed λ_{max} 211 mμ (ε 36,000), 286 (10,700). Infrared spectrum showed 1745 (C=O); 1520 (C=C) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{16}N_2O_4S$: C, 52.68; H, 5.44; N, 9.45; S, 10.82; OCH_3, 10.47. Found: C, 53.01; H, 5.28; N, 9.68; S, 10.87; OCH_3, 10.58.

Methyl 1-Methyl-3-(piperidinosulfinyl)indole-2-carboxylate (XId).—Sulfinyl chloride, VI (prepared from 0.1 mole of V) was added during 3 min. to a solution of piperidine (17 g., 0.2 mole) in 150 ml. of ether with stirring and cooling at 2°. The mixture was then stirred in an ice bath for 2 hr. and evaporated to dryness. Water (50 ml.) was added and the solid was filtered and washed with water, m.p. 102–104°. Crystallization from methanol–water afforded 25.8 g. (78%) of product which had the same melting point. Ultraviolet spectrum showed λ_{max} 215 mμ (ε 24,750), 234.5 (26,650), 303 (14,900), sh 324 (7600), sh 336 (4600). Infrared spectrum showed 1715 (C=O); 1505 C=C; 1245 (C—O) cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{20}N_2O_3S$: C, 59.97; H, 6.29; N, 8.75; S, 10.00; OCH_3, 9.68. Found: C, 59.83; H, 6.15; N, 8.45; S, 10.04; OCH_3, 9.32.

Methyl 1-Methyl-3-(piperidinosulfonyl)indole-2-carboxylate (XIId).—Sulfinamide XId (3.2 g., 0.01 mole) was oxidized[12] during 15.5 hr. The resulting oily mixture was extracted with three 50-ml. portions of ether, the extract was washed with saturated salt solution and evaporated to give 3.2 g. of an oil. Crystallization from methanol–water afforded 1.3 g. (39%), m.p. 111–113°, raised to 113.5–115° on recrystallization. Ultraviolet spectrum showed λ_{max} 287 mμ (ε 10,600). Infrared spectrum showed 1765, 1755 (C=O); 1515 (C=C) cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{20}N_2O_4S$: C, 57.12; H, 5.99; N, 8.33; S, 9.53; OCH_3, 9.22. Found: C, 57.69; H, 6.12; N, 8.38; S, 9.59; OCH_3, 9.02.

About 30% of the starting material could be recovered from the original aqueous methanolic filtrate.

Reaction of N,1-Dimethylindole-2-carboxamide (XIX) with Thionyl Chloride.—Thionyl chloride (50 ml.) was added all at once to amide XIX[11] (18.8 g., 0.1 mole). The resulting brown solution was allowed to stand for 5 min. Anhydrous ether (750 ml.) was added and the solution was allowed to crystallize during 30 min. It was then filtered, the solid was washed with ether and crystallized from methanol to give 3.05 g. of sulfide XX, m.p. 237–238°. Recrystallization afforded colorless needles, m.p. 239–240.5°. Ultraviolet spectrum showed λ_{max} 230 mμ (ε 49,200), 294 (20,200), sh 328 (8900). Infrared spectrum showed 3400, 3200 (NH); 1655 (amide I); 1530 (amide II) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{22}N_4O_2S$: C, 65.00; H, 5.46; N, 13.77; S, 7.89. Found: C, 64.74; H, 5.29; N, 13.90; S, 7.57 (no methoxyl).

The ether filtrate was allowed to stand overnight and afforded 10.2 g. of yellow solid, m.p. 180–190°. Crystallization from methanol gave colorless needles of imide XXI (and imide filtrate), 5.7 g., m.p. 194–195° dec., discolors at 150°. Since previous experience has shown that this material decomposes on recrystallization from methanol, it was analyzed without further purification. Ultraviolet spectrum showed λ_{max} 213 mμ (ε 37,300), 233 (23,200), 262 (3600), 305 (8300). Infrared spectrum showed 1705 (C=O); 1540, 1500, 1485 (C=C) cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{10}N_2SO_2$: C, 56.39; H, 4.30; N, 11.96; S, 13.69. Found: C, 56.82; H, 4.60; N, 12.15; S, 13.88 (no methoxyl).

The imide filtrate referred to above was concentrated and allowed to crystallize to give 1.85 g. of impure solid, which on crystallization from methanol afforded an additional 1.2 g. of sulfide XX, m.p. 238–239°.

1-Methyl-2-carbomethoxyindole-3-sulfenic Acid (XV).—Sulfinyl chloride VI (prepared from 0.01 mole of ester V) was added during 3 min. to a solution of acetamide (0.591 g., 0.01 mole) in 10 ml. of pyridine. The suspension was stirred for 1 hr., cooled in ice, and acidified with a solution of 12 ml. of concentrated hydrochloric acid in 30 ml. of water. The yellow solid was filtered and washed with water to yield 1.75 g., m.p. 110–113° dec. Crystallization from methanol afforded 0.3 g. of small plates, m.p. 194–195° (purple melt), unchanged on recrystallization. Ultraviolet spectrum showed λ_{max} 213 mμ (ε 24,900), sh 236 (12,700), 296.5 (9850). Infrared spectrum showed 1712 (C=O); 1611, 1575, 1495 (C=C) cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90; S, 13.51; OCH_3, 13.08. Found: C, 56.11; H, 4.17; N, 5.86; S, 13.44; OCH_3, 12.28 (no acetyl).

The methanolic filtrate was evaporated to a small volume and afforded 1.25 g. of impure VII, which on one recrystallization from methanol afforded pure VII (identified by ultraviolet and infrared spectra).

Transformations of XId. A. Treatment with Acetic Acid.—Sulfinamide XId (1.6 g., 0.005 mole) was suspended in 5 ml. of acetic acid. Immediately a yellow color developed in the supernatant. The suspension was warmed for a few seconds to achieve solution. After 2 hr., crystallization was induced by scratching. Four hours later the solid was filtered, washed with dilute acetic acid, then with water to give 0.3 g., m.p. 140–143°, discolors at 125°. Crystallization from acetone afforded 85 mg. of sulfenic acid XV, m.p. 185–186° dec. It was identical with the compound obtained previously (by C, H, N, S analyses, ultraviolet and infrared spectra).

The acetone filtrate was diluted with methanol and concentrated to give a solid, which on fractional crystallization from methanol afforded needles, m.p. 149–150°. This product was identical with monosulfide VIII obtained previously (by C, H, N, S analyses, ultraviolet and infrared spectra).

B. Treatment with H_2O_2 in Acetic Acid.—Sulfinamide XId (3.2 g., 0.01 mole) was dissolved in 10 ml. of acetic acid. Hydrogen peroxide (2.3 g. of 30% solution, 0.02 mole) was added during 2 min. A yellow solution resulted and there was a considerable rise in temperature. It was allowed to stand for 1 hr. Water (50 ml.) was added and the resulting suspension was filtered to give a yellow solid, 1.1 g., m.p. 109° dec. Fractional crystallization from methanol afforded 0.8 g. of XVII as colorless plates, m.p. 124–124.5° dec. Ultraviolet spectrum showed λ_{max} 215 mμ (ε 43,800), 233 (42,400), 299 (25,600), sh 328 (13,500), sh 344 (8700). Infrared spectrum showed 1720, 1705 (C=O); 1610, 1500 (C=C); 1255 (C—O) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{20}N_2O_6S$: C, 62.25; H, 4.75; N, 6.60; S, 7.55; OCH_3, 14.62. Found: C, 62.34; H, 4.58; N, 6.72; S, 7.69; OCH_3, 14.29.

C. Treatment with H_2O_2 in Methanol.—Hydrogen peroxide (0.55 g. of 30% solution, 0.0055 mole) was added to a solution of sulfinamide XId (1.6 g., 0.005 mole) in 5 ml. of methanol. The resulting pale yellow solution was allowed to stand for 19 hr. Water (20 ml.) was added, and the resulting oily solid was isolated by decantation and washing with water. It was then triturated with 2 ml. of cold methanol to give 0.4 g. of a compound, m.p. 107–109°, which was identical with VII (C, H, N, S, OCH_3 analyses, ultraviolet and infrared spectra).

Treatment of VI with Anhydrous Hydrazine.—Sulfinyl chloride VI (prepared from 0.8 mole of V) was added over a period of 2 hr. to a stirred solution of anhydrous hydrazine (Matheson 95+%, 51.3 g., 1.6 moles) in 4 l. of ether while cooling at 5°. The mixture was then evaporated to dryness *in vacuo* and 500 ml. of water was added. The solid was filtered and washed with water. It was crystallized from 4 l. of benzene overnight. The yellow prisms were filtered and washed with methanol to give 99 g., m.p. 199–201°, unchanged on recrystallization. The second crop amounted to 22 g. of the same melting point (yield, 70%). This compound was identical with disulfide IV obtained before (mixture melting point, ultraviolet and infrared spectra).

Conversion of Disulfide IV to XXVII with Hydrazine Hydrate.—A mixture of disulfide IV (27.5 g., 0.0625 mole) and 125 ml. of hydrazine hydrate was refluxed in an oil bath (140°) with stirring for 1 hr. It was allowed to stand overnight and evaporated to dryness on the steam bath *in vacuo*. Methanol (200 ml.) was added to the resulting yellow oil and the solution was stirred for 4 hr., during which time precipitation occurred. The suspension was filtered to give 18.4 g., m.p. 236.5–238°, unchanged on crystallization from dimethylformamide. The second crop (2.48 g., same melting point) was collected after standing overnight. Air was then bubbled through the filtrate for 6 hr. and the third crop was obtained (1.15 g.) of the same melting point. Total yield of XXII was 80%. Ultraviolet spectrum showed λ_{max} 219 mμ (ε 46,600), 280 (20,300), 296 (19,200), sh 344 (6600). Infrared spectrum showed 3320, 3300, 3180 (NH); 1670, 1645, 1625 (C=O); 1525, 1505 (C=C) cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{20}N_6O_2S_2$: C, 54.54; H, 4.58; N, 19.08; S, 14.56. Found: C, 54.72; H, 4.10; N, 18.67; S, 14.56.

Bisbenzylidene Derivative of XXVII.—Benzaldehyde (0.53 g., 5 mmoles) was added to a warm solution of XXVII (1.05 g., 2.4 mmoles) in 15 ml. of dimethylformamide. The solution was heated on the steam bath for 2 hr. It was then evaporated to dryness *in vacuo* and the residue was triturated with hot methanol, to give 1.2 g., m.p. 220–225° (fast). Crystallization from dimethylformamide–methanol afforded yellow prisms, m.p. 222–223°. Ultraviolet spectrum showed λ_{max} 214 mμ (ε 61,000), 303 (56,500), sh 324 (46,700), sh 376 (7450). Infrared spectrum showed 3215 (vw), 3270 (vw) (NH/OH); 1690 (C=O); 1610, 1530, 1580, 1520, 1485 (C=C/C=N); 1225, 1125 (C—N); 750, 730, 690 (aromatic) cm.$^{-1}$.

Anal. Calcd. for $C_{34}H_{28}N_6O_2S_2$: C, 66.21; H, 4.58; N, 13.62; S, 10.40. Found: C, 66.34; H, 4.60; N, 13.47; S, 10.19.

Tetraacetyl Derivative of XXVII.—Acetic anhydride (5 ml.) was added dropwise during about 5 min. to a hot solution of XXVII (1.05 g., 2.4 mmoles) in 15 ml. of pyridine and the solution was allowed to stand at room temperature. Water (25 ml.) was added and the mixture was heated on the steam bath for a few minutes until a clear solution resulted. Further addition of water (25 ml.) caused the separation of an oil which solidified. Crystallization from acetic acid afforded 0.75 g. of yellow needles, m.p. 240–241°. Ultraviolet spectrum showed λ_{max} 211.5 mμ (ε 52,300), 278 (20,000), 291 (19,700), sh 348 (7600). Infrared spectrum showed 3340 (vs) (NH); 1735, 1695 (C=O); 1500 (C=C) cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{28}N_6O_6S_2$: C, 55.26; H, 4.64; N, 13.81; S, 10.54. Found: C, 55.46; H, 4.61; N, 13.44; S, 10.79.

Bisisopropylidene Derivative of XXVII.—A mixture of XXVII (15 g., 0.034 mole) and 3 l. of acetone was refluxed for 2.5 hr. The resulting solution was evaporated to about 400 ml. and allowed to cool. The solid amounted to 17.82 g., m.p. 218–220° (quantitative yield). Recrystallization from benzene afforded prisms, m.p. 219–220°. Ultraviolet spectrum showed λ_{max} 219 mμ (ε 46,500), 295 (37,000), sh 320 (32,800), sh 372 (6000).

Infrared spectrum showed 3280 (m) (NH); 3040 (=CH); 1700 (C=O); 1615, 1525 (C=C/C=N); 1225, 1130, 1015 (C—N) 800, 760, 750 (aromatic) cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{28}N_6O_2S_2$: C, 59.99; H, 5.42; N, 16.15; S, 12.32. Found: C, 60.18; H, 5.38; N, 15.94; S, 12.37.

1-Methyl-2-carbomethoxy-3-[(butylcarbamoyl)sulfamoyl]-indole (XVIIIa).—Triethylamine[13] (94 ml.), followed by butyl isocyanate (19.8 g., 0.2 mole) was added to a suspension of XIIa (53.7 g., 0.2 mole) in 50 ml. of dimethylformamide. The mixture was stirred for 22 hr. Two clear layers resulted, water (350 ml.) was added, and the mixture was stirred for 30 min. when a small amount of solid appeared. The mixture was extracted with ether (100 ml.), and the clear aqueous layer was acidified with 5% hydrochloric acid with cooling. The resulting oil solidified after a few minutes. The product was filtered and washed with water. It was crystallized from methanol to give 46.75 g. (63%) in three crops, m.p. range 190–193.5°. Recrystallization afforded rods, m.p. 191–192°. Ultraviolet spectrum showed λ_{max} 210 mμ (ε 32,400); sh 236, 292 (10,900). Infrared spectrum showed 3380 (NH); 1730 (ester C=O); 1680 (amide I); 1550 (amide II); 1515 (C=C) cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{21}N_3O_5S$: C, 52.31; H, 5.76; N, 11.44; S, 8.73; OCH_3, 8.45. Found: C, 52.41; H, 5.44; N, 11.60; S, 8.96; OCH_3, 8.11.

1-Methyl-3-[(butylcarbamoyl)sulfamoyl]indole-2-carboxylic Acid (XVIIIb).—A solution of XVIIIa (36.6 g., 0.1 mole) in aqueous sodium hydroxide (200 ml. of 1 *N* diluted to 700 ml.) was heated on the steam bath for 2 hr. It was then cooled in ice and acidified with 35 ml. of concentrated hydrochloric acid. The resulting solid was filtered and washed with water. It was crystallized from acetone–water to give 27 g. (77%), m.p. 194° (effervescent), unchanged on recrystallization. Ultraviolet spectrum showed λ_{max} 212 mμ (ε 33,950), sh 222 (29,450), sh 282 (10,050), 286 (10,650), sh 300 (5900). Infrared spectrum showed 3400, 3190, 2540 (OH/NH); 1712 (acid C=O); 1650 (amide I); 1550, 1510 (amide II) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{19}N_3O_5S$: C, 50.99; H, 5.42; N, 11.89; S, 9.08; neut. equiv., 176.7. Found: C, 51.00; H, 5.06; N, 11.60; S, 9.04; neut. equiv., 175.0.

Ethyl 3-(aminosulfinyl)indole-2-carboxylate (XXIV).—Thionyl chloride (5 ml.) was added all at once to ethyl indole-2-carboxylate (XXII,[14] 1.89 g., 0.01 mole). The resulting yellow solution solidified within 5 min. and was allowed to stand for 1 hr. Anhydrous ether (15 ml.) was added, the suspension was broken up, filtered, and the yellow sulfinyl chloride (XXIII) washed three times with ether. It was added during 1 min. to a solution of liquid ammonia (25 ml.) in 50 ml. of ether while cooling in a Dry Ice bath. Tap water bath was then used to evaporate the ammonia. The suspension was evaporated to dryness *in vacuo*, water was added, and the solid was filtered and washed with water to yield 2.2 g. (87%), m.p. 174–175°. Crystallization from dimethylformamide (just warm)–ether afforded needles, m.p. 169–170° dec., discolors at 150°. Ultraviolet spectrum showed λ_{max} 301 mμ (15,750). Infrared spectrum showed 3340, 3240, 3120 (NH); 3060, 3020 (=CH); 1690 (C=O) cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 52.36; H, 4.80; N, 11.11; S, 12.71. Found: C, 51.76; H, 5.09; N, 11.15; S, 12.74.

Ethyl 2-Sulfamoylindole-2-carboxylate (XXV).—Sulfinamide XXIV (1.45 g., 5.8 mmoles) was oxidized[12] during 3.75 hr. Water (20 ml.) was added, and the yellow precipitate was filtered (aqueous filtrate) and washed with water to yield 1.1 g., m.p. 180–187°. Crystallization from aqueous ethanol afforded 0.7 g. of XXV (46%), m.p. 205–209°, raised to 209–211° on recrystallization. Ultraviolet spectrum showed λ_{max} 233 mμ (ε 16,300), 302 (17,300). Infrared spectrum showed 3320, 3240 (NH); 3020 (=CH); 1708 (C=O); 1620, 1575, 1548, 1528, 1500 (C=C) cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{12}N_2O_4S$: C, 49.24; H, 4.51; N, 10.44; S, 11.95. Found: C, 49.39; H, 4.51; N, 9.93; S, 11.97.

The aqueous filtrate was extracted with ether (discarded the ether) and acidified with concentrated hydrochloric acid. The mixture was extracted with ether and the ether extracts dried over sodium sulfate and evaporated to dryness to give an orange oil. Trituration with acetone afforded a colorless solid, which on recrystallization from acetone formed prisms of XXVI (8 mg.), m.p. 178° dec. Ultraviolet spectrum showed λ_{max} 214 mμ (ε 47,800), 232 (41,000), 301 (28,700), sh 335 (9600). Infrared spectrum showed 3320, 3060 (NH); 1715, 1700 (C=O); 1575, 1515 (C=C) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{20}N_2O_5S$: C, 62.26; H, 4.75; N, 6.60; S, 7.56. Found: C, 62.08; H, 4.50; N, 6.10; S, 7.61.

1-Methylindole-2-carboxylic Acid Hydrazide (XXX).—Hydrazine hydrate (30 g., 0.6 mole) was added during 3 min. to a refluxing solution of V (37.8 g., 0.2 mole), and the resulting solution was refluxed 8 hr. It was allowed to crystallize overnight, to yield 22.7 g., m.p. 159–160°. The second crop amounted to 9.8 g., m.p. 156–158° (86%). Recrystallization from methanol afforded colorless needles, m.p. 159.5–160.5°. Ultraviolet spectrum showed λ_{max} 217.5 mμ (ε 27,950), sh 234 (17,500), 293 (15,950). Infrared spectrum showed 3290 (vs), 3200, 3180 (NH); 3070, 3050, 3020 (=CH); 1660, 1615 (C=O); 1600 sh, 1565, 1510 sh (C=C); 1535 (amide II); 817, 806, 746, 735 (ring) cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.32; H, 5.72; N, 21.67.

3,X-Dichloro-1-methylindole-2-carboxylic Acid Hydrazide (XXXIa).—A hot solution of XXX (1.89 g., 0.01 mole) in 50 ml. of methylene chloride was allowed to cool to room temperature with stirring whereupon partial crystallization occurred. A solution of sulfuryl chloride (1.5 g., 0.011 mole) in 10 ml. of methylene chloride was added dropwise during 15 min., and the suspension was stirred at room temperature for 5 hr. and then allowed to stand overnight. It was filtered and the solid washed with ether to give 1.0 g. of small plates, m.p. 230–235° dec. (effervescent, discolors at 210°), unchanged on crystallization from methanol–ether. Ultraviolet spectrum shows λ_{max} 223 mμ (ε 27,600), 292.5 (13,900). Infrared spectrum showed 3200, 2640 (NH); 1665 (C=O) cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_9Cl_2N_3O$: C, 46.53; H, 3.52; Cl, 27.47; N, 16.28. Found: C, 46.26; H, 3.89; Cl, 27.15; N, 16.60.

Reaction of V with Sulfuryl Chloride.—Sulfuryl chloride (50 ml., 0.616 mole) was added all at once to 18.9 g. (0.1 mole) of V. Vigorous evolution of gas ensued. After 1 hr. the brown oil began to crystallize. Fifty milliliters of petroleum ether (b.p. 30–60°) was added, the resulting solid was filtered and washed with cold petroleum ether to give 7.5 g., m.p. 124–130°. A sample of this tetrachloromethyl ester (XXXIb) was crystallized from methanol to colorless silky needles, m.p. 139–140°. Ultraviolet spectrum showed λ_{max} 216 mμ (ε 19,500), 245 (31,700), sh 298 (11,000), 307 (13,200), sh 328 (6500), sh 344 (4200). Infrared spectrum showed 1725 (C=O); 1515, 1505 (C=C); 1255, 1240 (C—O) cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{17}Cl_4NO_2$: C, 40.40; H, 2.16; Cl, 43.37; N, 4.28; OCH_3, 9.49. Found: C, 40.28; H, 2.07; Cl, 44.40; N, 4.03; OCH_3, 9.77.

The original filtrate was evaporated to dryness *in vacuo* at room temperature. The residue was dissolved in 15 ml. of petroleum ether and allowed to stand overnight. The resulting hard solid was broken up and filtered to give 16.6 g., m.p. 105–110° (softening at 80°). It was crystallized from 15 ml. of benzene and 100 ml. of petroleum ether to give 3.5 g. of XXXII, m.p. 132–133°. Ultraviolet spectrum (in isooctane) showed λ_{max} 232 mμ (ε 26,700), 274 (6150), 304 (2150), 333 (2600). Infrared spectrum showed 1765 (C=O); 1610, 1565 (C=C); 1235 (C—O) cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_7Cl_6NO_2$: C, 33.20; H, 1.77; Cl, 53.47; N, 3.52; OCH_3, 7.80. Found: C, 33.50; H, 2.09; Cl, 53.54; N, 3.16; OCH_3, 7.55.

The hexachloro compound (XXXII) after standing for 2 months in a closed brown bottle became yellow and the odor of hydrogen chloride was detected. The solid (3.35 g.) was refluxed with 100 ml. of methanol for 15 min. The yellow solution was evaporated to dryness and the resulting solid was dissolved in 10 ml. of ether. After standing overnight in the refrigerator, 0.48 g. of yellow solid was obtained, m.p. 160–167° (fast). Recrystallization from acetone–methanol afforded yellow plates of XXXIII, m.p. 172–174°. Ultraviolet spectrum showed λ_{max} 256 mμ (ε 31,200), sh 276 (7800). Infrared spectrum showed 1770, 1725 (C=O) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{10}NCl_3O_4$: C, 42.56; H, 2.98; Cl, 31.42; N, 4.14; OCH_3, 18.33. Found: C, 43.01; H, 3.43; Cl, 31.37; N, 4.14; OCH_3, 19.19.

(13) *Cf.* procedure described by G. F. Holland, D. A. Jaeger, R. L. Wagner, C. D. Laubach, W. M. McLamore, and S. Y. Pan, *J. Med. Pharm. Chem.*, **3**, 99 (1961).

(14) Available from Aldrich Chemical Co., Milwaukee, Wis.

Derivatives of (+)-Limonene. III. A Stereospecific Synthesis of *cis*- and *trans*-$\Delta^{8(9)}$-*p*-Menthene 1,2-Epoxides[1]

WILLIAM F. NEWHALL

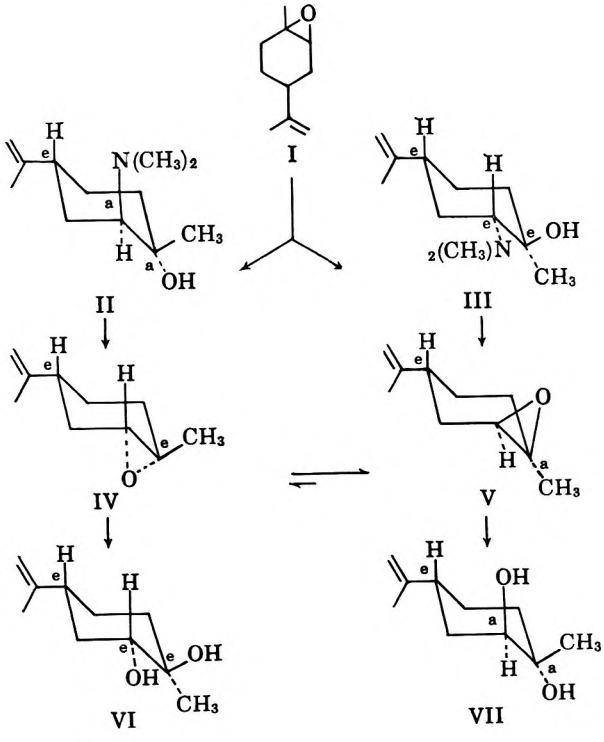
The Citrus Experiment Station of the University of Florida, Lake Alfred, Florida

Received July 8, 1963

The *cis* and *trans* isomers of $\Delta^{8(9)}$-*p*-menthene 1,2-epoxide have been prepared by Hofmann degradation of the two isomeric *trans*-2-dimethylamino-$\Delta^{8(9)}$-*p*-menthen-1-ols. Both degradations proceed by displacement of the C-2 nitrogen by C-1 oxygen with consequent reformation of the epoxide ring. The conformations of the amino alcohol precursors, the epoxides, and the glycols formed from the epoxides are discussed.

Epoxidation of the endocyclic double bond in (+)-limonene with organic peracids affords an equal mixture of *cis*- and *trans*-1,2-epoxides[2-4] (I). This has been verified by gas chromatographic analysis which shows two partially resolved peaks of equal intensity. This epoxide mixture is difficult to separate even by gas chromatographic methods and rearrangement to carbonyl compounds occurs to some extent.[5] These epoxides were found to be inseparable by even the most efficient methods of fractional distillation. The reason for this became evident during the course of this work when the pure *cis* (IV) and *trans* (V) epoxides were prepared by chemical means and found to have boiling points of 82.3° and 81.1°, respectively, at 15.0 mm.

For these reasons and also to simplify synthetic work based on $\Delta^{8(9)}$-*p*-menthene 1,2-epoxide (I) as a starting material, a convenient synthesis of IV and V has been developed. The *cis* epoxide (IV) has been prepared from *trans*-$\Delta^{8(9)}$-*p*-menthene-1,2-diol (VII) by Kuczynski and Piatkowski,[6] but the *trans* isomer (V) has not been reported previously. These authors refer to IV as a "*trans*" oxide because it is the *trans*-1,4-isomer with respect to the methyl and isopropenyl groups.



The reaction of the mixed *cis*–*trans* epoxides[7] (I) with aqueous dimethylamine gave the two *trans* isomers of 2-dimethylamino-$\Delta^{8(9)}$-*p*-menthen-1-ol[8] (II, III) which were separated by fractional crystallization of their picrate salts. The solubility differences between these two picrates were so great that the more insoluble one was removed completely from the mixture after two successive crystallizations from benzene–methanol solution. The two picrates were found to occur in equal quantities in the mixture. The regenerated amino alcohols (II, III) were converted separately to their quaternary ammonium iodide derivatives which were then degraded by brief warming with aqueous potassium hydroxide solution (30%). Each amino alcohol gave a single 1,2-epoxide (IV or V) in high yield. The purity of both epoxides was verified by gas chromatographic analysis. The formation of IV and V as the sole products of these degradations indicates that a displacement of the C-2 nitrogen, from the rear, by C-1 oxygen has occurred in each case.

The conformations of IV and V were established from a consideration of the 1,2-diols obtained on cleaving them with dilute aqueous acid. In each case, acid cleavage should proceed by way of the more stable tertiary carbonium ion at C-1.[9] *trans* diols would be expected, since the over-all result of oxide formation and cleavage is equivalent to *trans* addition.[10] One oxide gave the known $\Delta^{8(9)}$-*p*-menthene-1,2-diol[11-13] (VII, m.p. 70–71.6°) which was first prepared by Prileschaev[14] and is the main product of the peracetic acid oxidation of (+)-limonene.[15] By analogy with the work of Jefferies and Milligan[16] and Cole and Jefferies[17] on the *racemic* *p*-menthane-1,2-diols, VII must be the *trans*-1,2-*trans*-1,4 isomer in which both hydroxyls are axial. Thus the parent epoxide must have the *trans* conformation (V) in which the oxide ring and isopropenyl group are on opposite sides of the plane of the cyclohexane ring.

(1) Florida Agricultural Experiment Stations Journal Series No. 1617.

(2) H. Kuczynski and K. Piatkowski, *Roczniki Chem.*, **33**, 299 (1959).

(3) W. F. Newhall, *J. Org. Chem.*, **24**, 1673 (1959).

(4) Z. Chabudzinski, *Bull. Acad. Polon. Sci. Ser. Sci. Chim.*, **10**, 157 (1962).

(5) Complete separation has been achieved by G. L. K. Hunter, Citrus Products Laboratories, U.S.D.A., Winter Haven, Fla., private communication.

(6) H. Kuczynski and K. Piatkowski, *Roczniki Chem.*, **33**, 311 (1959).

(7) Samples of this epoxide mixture were supplied by the Chemicals and Plastics Division of Food Machinery and Chemical Corp., New York, N. Y.

(8) R. Patrick and W. F. Newhall, *J. Agr. Food Chem.*, **8**, 397 (1960).

(9) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(10) L. F. Fieser and M. Fieser, "Organic Chemistry," 2nd Ed., D. C. Heath and Co., Boston, Mass., 1950, p. 287.

(11) H. Meerwein, A. Ogait, W. Prang, and A. Serini, *J. prakt. Chem.*, **113**, 9 (1926).

(12) H. Schmidt, *Ber.*, **82**, 11 (1949).

(13) W. F. Newhall, *J. Org. Chem.*, **23**, 1274 (1958).

(14) N. Prileschaev, *Ber.*, **42**, 4814 (1909).

(15) J. Sword, *J. Chem. Soc.*, **127**, 1632 (1925).

(16) P. R. Jefferies and B. Milligan, *ibid.*, 4384 (1956).

(17) A. R. H. Cole and P. R. Jefferies, *ibid.*, 4391 (1956).

The other oxide gave the same 1,2-diol (VII) on acid cleavage plus a second diol (m.p. 65–66°) which must have the *trans*-1,2-*cis*-1,4-conformation (VI) in which both hydroxyls are equatorial. The latter has not been reported previously as an oxidation product of (+)-limonene. Although the melting point is somewhat lower, this is undoubtedly the *trans* diol synthesized by Schmidt[12] from *d*-terpineol. The parent epoxide of VI must then have the *cis* conformation (IV) in which the oxide ring and the isopropenyl group are on the same side of the plane of the ring. Further evidence that IV is the *cis* epoxide is furnished by a comparison of its physical constants with those reported by Kuczynski[2] for this isomer. With the exception of the specific rotation (+92.7) which is slightly higher than the value reported (+83.7), agreement is good. The higher rotation is indicative of higher purity. It is interesting to note that the specific rotation of the *trans* epoxide V (+55.0) is much lower than that of the *cis* isomer (IV). As would be expected, the arithmetic average of these two rotation values (+73.8) is in close agreement with the specific rotation (+70.9) of the original $\Delta^{8(9)}$-*p*-menthene-1,2-epoxide (I).

The formation of two diols from IV may proceed by an acid-catalyzed rearrangement of IV to the *trans* epoxide[16] (V). This would explain why VII is the major product of the peracid hydroxylation of (+)-limonene. This is in contrast to the alkaline cleavage of the mixed epoxides (I) with amines which has been shown to give equal amounts of the two *trans* amino alcohols (II, III).

The infrared absorption curves of the two *trans* amino alcohols (II, III) and the two *trans* diols (VI, VII), were almost identical from 1 to 7 μ, as would be expected. The only differences were in the molecular vibration region from 7 to 15 μ. The same was true for the *trans* (V) and *cis* (IV) epoxides, the greatest difference being one sharp peak of medium intensity at 10.53 μ in V which is totally absent in IV. The absorption maxima for these compounds are tabulated in Experimental.

During the course of this work, the mixed *trans* isomers of 2-amino- and 2-methylamino-$\Delta^{8(9)}$-*p*-menthen-1-ol also were prepared by reaction of I with the appropriate amines. In general these compounds were prepared in a similar manner to their saturated analogs reported previously.[3]

Experimental

All melting points reported are uncorrected.

2-Dimethylamino-$\Delta^{8(9)}$*p*-menthen-1-ols (II and III).—Sixty-four milliliters (59.5 g.) of $\Delta^{8(9)}$-*p*-menthene-1,2-epoxide (I) and 100 ml. of aqueous dimethylamine (25%) were stirred and heated in a 300 ml. bench-scale autoclave at 135–140° for 7 hr. This procedure was repeated and the two crude products were combined, concentrated to dryness, and then vacuum distilled through an 18-in. Vigreux column. At 98–103° (1.5 mm.), 119.4 g. (77.4%) of the mixed *trans* isomers (II and III) distilled as a colorless, slightly viscous liquid. A redistilled sample boiled at 86–93° (1.1 mm.), d^{23} 0.9538, $n^{23}D$ 1.4890, $[\alpha]^{23}D$ +24.6.

Anal. Calcd. for $C_{12}H_{23}ON$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.94; H, 11.62; N, 7.01.

The 119.4 g. of the mixed *trans* isomers was dissolved in 1.5 l. of 10% methanol in benzene, and sufficient solid picric acid added to make the solution just acidic. On cooling, yellow needles of the picrate of II (88.5 g., m.p. 152–157°) separated from solution. The filtrate was concentrated to 500 ml. and a second crop obtained (9.3 g., m.p. 150–156°). The combined batches (97.8 g.) after recrystallization once from benzene–methanol solution afforded 92.5 g. of the picrate of II, m.p. 156–158°. This corresponds to 42.8 g. of II and represents a separation yield of 71.7% since the theoretical yield of II is half of the 119.4 g. or 59.7 g.

A small sample of this picrate recrystallized from benzene–methanol solution melted at 156.4–157.4°.

Anal. Calcd. for $C_{18}H_{26}O_8N_4$: C, 50.70; H, 6.15; N, 13.14. Found: C, 51.37; H, 6.25; N, 12.43.

The free base (II) was isolated by treating the picrate (92.5 g.) with excess dilute aqueous sodium hydroxide solution followed by ether extraction. The combined ether extracts were washed several times with dilute aqueous sodium hydroxide solution and dried over anhydrous sodium sulfate. After removal of the ether at reduced pressure, the residual oil was distilled under vacuum. At 86° (0.7 mm.), 37.8 g (63%, based on half the original 119.4 g.) of II distilled as a colorless slightly viscous liquid, d^{25} 0.9528, $n^{25}D$ 1.4872, $[\alpha]^{25}D$ +35.5 (pure liquid); $\lambda_{film}^{capillary}$ 2.87, 3.38, 6.07, 6.83, 7.27, 8.45, 8.81, 9.66, 11.27 μ.

Anal. Calcd. for $C_{12}H_{23}ON$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.84; H, 11.66; N, 7.05.

The filtrates from the 97.8 g. of the picrate of II were combined and concentrated to dryness at reduced pressure. An orange gum (98.0 g.) was obtained which could not be induced to crystallize. Amino alcohol (III) was regenerated from this amorphous picrate exactly as described previously. The residual oil from the ether extracts was distilled under vacuum. At 92° (0.7 mm.), 40.0 g. (67%, based on half the original 119.4 g.) of III distilled as a colorless viscous liquid which crystallized on standing to colorless oily needles (indeterminate melting point at about 50°), $n^{25}D$ (supercooled liquid) 1.4949, $[\alpha]^{25}D$ +34.4 (10% acetone solution); λ_{max}^{KBr} 2.92, 3.38, 6.06, 6.82, 7.28, 8.00, 8.40, 9.55, 9.70, 9.82, 11.20, 11.33 μ.

Anal. Calcd. for $C_{12}H_{23}ON$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.85; H, 11.78; N, 6.96.

***cis*-$\Delta^{8(9)}$-*p*-Menthene 1,2-Epoxide (IV).**—Twenty-five grams of II was refluxed for 4 hr. in 100 ml. of acetone containing excess (18 ml.) methyl iodide. The solution was concentrated to dryness at reduced pressure. The residue rapidly crystallized (colorless needles) to give a quantitative yield (43.0 g.) of the methiodide of II (*p*-menth-8-en-1-ol,2-dimethylamino-methiodide). A small sample recrystallized twice from acetone melted at 167.4–168°, $[\alpha]^{25}D$ −9.5 (10% aqueous solution).

Anal. Calcd. for $C_{13}H_{26}ONI$: C, 46.02; H, 7.72; N, 4.13. Found: C, 46.29; H, 7.81; N, 4.23.

Forty-two grams of the methiodide of II was warmed at 75–80° for 1.5 hr. in 200 ml. of 30% aqueous potassium hydroxide solution. During this time there was a copious evolution of trimethylamine and the epoxide generated in the degradation formed an upper liquid level. The cooled mixture was diluted with 100 ml. of water and extracted three times with ether. The combined extracts were washed several times with water, dried over anhydrous sodium sulfate, and the ether removed at reduced pressure. The residue was 17.7 g. (94%) of the colorless fluid *cis* epoxide (IV). The purity of this product was indicated when vacuum distillation of the 17.7 g. through an 18 in., 0.5-in. i.d. column packed with stainless steel rings and having a "hold-up" of 3–4 g. gave 14.1 g. (75%) of pure IV, b.p. 82.3° (15.0 mm.), d^{25} 0.9305, $n^{25}D$ 1.4661, $[\alpha]^{25}D$ +92.7 (pure liquid); $\lambda_{max}^{path\ 0.0114\ mm.}$ 3.37, 6.06, 6.90, 7.23, 8.27, 8.93, 9.12, 9.78, 9.88, 10.31, 10.91, 11.25, 11.88, 13.17 μ.

***trans*-$\Delta^{8(9)}$-*p*-Menthene 1,2-Epoxide (V).**—Twenty-five grams of the amino alcohol (III) was refluxed for 4 hr. in 100 ml. of acetone containing excess (18 ml.) methyl iodide. The quaternary methiodide of III was isolated exactly as described for the preparation of the methiodide of II. This procedure gave a quantitative yield (43.0 g.) of III methiodide as a colorless amorphous glass which could not be crystallized.

Therefore, the entire product was degraded to the *trans* epoxide (V) using the same procedure described previously. This afforded 16.2 g. (86%) of the colorless fluid *trans* epoxide (V) which was vacuum distilled through the same 18-in. packed column used to distil IV. This gave 13.0 g. (69%) of pure V, b.p. 81.1° (15.0 mm.), d^{25} 0.9259, $n^{25}D$ 1.4643, $[\alpha]^{25}D$ +55.0 (pure liquid); $\lambda_{max}^{path\ 0.0114\ mm.}$ 3.37, 6.06, 6.90, 7.23, 8.27, 8.48, 8.93, 9.62, 10.53, 11.25, 11.88, 13.15 μ.

***trans*-$\Delta^{8(9)}$-*p*-Menthene-1,2-diols (VI and VII).**—Three milliliters (2.79 g.) of the *cis* epoxide (IV) was shaken with 30 ml. of

4% aqueous sulfuric acid at room temperature for 20 min. The mixture was cooled to 0° and the crystalline glycol hydrates were collected on a filter, dissolved in ethyl ether, and the solution dried over anhydrous sodium sulfate. The ether was removed at reduced pressure, and the residue dissolved in benzene–petroleum ether and seeded with a crystal of the known diol (VII). Crystallization was allowed to proceed for 24 hr. at room temperature. This gave 0.870 g. (28%) of large colorless prisms, m.p. 69–71.4°. A recrystallized sample melted at 70–71.6° and had an infrared absorption curve identical in all respects with that of an authentic sample of diol VII. The filtrate from the 0.870 g. gave a mixture of diols (VII in prisms and VI in needles), 0.60 g., m.p. 48–68°.

The aqueous filtrate from the glycol hydrates was made weakly basic with aqueous sodium bicarbonate solution and extracted three times with ethyl ether. The combined extracts were dried over anhydrous sodium sulfate and the ether removed under vacuum. The residue was dissolved in petroleum ether (b.p. 30–60°) and crystallized at 40°. Long colorless needles, m.p. 55–61°, separated from the solution. Several crystallizations afforded 0.230 g. (7.4%) of diol VI melting at 65–66° which was further purified by vacuum sublimation. A mixture melting point of this diol with VII was 40–48°. The yield of VI obtained using this procedure is not representative of the amount actually present. These losses were necessary in order to obtain a sample free of the more insoluble diol (VII). The specific rotation of VI was $[\alpha]^{25}D$ +28 (10% acetone solution).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.52; H, 10.64.

The infrared absorption maxima of VI and VII are compared: λ_{max}^{KBr} (VI) 2.97, 3.38, 6.05, 6.85, 7.23, 8.74, 9.26, 11.30 μ; (VII) 2.93, 3.38, 6.04, 6.83, 7.23, 8.40, 9.48, 9.68, 11.29 μ.

One milliliter (0.926 g.) of the *trans* epoxide (V) was shaken for 15 min. at room temperature with 15 ml. of 4% sulfuric acid. The glycol hydrate which formed was collected on a filter, dissolved in ether, and the ether layer dried over anhydrous sodium sulfate. Removal of the ether at reduced pressure afforded 0.677 g. (66%) of colorless prisms, m.p. 66–69°. One recrystallization from benzene–petroleum ether solution gave 0.537 g. melting at 70–71.4° which proved to be identical in all respects to the known *trans* diol (VII). The yield and high degree of purity of VII obtained directly from the ether residue indicate that it is the main product. None of the more soluble diol (VI) could be recovered from the filtrates.

2-Amino-$\Delta^{8(9)}$-*p*-menthen-1-ol.—A 300-ml. capacity autoclave (Autoclave Engineers, Inc., Model No. ABA-300) was charged with 64 ml. (59.4 g.) of $\Delta^{8(9)}$-*p*-menthene 1,2-epoxide (I) and 100 ml. of aqueous ammonium hydroxide (28%). The mixture was stirred and heated at 135–140° for 4 hr. The crude product was then concentrated to dryness under vacuum using a film evaporator (water bath temp. 40°) and the residual dark viscous oil was vacuum distilled. At 95–99° (1.2 mm.), 49.0 g. (75%) of the mixed *trans* isomers of 2-amino-$\Delta^{8(9)}$-*p*-menthen-1-ol distilled as a colorless viscous oil. Redistillation afforded material boiling at 96–99° (1.2 mm.), d^{23} 0.9868, $n^{23}D$ 1.5032, $[\alpha]^{23}D$ +28.5.

Anal. Calcd. for $C_{10}H_{19}ON$: C, 70.96; H, 11.31; N, 8.28. Found: C, 71.25; H, 11.21; N, 8.26.

2-Methylamino-$\Delta^{8(9)}$-*p*-menthen-1-ol.—Sixty-four milliliters (59.4 g.) of $\Delta^{8(9)}$-*p*-menthene 1,2-epoxide (I) and 100 ml. of aqueous methylamine (30%) were stirred and heated at 135–140° in an autoclave for 5 hr. Concentration of the crude product to dryness gave a viscous oil which was vacuum distilled. At 89–94° (1.2 mm.), 46.7 g. (65%) of the mixed *trans* isomers of 2-methylamino-$\Delta^{8(9)}$-*p*-menthen-1-ol distilled as a colorless viscous oil. Redistillation afforded material boiling at 93–96° (1.3 mm.), d^{23} 0.9703, $n^{23}D$ 1.4964, $[\alpha]^{23}D$ +30.3.

Anal. Calcd. for $C_{11}H_{21}ON$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.84; H, 11.43; N, 7.68.

Synthesis of β-Carotene and Certain Polyenes *via* Thiapyran Intermediates

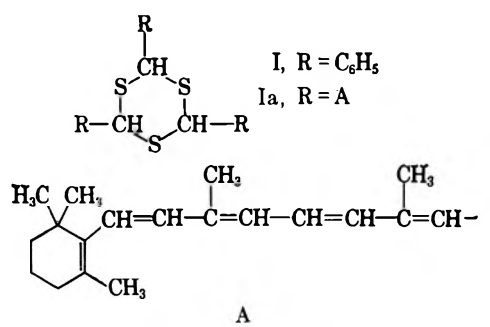
ALBERT J. CHECHAK, MAX H. STERN, AND CHARLES D. ROBESON

Communication 301 from the Research Laboratories of Distillation Products Industries, Division of Eastman Kodak Company, Rochester 3, New York

Received July 8, 1963

β-Carotene has been synthesized by treating retinal with hydrogen sulfide and desulfurizing the new thio derivative thus formed, with metals in a basic solvent. The intermediate sulfur derivative of retinal has been assigned a 2,4-disubstituted 2*H* thiapyran structure (IIIa, R = B). Desulfurization of this thiapyran with amalgamated zinc in pyridine gave a good yield of β-carotene (70% over-all from retinal). Other β-methyl substituted conjugated aldehydes, such as β-ionylidene acetaldehyde, likewise gave 2,4-disubstituted thiapyrans and were desulfurized to polyenes.

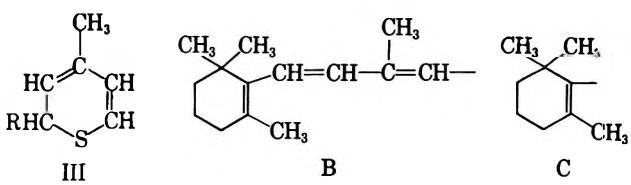
The reaction of aromatic aldehydes with hydrogen sulfide to form trimeric thioaldehydes which can be desulfurized to ethylenic hydrocarbons is known. The reactions are illustrated by the conversion of trithiobenzaldehyde I to stilbene.[1]



A

An attempt to prepare β-carotene in good yield from trithioretinal was, however, unsuccessful. Reaction of all *trans*-retinal with hydrogen sulfide, in ethanol, under conditions similar to those previously employed to prepare trimers[2] gave a compound Ia having properties consistent with I. This gave less than a 4% yield of β-carotene by the usual desulfurization procedures[1].

However, when hydrogen sulfide reacted with either all *trans*-retinal or 13-*cis*-retinal at low temperatures in amine solvents (*e.g.*, aniline, pyridine, etc.) a different type of sulfur containing intermediate was formed. Studies provided evidence that this intermediate had the thiapyran structure IIIa (R = B). We consider a 1,6-addition of hydrogen sulfide to retinal followed by ring closure to be a plausible mechanism for the forma-



III B C

IIIa, R=B IIIb, R=C

(1) E. Campaigne, *Chem. Rev.*, **39**, 52 (1946).

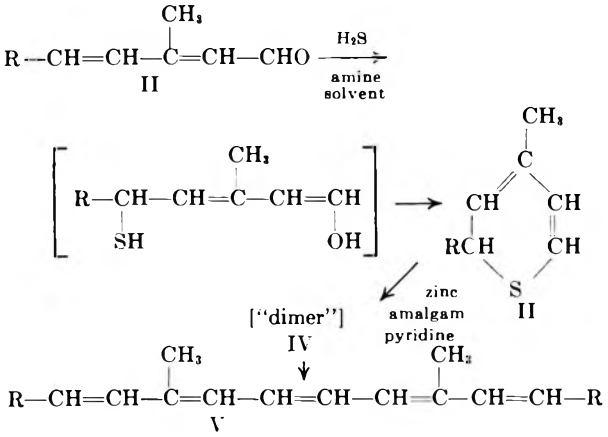
(2) E. Campaigne, *ibid.*, **39**, 4, 11 (1946).

TABLE I

SPECTRAL PROPERTIES OF THIAPYRAN INTERMEDIATES, III, AND POLYENE ALDEHYDE PRECURSORS, II

R		Ultraviolet absorption λ_{max}	Ultraviolet absorption ϵ	Infrared absorption λ_{max} (*trans* CH=CH)	Infrared absorption *K*	Infrared absorption λ_{max} (*cis* CH=CH)	Infrared absorption *K*
B	Aldehyde	380	43,400	10.36	1.2	No peak	
	Thiapyran	274	16,650	10.28	0.52	14.2	0.38
$C_6H_5CH=CH-$	Aldehyde	351	32,500	10.17	1.3	No peak	
	Thiapyran	260	20,100	10.42	0.78	14.3	0.64
C_6H_5-	Aldehyde	322	25,800	10.42	0.56	No peak	
	Thiapyran	End absorption		No peak		14.3	0.90
C	Aldehyde	326	15,600	10.31	0.75	No peak	
	Thiapyran	End absorption		No peak		14.3	0.60

tion of a thiapyran. The compound readily desulfurized to β-carotene in good yield when heated with amalgamated zinc in pyridine solution. Evidence was obtained that the desulfurization reaction proceeds



via an intermediate dimer IV, probably a substituted 1,2- or 1,3-dithietane.

Thiapyran Formation.—The 1,6-addition of thiols to unsaturated steroidal ketones has been described.[3,4] However, no reports have been found which describe either the preparation of 2,4-dialkyl substituted thiapyrans or 1,6-addition of hydrogen sulfide to conjugated aldehydes.

Factors influencing the formation of thiapyrans from conjugately unsaturated aldehydes were hence investigated. A methyl substituent on the carbon atom β to the aldehyde group, as in retinal, appeared to be one requirement. For example, we were unable to prepare thiapyrans from 13-desmethylretinal or from 7-phenylheptatrienal.

Stereochemical configuration is a second factor influencing the formation of thiapyrans. When hydrogen sulfide reacted with 13-*cis*-retinal, under our preferred conditions, (in pyridine, −10°) a 95% yield of thiapyran IIIa was obtained. The corresponding yield from all *trans*-retinal was only 50%. It appears that the *cis* configuration either favors 1,6-addition of hydrogen sulfide to the aldehyde or leads to an intermediate which forms the thiapyran ring more readily.

The yield from the *trans* isomer was improved by the addition of certain amine hydrochlorides. Thus, it was found that by incorporating a small amount of aniline hydrochloride in the reaction, the yield of thiapyran from the all *trans* isomer was increased to that obtained from the 13-*cis* isomer. Although no *cis* isomer could be detected when all *trans*-retinal in cold pyridine or aniline was treated with aniline hydrochloride in the absence of hydrogen sulfide, this does not exclude the possibility of a *trans*-to-*cis* conversion in the presence of hydrogen sulfide.

A 2,4-disubstituted 2*H* thiapyran structure (IIIa, R = B) is proposed for the thiointermediate from the following evidence: (1) molecular weight determination and elemental analysis indicated it to be a monomeric derivative of retinal in which oxygen had been replaced by sulfur; (2) the infrared absorption spectrum showed that the absorption band at 6.01 μ, characteristic of the carbonyl group in the original aldehyde, was no longer present; (3) the intensity of absorption at 10.28 μ for the thiapyran corresponded approximately to the loss of one of the two nonmethyl substituted *trans* double bonds in retinal; (4) the ultraviolet absorption spectrum showed a maximum at 274 mμ characteristic of a conjugated triene.

Thiapyrans were prepared from other β-methylpolyene aldehydes. Their infrared and ultraviolet absorption properties (Table I) were likewise consistent with a III-type structure.

For example, the intensity of the *trans* CH=CH band at 10.4 μ in the infrared spectrum of the product from 7-phenyl-3-methylheptatrienal, as in the case of retinal, corresponded approximately to the loss of one of the two such groups present in the parent aldehyde. In the case of β-ionylidene acetaldehyde (II, R = C) and 5-phenyl-3-methylpentadienal (R = C_6H_5) which have only one *trans* CH=CH bond, the 10.4-μ band was not present in the spectra of the thio derivatives. A band at 14.2–14.3 μ in the infrared spectra of all these compounds, not present in the spectra of the precursor aldehydes, may be characteristic of the *cis* double bond of the heterocyclic ring. Disubstituted *cis* ethylenic centers are known to absorb in this region of the spectrum.[5]

In the case of each of these aldehydes, the ultraviolet absorption maximum of the corresponding derivative is at a wave length consistent with the new shorter chromophore in the proposed formula for the thio derivative.

Desulfurization.—Evidence for the formation of the intermediate (IV) in the desulfurization reaction came from the ultraviolet spectra of aliquots of the reaction mixture taken at intervals (Fig. 1). After heating a pyridine solution of thiapyran IIIa (R = B), λ_{max} 274 mμ, for 2 hr. in the presence of zinc amalgam, the absorption maximum was shifted to 335 mμ accompanied

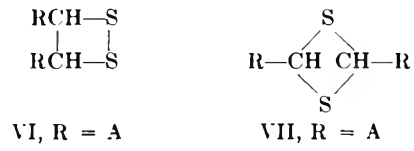
(3) J. W. Ralls, R. M. Dodson, and B. Riegel, *J. Am. Chem. Soc.*, **71**, 3320 (1949).

(4) J. Romo, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.*, **17**, 1413 (1952).

(5) H. Henbest, G. Meakins, and G. Wood, *J. Chem. Soc.*, 800 (1954).

by a small build-up of extinction in the 450-mμ region due to β-carotene. After 8 hr., substantial amounts of β-carotene had formed and the absorption at 335 mμ was reduced.

The properties of a purified sample of IV were consistent with dithietane structures VI or VII (R = A).

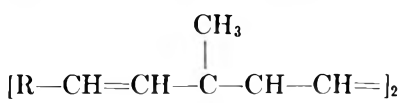


VI, R = A VII, R = A

Molecular weight determination and elemental sulfur analysis indicated it to be a dimer. From its ultraviolet absorption maximum, which is at the same wave length (335 mμ) as that of trithiane Ia (R = A), and from its infrared absorption spectrum, (no hydroxyl or carbonyl band, strong 10.3-μ band (*trans* CH=CH), no 14.3-μ band), either of the proposed dithietane structures are reasonable. The instability of the compound, evidenced by a tendency to decompose to polymeric tars on storage and its ready desulfurization to β-carotene favors the 1,2-dithietane structure (VI). Cyclic 1,2-disulfides are known to be unstable[6] and a 1,3-dithietane structure has been proposed[7] for one highly stable fluorocarbon heterocyclic compound.

Optimum yields (*ca.* 70%) of β-carotene were obtained by heating pyridine or quinoline solutions of the thiapyran III for a period of 5 to 10 hr. at 70°, in the presence of zinc amalgam, prepared according to Martin.[8] Lower yields were obtained when the metal was omitted or when the reaction was run in other solvents including benzene, toluene, or triethylamine. A variety of metal catalysts including Raney nickel, palladium–calcium carbonate, precipitated copper, magnesium amalgam, lithium, phenyllithium, and others were tested and found to give lower yields of β-carotene than zinc amalgam.

Desulfurization of the other thiapyrans listed in Table I gave concentrates of polyene hydrocarbons with ultraviolet absorption spectra in the range expected for the compounds of the following structure.



The pure hydrocarbons were not prepared.

Experimental

The ultraviolet and infrared spectrographic measurements were made by Mr. W. Blum of this laboratory using a Cary recording spectrophotometer, Model 11M, and a Perkin-Elmer spectrophotometer, Model 21, respectively. Ultraviolet spectra were determined in ethanol solution unless otherwise stated. Melting points were determined in capillary tubes, using 3-in. immersion thermometers. The microanalyses were done by the Microanalytical Laboratory of the Eastman Kodak Company under the direction of Mr. D. Ketchum. Molecular weight values were determined (benzene) using a Beckman molecular weight apparatus.[9]

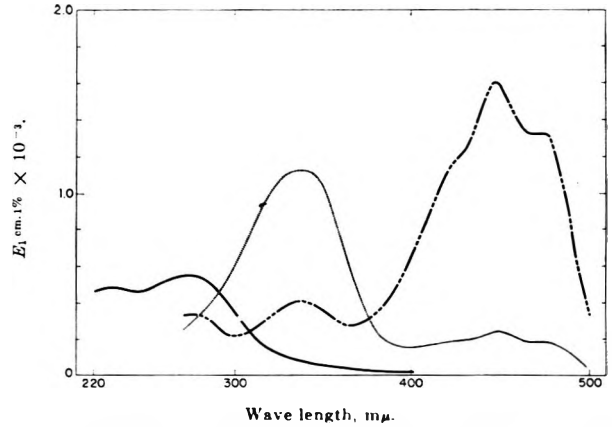


Fig. 1.—Change in ultraviolet and visible absorption spectrum during desulfurization: thiapyran, ———: after 2 hr., ⋯⋯⋯; after 8 hr., - - ——.

Preparation of Trithioretinal (Ia, R = A).—Hydrogen sulfide gas was passed through a stirred solution of *trans*-retinal (14.2 g.) in 85% aqueous ethanol (142 ml.) at room temperature for 6 hr. The yellow-orange solids which separated were collected by filtration, dissolved in chloroform (100 cc.) and reprecipitated by adding the chloroform solution to 250 cc. of methanol. The bright yellow solids were collected, washed repeatedly with methanol, and dried under vacuum yielding 7.6 g. of product, ε (335 mμ) 107 200 (in petroleum ether, b.p. 60–71°); strong infrared absorption band at 10.3 (*trans* CH=CH), no band at 6.01 μ (carbonyl).

Anal. Calcd. for $C_{60}H_{84}S_3$: C, 79.9; H, 9.4; S, 10.7; mol. wt., 901. Found: C, 79.5; H, 9.8; S, 10.9; mol. wt., 927.

Desulfurization of Ia.—A portion (3.0 g.) of trithioretinal (Ia) was mixed with freshly precipitated copper (3.0 g.) prepared according to the method of Stanfield and Reynolds.[10] This mixture was stirred under an atmosphere of nitrogen while the temperature was gradually raised to 100° over a period of 0.5 hr. The reaction mixture was then cooled and extracted with benzene. Evaporation of the solvent gave a dark colored residue (2.97 g.) whose ultraviolet absorption spectrum showed E (1%, 1 cm., 290 mμ) 344. No absorption characteristic of β-carotene was evident.

Modification of these conditions in which solutions of the trithioretinal (1.0 g.) in benzene (6 ml.) were stirred with the copper at room temperature for 15 hr. or refluxed for periods up to 8 hr. likewise gave products with changed ultraviolet absorption spectra indicating that decomposition of the trithioretinal had occurred. From the absorption measured at 450 mμ, it was calculated that they contained, at most, 1.3% β-carotene.

Other attempts to desulfurize the trithioretinal included refluxing a xylene solution of the compound with Raney nickel and heating it in pyridine solution in the presence of amalgamated zinc. In every case the ultraviolet absorption spectra of aliquots showed that β-carotene was not formed in yields greater than 4% as estimated from the absorption at 450 mμ.

Preparation of Aldehydes (II).—The preparation of β-ionylidene acetaldehyde (II, R = C) and of retinal (II, R = B) has been previously reported.[11,12] (In the new nomenclature[13] for vitamin A isomers, 13-*cis*-retinal corresponds to 2-*cis*-vitamin A aldehyde of ref. 11.)

The II aldehydes (R = C_6H_5 and C_6H_5CH=CH—) were prepared from the corresponding 5-phenyl-3-methyl-2,4-pentadienoic and 7-phenyl-3-methyl-2,4,6-heptatrienoic acids[14] by the steps reported for the preparation of β-ionylidene acetaldehyde from β-ionylideneacetic acid.[11]

5-Phenyl-3-methyl-2,4-pentadienoic acid (10 g.) was converted to its methyl ester (10.6 g., ε (311 mμ) 29,000). The ester was dissolved in dry ethyl ether (175 ml.) and treated with lithium aluminum hydride (33 ml. of 1 *M* solution) for 3 min. at 5°.

(6) J. Affleck and G. Dougherty, *J. Org. Chem.*, **16**, 865 (1950).
(7) M. Hauptschein and M. Braid, *J. Am. Chem. Soc.*, **80**, 853 (1958).
(8) E. Martin, *ibid.*, **58**, 1438 (1936).
(9) F. Daniels, J. H. Mathews, and J. W. Williams, "Experimental Physical Chemistry," 4th Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1949, pp. 84–86.
(10) J. Stanfield and L. Reynolds, *J. Am. Chem. Soc.*, **74**, 2878 (1952).
(11) C. D. Robeson, J. D. Cawley, L. Weisler, M. H. Stern, C. C. Eddinger, and A. J. Chechak, *ibid.*, **77**, 4111 (1955).
(12) C. D. Robeson, W. P. Blum, J. M. Dieterle, J. D. Cawley, and J. G. Baxter, *ibid.*, **77**, 4120 (1955).
(13) Commission on the Nomenclature of Biological Chemistry, *ibid.*, **82**, 5575 (1960).
(14) J. D. Cawley and D. R. Nelan, *ibid.*, **77**, 4130 (1955).

The reaction mixture was hydrolyzed with dilute (5%) sulfuric acid. The ether solution was washed successively with dilute acid, 0.5 *N* potassium hydroxide, and water, dried over anhydrous sodium sulfate, and filtered. Evaporation of the solvent gave 8.8 g. of 5-phenyl-3-methyl-2,4-pentadien-1-ol which crystallized from ethanol at 5°, m.p. 68–69°; ϵ (280, 288 mμ) 27,650 and 29,300.

Anal. Calcd. for $C_{12}H_{14}O$: C, 82.7; H, 8.1. Found: C, 82.8; H, 8.1.

A solution of the alcohol (5.0 g.) in diethyl ether (75 ml.) was mixed with manganese dioxide powder[15] (75 g.) and allowed to stand at room temperature for 20 hr. After filtering and washing the filter cake thoroughly with ether, the filtrate and washings were evaporated to give a residue of yellow oil [*E* (1%, 1 cm., 322 mμ) 1450]. Crystallization from petroleum ether (b.p. 60–71°) at 20° gave pure II (R = C_6H_5), m.p. 25°; ϵ (239, 322 mμ) = 12,250 and 25,800.

Anal. Calcd. for $C_{12}H_{12}O$: C, 83.7; H, 7.0. Found: C, 83.3; H, 7.1.

7-Phenyl-3-methyl-2,4,6-heptatrienoic acid [6.8 g., ϵ (335 mμ) 40,800] was converted to its methyl ester [7.0 g., ϵ (337 mμ) 46,300]. The ester was dissolved in dry ethyl ether (100 ml.), treated with lithium aluminum hydride and worked up as described before for 5-phenyl-3-methyl-2,4-pentadien-1-ol to yield 6.1 g. of tan colored solids. Crystallization of the solids from aqueous ethanol at 5° gave 7-phenyl-3-methyl-2,4,6-heptatrien-1-ol as light yellow prisms, m.p. 75°; ϵ (304, 318, 333 mμ) 39,800, 49,800, 37,400.

Anal. Calcd. for $C_{14}H_{16}O$: C, 83.9; H, 8.0. Found: C, 83.7; H, 7.9.

A solution of the alcohol (3.0 g.) in ethyl ether was oxidized with manganese dioxide powder (45 g.) as described for II (R = C_6H_5). The product II (R = $C_6H_5CH{=}CH{-}$, 2.65 g.) consisted of a light yellow oil having *E* (1%, 1 cm., 261 and 351 mμ) 800 and 1735. Its infrared absorption spectrum showed a strong band at 6.01 (carbonyl) and no band at 2.76 μ (hydroxyl). It was not further purified.

Preparation of Thiapyrans (III).—The thiapyrans listed in Table I were made and purified by the general method illustrated by the following example for the thiapyran from 13-*cis*-retinal.

A solution of 13-*cis*-retinal (10.0 g.) in dry pyridine (15 ml.) was added dropwise to cold (−10°) pyridine (85 ml.), previously saturated with hydrogen sulfide gas. The reaction mixture was stirred at this temperature with continuous flow of a stream of hydrogen sulfide gas through the solution for 4 hr. The reaction mixture was then diluted with isopropyl ether (300 ml.) and the ether phase washed successively with two portions of cold dilute (5%) hydrochloric acid, once with saturated aqueous sodium bicarbonate solution, and finally with water until the washings were neutral. After drying over anhydrous sodium sulfate, the ether was evaporated, leaving a residue (10.4 g.) of red oil having *E* (1%, 1 cm., 274 mμ) 527.

This oil was dissolved in petroleum ether (b.p. 60–71°) and chromatographed on a column (6 cm. × 24 cm.) of magnesium silicate adsorbant (Florisil, 60–100 mesh, Floridin Co.). Continued washing of the column with petroleum ether gave a filtrate containing the nonadsorbed fraction which showed up as a greenish yellow zone on the column. Evaporation of the solvent from this fraction gave 8.0 g. of purified IIIa (R = B) as a pale yellow oil, ϵ (274 mμ) 16,650.

Anal. Calcd. for $C_{20}H_{28}S$: C, 79.9; H, 9.4; S, 10.7; mol. wt., 300. Found: C, 79.5; H, 9.4; S, 10.5; mol. wt., 325.

Similar results were obtained in experiments when other amines including quinoline, N-ethylaniline, or aniline were substituted for pyridine in the previous procedure.

Substitution of all *trans*-retinal for the 13-*cis* isomer in this procedure gave a compound having the same properties after the chromatographic purification as those for the product from the 13-*cis* isomer, but the yield was lower (estimated 50%). The remainder of the reaction product was judged to be mainly trithioretinal as indicated by ultraviolet and infrared absorption properties of the more strongly absorbed fractions. To obtain high yields of III from the all *trans* isomer, it was necessary in the procedure described before to add the pyridine solution of retinal to cold aniline saturated with hydrogen sulfide and containing also approximately 0.4% aniline hydrochloride. The product, after purification by chromatography, had ϵ (274 mμ) 16,700.

Anal. Calcd. for $C_{20}H_{28}S$: C, 79.9; H, 9.4; S, 10.7; mol. wt., 300. Found: C, 79.6; H, 9.4; S, 10.7; mol. wt., 311.

For III (R = $C_6H_5CH{=}CH{-}$), there was obtained 1.56 g. from 2.0 g. of aldehyde.

Anal. Calcd. for $C_{14}H_{14}S$: C, 78.5; H, 6.6; S, 14.9; mol. wt., 214. Found: C, 78.8; H, 6.8; S, 14.8; mol. wt., 268.

For III (R = C_6H_5), there was obtained 0.72 g. from 1.5 g. of aldehyde.

Anal. Calcd. for $C_{12}H_{12}S$: C, 76.5; H, 6.5; S, 17.0; mol. wt., 188. Found: C, 77.3; H, 6.9; S, 17.2; mol. wt., 216.

For IIIb (R = C), there was obtained 2.6 g. from 5.95 g. of aldehyde.

Anal. Calcd. for $C_{15}H_{22}S$: C, 76.9; H, 9.4; S, 13.7; mol. wt., 234. Found: C, 76.9; H, 8.9; S, 13.7; mol. wt., 250.

Preparation of "Dimer" (IV).—A solution of IIIa (R = B, 8.0 g.) in pyridine (80 ml.) was added to freshly prepared amalgamated zinc (16 g.) and allowed to stand at room temperature overnight. The reaction mixture was filtered and the filter cake was washed with 200 ml. of diethyl ether. The filtrate and washings were combined, and the ether phase was washed several times with dilute (5%) hydrochloric acid, twice with saturated aqueous sodium bicarbonate solution, and finally with water until the washings were neutral. After drying over anhydrous sodium sulfate, the ether was evaporated leaving 8.2 g. of an orange solid. These were recrystallized from chloroform–methanol (1:1) to give yellow crystals having ϵ (335 mμ) 70,300. Its infrared absorption spectrum showed a strong band at 10.3 (-CH=CH-) and absence of bands at 14.25 and 6.01 μ.

Anal. Calcd. for $C_{10}H_{54}S_2$: C, 79.9; H, 9.4; S, 10.7; mol. wt., 600. Found: C, 80.0; H, 9.3; S, 11.1; mol. wt., 587.

Preparation of Polyenes (V).—Desulfurizations of the thiapyrans (III) were carried out by the general method illustrated by the following example for the preparation of β-carotene.

A solution of 9.9 g. of IIIa (R = B) in 100 ml. of dry pyridine was saturated with carbon dioxide by bubbling the gas through the solution for 15 min. It was then added to freshly prepared and pulverized amalgamated zinc (20 g.) and after 1 hr., the temperature was raised to 70° and the reaction held at this temperature for 9 hr. under an atmosphere of carbon dioxide. After cooling to 20°, the mixture was filtered and the filter cake washed throughly with isopropyl ether. The filtrate and ether washings were combined, and the ethereal phase was washed successively with 5% hydrochloric acid, saturated aqueous sodium bicarbonate solution, and water until washes were neutral. After drying over anhydrous sodium sulfate, the ether was distilled to yield 9.5 g. of a β-carotene concentrate as a red solid [*E* (1%, 1 cm., 450 mμ) 1580]. A sample was recrystallized twice from benzene–ethyl formate (1:1) at 0° to give pure all *trans*-β-carotene as violet plates having ϵ (432, 456, 485 mμ) 92,600, 135,300, 118,500 (cyclohexane). The crystals melted at 182–182.5°. The melting point, when mixed with a sample of authentic all *trans*-β-carotene, was undepressed.

The polyene product from IIIb (R = C) was an oil which had an ultraviolet absorption maximum at 369 mμ [*E* (1%, 1 cm.) 605] and was not further purified. A crystalline preparation made by a different method and having *E* (1%, 1 cm., 372 mμ) 1400 has been reported.[16]

The diphenyl polyene V (R = C_6H_5), was a yellow solid, *E* (1%, 1 cm., 390, 411, and 437 mμ) 1825, 2710, 2320 (in benzene). V (R = $C_6H_5CH{=}CH{-}$) was an orange solid, *E* (1%, 1 cm., 409, 433, and 462 mμ) 2630, 4090, 3800 (in petroleum ether, b.p. 60–71°). This was the expected range for the ultraviolet absorption of these polyenes based on values reported[17] for the corresponding diphenyl polyenes containing no branched methyl groups.

(15) "Precipitated" grade, General Metallic Oxides Co.

(16) H. Inhoffen, F. Bohlmann, H. Aldag, S. Bork, and G. Liebner, *Ann.* **573**, 1 (1951).

(17) K. Dimroth, *Angew. Chem.*, **52**, 545 (1939).

The Chemistry of Pyrazine and Its Derivatives. VIII. Diketones Derived from the Monoacylation of 2-Methyl-6-(acylmethyl)pyrazines and the Diacylation of 2,6-Dimethylpyrazine[1]

MARWAN R. KAMAL[2] AND ROBERT LEVINE

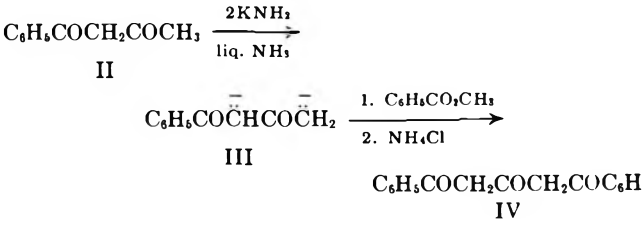
Department of Chemistry, University of Pittsburgh, Pittsburgh 13, Pennsylvania

Received August 15, 1963

2,6-Bis(acylmethyl)pyrazines have been synthesized by (A) the monoacylation of 2-methyl-6-acylmethylpyrazines and (B) the direct lateral diacylation of 2,6-dimethylpyrazine using sodium amide in liquid ammonia as the condensing agent. Method A gives diketones in which the acylmethyl groups may be the same or different depending on the acylating ester while both of the acylmethyl groups in the diketones prepared by method B must be identical. When the same product is produced by both routes, method A gives the higher yield.

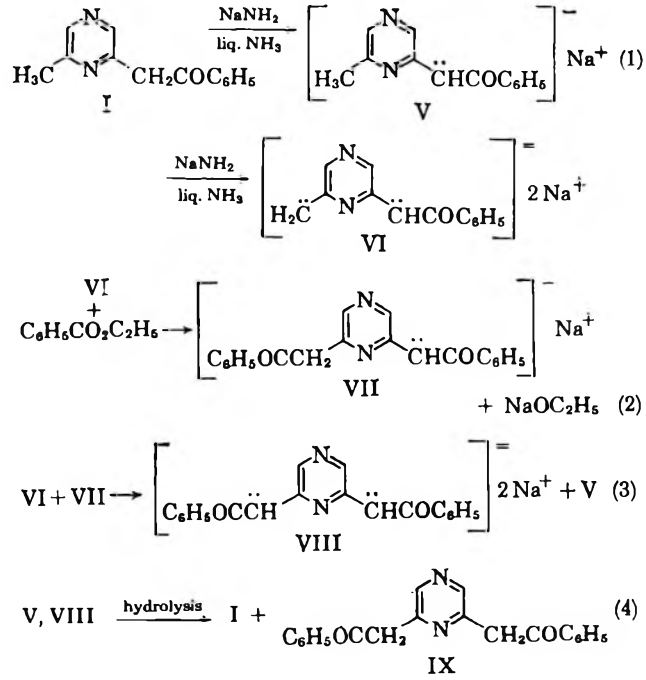
It has been demonstrated in these laboratories that 2-methyl-6-pyrazylmethylsodium, prepared by the reaction of 2,6-dimethylpyrazine with sodium amide in liquid ammonia, can be acylated[3] with esters to give 2-methyl-6-acylmethylpyrazines, alkylated[3] with alkyl halides to give 2-methyl-6-alkylpyrazines, and condensed with aldehydes and ketones[4] to give 2-methyl-6-pyrazylmethylcarbinols.

2-Methyl-6-phenacylpyrazine (I) is a typical 2-methyl-6-acylmethylpyrazine. It is structurally analogous to a β-diketone except that it contains an azomethine function of the ring in place of one of the carbonyl groups of the β-diketone. Hauser, *et al.*,[5,6] have shown that the β-diketones, acetylacetone and benzoylacetone, can be acylated with esters at a terminal methyl group by using *two equivalents* of potassium amide in liquid ammonia as the condensing agent for *each equivalent of β-diketone*. These workers envision the reactions as involving a dianion intermediate, *e.g.*, III. The benzoylation of benzoylacetone (II) to give the triketone (IV) illustrates this work.



It was, therefore, of interest to determine whether it would be possible to acylate 2-methyl-6-phenacylpyrazine (I) at its methyl group. In this compound the methyl hydrogen atoms may be considered as being activated by an azomethine function of the pyrazine ring towards anionic attack in much the same way that the methyl hydrogen atoms of benzoylacetone are activated by the adjacent carbonyl group. Both of these compounds may be regarded as fitting the general formula, CH_3ZCH_2COR, where R is the phenyl group and Z is the pyrazine ring or the carbonyl group.

As an orienting reaction, the benzoylation of 2-methyl-6-phenacylpyrazine (I) with ethyl benzoate was studied using sodium amide in liquid ammonia as the condensing agent. This reaction failed when a 1:1:1 molar ratio of sodium amide:I:ester was employed and most of the ester and ketone were recovered. However, when a 2:1:1 molar ratio of sodium amide:I:ester was used, an 81.0% yield of 2,6-diphenacylpyrazine (IX) was obtained assuming the reaction follows the course shown in the accompanying scheme. In addition, 49.5% of I was recovered.



It is suggested that, in step 1, I and sodium amide react to give the dianion VI, with monoanion V as an intermediate. Then, in step 2, VI is acylated at its methylene carbanion to give the monoanion VII of the diacylated product. Apparently monoanion V, which would be the expected product, *vide supra*, from the interaction of equivalents of I and sodium amide (since the methylene hydrogen atoms of I are more acidic than its methyl hydrogen atoms) is not sufficiently basic to displace an alkoxide ion from an ester molecule. Hence, V is not acylated, *vide infra*, to give 2-dibenzoyl-

(1) This work was supported by a grant from Wyandotte Chemicals Corp.

(2) This paper is based on part of a thesis presented by M. R. Kamal to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

(3) M. R. Kamal and R. Levine, *J. Org. Chem.*, **27**, 1355 (1962).

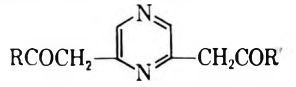
(4) M. R. Kamal and R. Levine, *ibid.*, **27**, 1360 (1962).

(5) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958).

(6) R. J. Light and C. R. Hauser, *J. Org. Chem.*, **25**, 538 (1960).

TABLE I

2,6-BIS(ACYLMETHYL)PYRAZINES OF THE TYPE

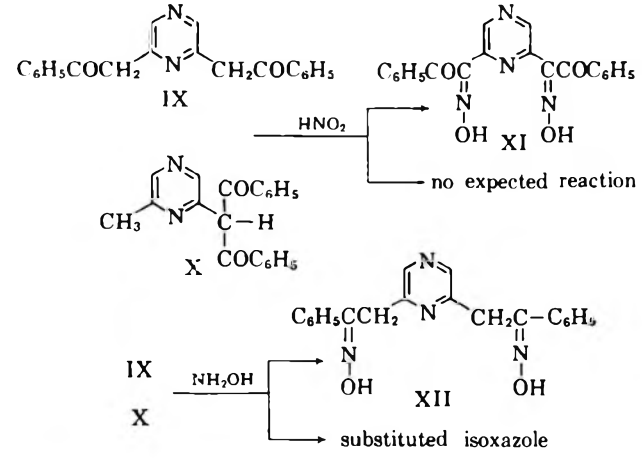


Compound	R	R′	Yield, %	M.p. or b.p. (mm.), °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	C_6H_5	C_6H_5	81.0[a,b] 38.5[c,d]	141–142[e]	$C_{20}H_{16}N_2O_2$	75.39	76.02	5.07	5.51
2	C_2H_5	C_2H_5	75.4[a,f]	64.6–65.4[g]	$C_{12}H_{16}N_2O_2$	65.43	65.76	7.32	7.62
3	i-C_3H_7	i-C_3H_7	42.0,[a,h] 0.6[c,i]	154–156 (0.9)	$C_{14}H_{20}N_2O_2$	67.71	67.44	8.12	8.15
4	t-C_4H_9	t-C_4H_9	19.8,[a,j] 21.0[a,k,l]	146–147 (0.4)	$C_{16}H_{24}N_2O_2$	69.53	69.59	8.75	9.06
5	t-C_4H_9	4-C_6H_4N[m]	97.6[d,n,o]	113.6–114.6[p]	$C_{17}H_{19}N_3O_2$	68.67	69.22	6.44	6.64
6	C_2H_5	t-C_4H_9	47.0[a,n,q]	146–149 (0.5)	$C_{14}H_{20}N_3O_2$	67.70	67.14	8.12	8.31
				Dioximes					
1a				171.5–172.2	$C_{20}H_{18}N_4O_2$	69.34	68.90	5.24	5.44
2a				102.6–103.2	$C_{12}H_{18}N_4O_2$	57.58	57.79	7.25	7.36
3a				106.2–106.6	$C_{14}H_{22}N_4O_2$	60.41	60.67	7.97	8.19
4a				166.4–167.0	$C_{16}H_{26}N_4O_2$	62.71	62.37	8.55	8.73
5a				177–178	$C_{17}H_{21}N_5O_2$	21.50[r]	21.52		
6a				109.8–110.6	$C_{14}H_{22}N_4O_2$	20.13[r]	20.01		

[a] Starting with the 2-methyl-6-(acylmethyl)pyrazine. [b] 49.5% of 2-methyl-6-phenacylpyrazine (A) was recovered. [c] Starting with 2,6-dimethylpyrazine. [d] 25.4% of A, m.p. 50–52° (see ref. 3), also was isolated. [e] Recrystallized from an acetone–water mixture. [f] 40.3% of 2-methyl-6-(propionylmethyl)pyrazine, b.p. 82–88° at 0.7 mm. (see ref. 3), was recovered. [g] Recrystallized from an ether–pentane mixture. [h] 45.0% of 2-methyl-6-(isobutyrylmethyl)pyrazine (B), b.p. 92–96° at 0.9 mm. (see ref. 3), and 33.3% of isobutyramide (C), m.p. 127–128°, alone and when mixed with an authentic sample, also were isolated. [i] 36.2% of B and 41.9% of C also were isolated. [j] 53.7% of 2-methyl-6-(pivalylmethyl)pyrazine (D), b.p. 102–106° at 1.0 mm. (see ref. 3), and 4.2 g. (46.0%) of pivalamide (E), m.p. 153–154°, alone and when mixed with an authentic sample, also were isolated. [k] Three hours were allowed for converting the starting pyrazine compound to its anion. In all other cases, a one-half hour anion time was used. [l] 73.5% of D and 33.6% of E also were isolated. [m] 4-C_5H_4N = 4-pyridyl radical. [n] Starting with D. [o] 32.8% of D was recovered. [p] Recrystallized from a benzene–pentane mixture. [q] 60.8% of D was recovered. [r] Nitrogen analysis.

methyl-6-methylpyrazine (X), an isomer of the product, 2,6-diphenacylpyrazine (XI), during the interaction of equivalents of the reactants. In step 3, VI reacts with VII to form the dianion VIII of the diacylated product and the monoanion V of the starting material. Finally, on hydrolysis (step 4) the monoketone I and the diketone IX are formed. Thus, one-half of I is regenerated in steps 3 and 4 and only one-half a mole of diketone can be obtained from each mole of starting ketone.

That the compound formed by the benzoylation of I is indeed IX and not its isomer X was shown by (1) nitrosating the product and obtaining 2,6-bis(1-oximinophenacyl)pyrazine[7] (XI) and (2) converting a sample of the product to its dioxime (XII) by reaction with hydroxylamine. These two reactions would not be expected to take place if the product were X since such a β-diketone could not be dinitrosated readily and it would be expected to give a substituted isoxazole when treated with hydroxylamine.[8]



Five other 2,6-bis(acylmethyl)pyrazines (Table I) of the general formula, 2-$RCOCH_2PzCH_2COR'$-6 (where Pz = the pyrazine ring) also were prepared. Three of these diketones (compounds 2–4) like 2,6-diphenacylpyrazine (compound 1) are symmetrical, *i.e.*, R = R′. The remaining two diketones (compounds 5 and 6) are unsymmetrical, *i.e.*, R ≠ R′. These two diketones, *viz.*, 2-(pivalylmethyl)-6-(isonicotinylmethyl)-pyrazine and 2-(propionylmethyl)-6-(pivalylmethyl)-pyrazine, were obtained in 97.6% and 47.0% yields, respectively, by the acylation of 2-methyl-6-pivalylmethylpyrazine with methyl isonicotinate and methyl propionate.

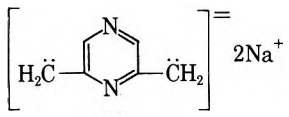
It was also of interest to determine whether the symmetrical diketones can be prepared by the direct diacylation of 2,6-dimethylpyrazine as well as by the acylation of the previously prepared[3] and isolated monoketones, *i.e.*, the 2-methyl-6-acylmethylpyrazines. Thus, from the interaction of a 1:3:2 molar ratio of 2,6-dimethylpyrazine:sodium amide:ethyl benzoate there was obtained a mixture of 2-methyl-6-phenacylpyrazine (I, 25.4%) and 2,6-diphenacylpyrazine (IX, 38.5%) as compared with the 81.0% yield of IX which was obtained by the benzoylation of I. Finally, the attempted diacylation of 2,6-dimethylpyrazine with ethyl isobutyrate gave a mixture of isobutyramide (41.9%), 2-methyl-6-(isobutyrylmethyl)pyrazine (36.2%), and 2,6-di(isobutyrylmethyl)pyrazine (0.6%) as compared with the 42.0% yield of this diketone which was obtained by the acylation of 2-methyl-6-isobutyrylmethylpyrazine. That such a low yield of diacylated product was obtained in the attempted diisobutyrylation of 2,6-dimethylpyrazine may be due to the probability that

(7) A sharp melting point was not obtained for XI. This may be due to the probability that a mixture of geometrical isomers of the dioximino compound was formed.

(8) V. Migrdichian, "Organic Synthesis," Vol. II, Reinhold Publishing Corp., New York, N. Y., 1957, p. 1366.

the ethyl isobutyrate reacts preferentially with the large amount of sodium amide which is present to give isobutyramide, rather than with the anion of 2,6-dimethylpyrazine to give the desired product.

Although it is tempting to assume that in the sodium amide-effected direct diacylation of 2,6-dimethylpyrazine a dianion (XIII) is formed which then can give rise to the mono- and diacylated products, no



XIII

conclusive data in support of its existence are available at the present time. The formation of the ketonic products may be explained also by envisioning that one equivalent of sodium amide converts one equivalent of 2,6-dimethylpyrazine to its monoanion which is then acylated to give the monoketone. Part of this monoketone may then react further as indicated in the reaction scheme described previously to give the diketone. More work must be done before a decision can be made as to which of these two alternative paths is followed when symmetrical 2,6-diacylmethylpyrazines are formed by the direct diacylation of 2,6-dimethylpyrazine.

Experimental[9]

A. Synthesis of 2,6-Diphenacylpyrazine by the Direct Benzoylation of 2,6-Dimethylpyrazine.—This reaction illustrates the preparation of the symmetrical diacylated products *via* the direct acylation of 2,6-dimethylpyrazine. To 0.45 mole of sodium amide,[10] prepared from sodium (10.4 g., 0.45 g.-atom), in 500 ml. of anhydrous liquid ammonia was added over a 15-min. period, 2,6-dimethylpyrazine (16.2 g., 0.15 mole) dissolved in 50 ml. of anhydrous ether. The reaction mixture, which became deep red in color, was stirred for 30-min. Then ethyl benzoate (45.0 g., 0.30 mole) dissolved in an equal volume of anhydrous ether was added over a 20-min. period and the reaction mixture was stirred for 90 min. Ammonium chloride (27.0 g.) was added to quench the reaction and the liquid ammonia was replaced by ether. The mixture was then carefully poured onto ice and was made slightly acidic with dilute hydrochloric acid. There was precipitated 18.5 g. (38.5%) of 2,6-diphenacylpyrazine, m.p. 141–142°, from an acetone–water mixture. In addition, 8.1 g. (25.4%) of 2-methyl-6-phenacylpyrazine, m.p. 50–52°,[3] was isolated.

B. Synthesis of 2,6-Diphenacylpyrazine by the Benzoylation of 2-Methyl-6-phenacylpyrazine.—This reaction illustrates the preparation of the symmetrical diacylated products *via* the acylation of a monoacylated 2,6-dimethylpyrazine. To sodium amide[10] (0.20 mole) in 200 ml. of anhydrous liquid ammonia was added 2-methyl-6-phenacylpyrazine[3] (21.2 g., 0.1 mole) over a 15-min. period. The red solution was stirred for 30 min. after which ethyl benzoate (15.0 g., 0.1 mole) was added over a 20-min. period. The reaction mixture was stirred for 90 min. and then was processed as in the previous reaction to give 12.9 g. (81.0%) of 2,6-diphenacylpyrazine, m.p. 141–142°, from an acetone–water mixture. In addition, 10.5 g. (49.5%) of 2-methyl-6-phenacylpyrazine, m.p. 50–52°,[3] was recovered.

When this reaction was performed using a 1:1:1 molar ratio of sodium amide:2-methyl-6-phenacylpyrazine:ethyl benzoate, none of the desired diketone was obtained and the starting materials were recovered.

C. Synthesis of 2-(Pivalylmethyl)-6-(isonicotinylmethyl)pyrazine.—This reaction illustrates the preparation of an unsymmetrically diacylated product *via* the acylation of a monoacylated 2,6-dimethylpyrazine. 2-Methyl-6-(pivalylmethyl)pyrazine[3] (19.2 g., 0.1 mole), sodium amide[10] (0.2 mole) in 200 ml. of anhydrous liquid ammonia, and methyl isonicotinate (0.1 mole, 13.7 g.) dissolved in an equal volume of anhydrous ether were allowed to react as described in reaction B and processed as described in reaction A to give 14.5 g. (97.6%) of 2-(pivalylmethyl)-6-(isonicotinylmethyl)pyrazine, m.p. 108–112°. Several attempts to recrystallize this material from the usual solvents did not give a sharp melting material. Finally, it was purified by dissolving it in benzene, adding a small amount of Florex, and shaking the mixture for 10 min. The Florex was removed by filtration. The addition of pentane to the filtrate caused the yellow crystalline product to precipitate. This material melted at 113–114° and on recrystallization from a benzene–pentane mixture, it melted at 113.6–114.6°.

D. Reaction of 2,6-Diphenacylpyrazine with Aqueous Sodium Nitrite.—Sodium nitrite (2.0 g., 0.028 mole) dissolved in 25 ml. of water, was added slowly (30 min.) to a stirred solution of 2.0 g. (0.006 mole) of 2,6-diphenacylpyrazine in 25 ml. of glacial acetic acid. The mixture was then stirred for 3 hr. with occasional cooling to maintain the reaction temperature at 25°. The addition of 50 ml. of water caused the precipitation of 0.4 g. of a yellow solid, which was removed by filtration and identified as 2,6-diphenacylpyrazine, m.p. 141–142°. The addition of 500 ml. of water to the filtrate resulted in the precipitation of 0.9 g. (40.3%) of 2,6-bis(1-oximinophenacyl)pyrazine, m.p. 100–110°. Several recrystallizations of this solid from an ethanol–water mixture failed to give a sharp melting material presumably due to the possibility that it consists of geometrical isomers. However, its elemental analysis agreed with the proposed structure.

Anal. Calcd. for $C_{20}H_{14}N_4O_4$: C, 64.17; H, 3.77; N, 14.97. Found: C, 63.69; H, 4.09; N, 14.70.

(9) The 2,6-dimethylpyrazine was supplied through the courtesy of Wyandotte Chemicals Corp.

(10) S. R. Harris and R. Levine, *J. Am. Chem. Soc.*, **70**, 3360 (1948).

Selective Hydrogenation of Haloalkenes to Haloalkanes Using Rhodium Catalyst[1]

G. E. HAM AND W. P. COKER

Texas Organic Research Department, The Dow Chemical Company, Freeport, Texas

Received June 17, 1963

Rhodium on alumina has been found to be a superior catalyst for the hydrogenation of a vinylic or allylic halogen-substituted olefin to a haloalkane. Yields of 40–60% chloroalkane were obtained from the hydrogenation of 1-chloropropene, allyl chloride, and 1,3-dichloropropene. Hydrogenation of 5-chlorohexene-1 gave 2-chlorohexane in 96% yield. Under hydrogenation conditions used, hydrogenolysis of the chloroalkanes did not occur when rhodium, platinum, or palladium was used as catalyst. Yields of chloroalkanes were found to be dependent on solvent, the presence of thiophene as a poison, and catalyst support. Dependency of yields on the catalyst was found to be in the following decreasing order: rhodium, palladium, platinum. Isomerization of *cis*- or *trans*-1,3-dichloropropene did not occur over rhodium catalyst in the absence of hydrogen. However, isomerization was noted in partially hydrogenated material.

In a preliminary investigation of the hydrogenation of 1,3-dichloropropene over rhodium, palladium, platinum, and platinum oxide catalysts it was found that only four products were formed. These were- 1,3 dichloropropane, propyl chloride, propane, and hydrogen chloride.

$$ClCH{=}CHCH_2Cl + H_2 \longrightarrow \begin{matrix} ClCH_2CH_2CH_2Cl \\ CH_3CH_2CH_2Cl \\ CH_3CH_2CH_3 \\ HCl \end{matrix}$$

The major products obtained using palladium, platinum, and platinum oxide catalysts were propane and hydrogen chloride. It was surprising to find, however, that using rhodium catalysts afforded high yields of 1,3-dichloropropane and propyl chloride.

The reductive dehalogenation of organic halides has been previously studied. Horner, Schläfer, and Kämmerer[2] found that when using Raney nickel in alkali methanol, primary and secondary monochlorides did not react but that a vinylic or allylic chloride would undergo hydrogenolysis as the double bond was reduced. These authors also found that 1,1-dihaloalkanes and 1,2-dihaloethanes gave hydrogenolysis of the carbon–halogen bond whereas very little or none was observed with 1,3- or 1,4-dihaloalkanes. Alkyl bromides or iodides underwent hydrogenolysis as compared with none for the chlorides. When the chlorine was not allylic or vinylic only partial hydrogenolysis was observed. Hydrogenation of 4-chlorohexene-1 gave some hydrogenolysis and some 3-chlorohexane.

In connection with some other work McCullen, Henze, and Wyatt[3] carried out hydrogenation of 2-bromopropene and 1,2-dibromopropene-1 in ethanol over palladium on carbon. These authors found that a pressure drop corresponding to 1.5 equivalents of hydrogen occurred with 2-bromopropene to give a 93.4% yield of bromide ion and that one equivalent of hydrogen reacted with 1,2-dibromopropene-1 without formation of bromide ion.

Kindler, Oelschlager, and Henrich[4] studied the selective hydrogenation of the double bond in 2-allyl-4-chlorophenol over palladium catalyst. Dehalogenation of the starting material or product was the major side reaction. These authors found that solvent affected the yield of chloride ion. The following chloride ion yields were reported: methanol, 6.2%; ethanol, 8.6%; isopropyl alcohol, 3.6%; benzene, 0%; cyclohexane, 0%. Poisons also were reported to retard dehalogenation. The following chloride ion yields were found using ethanol as solvent: no poison, 8.6%; nicotinamide, 0.4%; dimethylnicotinamide, 0.8%; thiophene, 0.6%.

Baltzly and Phillips[5] studied the dehalogenation of halogen-substituted compounds over palladium on charcoal. These authors found that saturated aliphatic bromides, such as isobutyl bromide, *t*-butyl bromide, and cyclohexyl bromide, did not undergo hydrogenolysis. Aromatic halides, such as bromobenzene, allyl chloride, and benzyl chloride, were readily dehalogenated, however.

The primary purpose of the work reported here was to find procedures which would allow the selective hydrogenation of the olefinic linkage in 1,3-dichloropropene. Initially it was considered that four different reactions might be occurring in this system. These are (1) hydrogenation of the double bond, (2) hydrogenolysis of an allylic chloride, (3) hydrogenolysis of a vinylic chloride, and (4) hydrogenolysis of an alkyl chloride. It was reasoned that these four reactions might be affected differently by changes in hydrogenation conditions.

It was found that alkyl halides do not undergo hydrogenolysis using rhodium, palladium, or platinum catalyst.

Table I shows the results of such attempted hydrogenolysis. Contrary to the results of Horner, Schläfer, and Kammerer, no hydrogenolysis was noted with an alkyl bromide, 1-bromo-3-chloropropane, and 1,2,3-trichloropropane.

TABLE I

ATTEMPTED HYDROGENOLYSIS OF ALKYL HALIDES[a]

Alkyl halide	Catalyst	H_2 pressure, lb./in.^{2}	% yield HCl
$Cl(CH_2)_3Cl$	5% Rh on alumina	860	0[b]
$CH_3CH_2CH_2Cl$	5% Rh on charcoal	380	0
$CH_3CHClCH_3$	5% Rh on charcoal	815	0
$CH_3C(CH_3)ClCH_3$	5% Rh on charcoal	1000	73.4
$CH_2ClCHClCH_2Cl$	5% Rh on charcoal	800	0
$Cl(CH_2)_3Cl$	5% Pd on alumina	500	0[c]
$Cl(CH_2)_3Cl$	5% Pt on alumina	500	0[c]
$Cl(CH_2)_3Br$	5% Rh on alumina	480	0

[a] At 100° for 3 hr. [b] 88.5% 1,3-dichloropropane recovered [c] 97% 1,3-dichloropropane recovered.

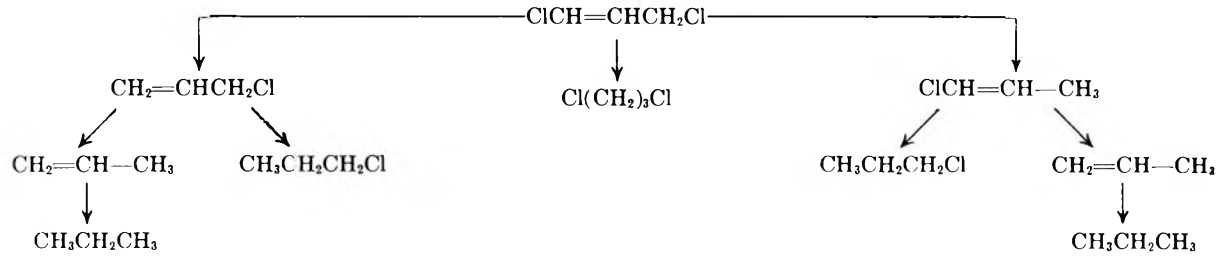
(1) A portion of this work was presented at the 18th Southwest Regional Meeting of the American Chemical Society, Dallas, Tex., December, 1962.

(2) L. Horner, L. Schläfer, and H. Kämmerer, *Ber.*, **92**, 1700 (1959).

(3) E. J. McCullen, H. R. Henze, and B. W. Wyatt, *J. Am. Chem. Soc.*, **76**, 5636 (1954).

(4) K. Kindler, H. Oelschlager, and P. Henrich, *Ber.*, **86**, 167 (1953).

(5) R. Baltzly and A. P. Phillips, *J. Am. Chem. Soc.*, **68**, 261 (1946).



Thus it is seen that in the hydrogenation of 1,3-dichloropropene the following reaction scheme is more nearly representative of reactions in this system.[6]

Hydrogenolysis of allylic and vinylic chloride are the only side reactions shown. The propyl chloride formed in the reaction can only result from 1-chloropropene or allyl chloride. The propane formed can result only from hydrogenation of propylene.

The superior selectivity of rhodium in this hydrogenation is shown in Table II, where the reaction is carried out with other noble metal catalysts. These reactions were run in cyclohexane as solvent and at the same mole ratio of catalyst metal to olefin.

TABLE II

EFFECT OF CATALYST METAL ON SELECTIVITY IN HYDROGENATION OF 1,3-DICHLOROPROPENE[a]

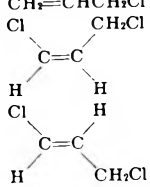
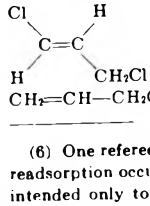
Catalyst	% yield $Cl(CH_2)_3Cl$	% yield $CH_3CH_2CH_2Cl$
5% Ru on alumina	No reaction	
5% Rh on alumina	47.9	35.4
5% Pd on alumina	19.2	33.0
5% Pt on alumina	6.1	32.2

[a] At 100° and 400–600 lb./in.² hydrogen pressure.

In Table III is shown the results of hydrogenating several chloro-substituted olefins using 5% rhodium on alumina in cyclohexane solvent. It is interesting to note that approximately the same yields of 1,3-dichloropropane and propyl chloride were obtained with the *cis* or *trans* isomer of 1,3-dichloropropene. *cis–trans* isomerization of 1,3-dichloropropene did not occur when heated in the presence of the catalyst at 105° for 2 hr. However, in an experiment where only a small amount of hydrogenation had taken place a small

TABLE III

HYDROGENATION OF CHLORO-SUBSTITUTED OLEFINS WITH 5% RHODIUM-ON-ALUMINA CATALYST

Olefin	T, °C.	H_2 pressure, lb./in.²	Products	% yield
ClCH=CHCH3 cis–trans	100	620	$CH_3CH_2CH_2Cl$	42.4
CH_2=CHCH2Cl	100	580	$CH_3CH_2CH_2Cl$	57.8
	100	710	$Cl(CH_2)_3Cl$	42.9
			$CH_3CH_2CH_2Cl$	31.4
	100	680	$Cl(CH_2)_3Cl$	47.0
			$CH_3CH_2CH_2Cl$	33.5
CH_2=CH—$CH_2CH_2CHClCH_3$	52	500	$CH_3(CH_2)_3CHClCH_3$	96.9

(6) One referee suggested that this scheme may imply that desorption and readsorption occurs with the intermediate unsaturated species. The authors intended only to emphasize that propane and propyl chloride do not result from hydrogenolysis of 1,3-dichloropropane. The hydrogenolysis reactions may certainly proceed during one period of adsorption of 1,3-dichloropropene *via* surface intermediates.

per cent of the olefin had isomerized. When the chlorine was substituted in a position which was not allylic or vinylic to the double bond, as in 5-chlorohexene-1, there was no hydrogenolysis of the carbon–chlorine bond.

The yield of chloroalkanes, as well as the rate of hydrogenation, was affected by the catalyst support. In Table IV is shown the effect of three different supports. These experiments were all carried out at the same mole ratio of olefin to rhodium metal.

TABLE IV

EFFECT OF CATALYST SUPPORT ON SELECTIVITY IN THE RHODIUM-CATALYZED HYDROGENATION OF 1,3-DICHLOROPROPENE[a]

Catalyst	% yield $Cl(CH_2)_3Cl$
5% Rh on alumina powder[b]	47.9
5% Rh on charcoal powder[b]	37.4
0.5% Rh on 1/8-in. alumina pellets[c]	29.8

[a] In 150 g. of cyclohexane (0.334 mole of olefin) at 100° and 400–600 lb./in.² hydrogen pressure. [b] 2.4 g. of catalyst. [c] 24 g. of catalyst.

Kindler, Oelschlager, and Henrich found that in the hydrogenation of 2-allyl-4-chlorophenol certain solvents and poisons retard the dehalogenation reaction. The results on solvent effect obtained in this work agree with these authors in that the less polar solvents gave the highest yields of chloroalkane. However, the opposite effect was noted when thiophene was added as a poison. Whereas these authors found a reduction in hydrogenolysis from 8.6% to 0.6%, an increase was found in this work.

Tables V and VI show the effect of thiophene and solvents, respectively, on the selectivity in hydrogenation of 1,3-dichloropropene using rhodium catalyst.

TABLE V

EFFECT OF THIOPHENE ON SELECTIVITY IN HYDROGENATION OF 1,3-DICHLOROPROPENE USING 5% RHODIUM-ON-ALUMINA CATALYST[a]

Poison	% yield $Cl(CH_2)_3Cl$
None	45.6
Thiophene[b]	28.8

[a] In 150 g. of cyclohexane (0.334 mole of olefin and 2.4 g. of catalyst) at 100° and 700–800 lb./in.² hydrogen pressure. [b] 0.05 ml./44 g. of olefin.

Temperature was found to have only a very slight effect on the selectivity in the hydrogenation of 1,3-dichloropropene. These results are shown in Table VII.

There was no attempt made to measure carefully the rate or kinetics of the hydrogenation of the chloroalkenes. However, it was noted consistently that decrease in total pressure *vs.* time was linear and that

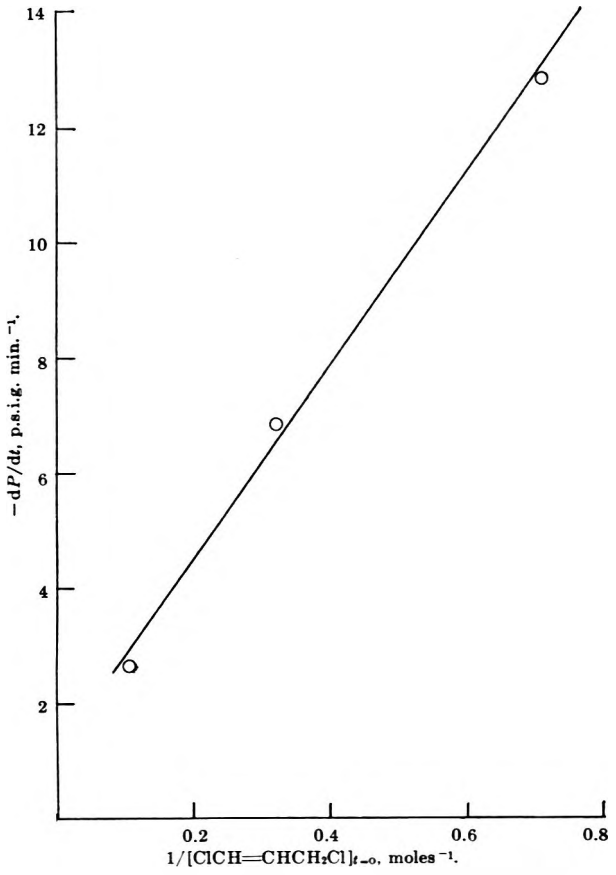


Fig. 1.—Effect of initial olefin concentration on rate of hydrogenation of 1,3-dichloropropene.

TABLE VI

EFFECT OF SOLVENT ON SELECTIVITY IN HYDROGENATION OF 1,3-DICHLOROPROPENE USING 5% RHODIUM-ON-ALUMINA CATALYST[a]

Solvent	T, °C.	% yield $Cl(CH_2)_3Cl$
1,3-Dichloropropane[b]	100	39.4
Cyclohexane	100	47.9
Diethyl ether	100	30.8
	30–35	29.9
Ethanol[c]	100	2.5
	30–35	12.1
Acetic acid[c,d]	100	2.5

[a] At 400–600 lb./in.^{2} hydrogen pressure with 150 g. of solvent, 0.334 mole of olefin, and 2.4 g. of catalyst. [b] Yield of 1,3-dichloropropane determined by weight gain in pure $Cl(CH_2)_3Cl$ recovered. Loss of 4 g. of material in handling would account for yield loss of 9.8%. [c] Reaction mixture darkened. Solvolysis of allylic chloride in 1,3-dichloropropene does not occur under these conditions. [d] Catalyst appeared degraded.

TABLE VII

EFFECT OF TEMPERATURE ON SELECTIVITY IN HYDROGENATION OF 1,3-DICHLOROPROPENE USING 5% RHODIUM ON ALUMINA[a]

T, °C.	% yield $Cl(CH_2)_3Cl$	% yield $CH_3CH_2CH_2Cl$
100	47.9	35.4
35–40	53.3	21.0

[a] In 150 g. of cyclohexane solvent (0.334 mole of olefin and 2.4 g. of catalyst) at 400–600 lb./in.^{2} hydrogen pressure.

this rate of decrease for a given experiment could be repeatedly observed, *i.e.*,

$$-dP/dt = K$$

Since one mole of gas is liberated for each mole of hydrogen consumed which is not used for saturation of the double bond, the observed pressure drops may be used as a rough measure of the relative rates of double bond hydrogenation in the various experiments. Thus it was noticed that the order of rates for reduction of the various olefins under approximately the same conditions was as follows: cyclohexene > 5-chlorohexene-1 > allyl chloride > 1-chloropropene > 1,3-dichloropropene.

The conditions under which this order was observed were about 100° in cyclohexane as solvent at about 400–600 lb./in.^{2} hydrogen pressure. These conditions afforded an almost instantaneous hydrogenation of cyclohexene and about 20 min. for completion with 1,3-dichloropropene. The presence of thiophene in the reaction mixture in trace amounts caused a very marked reduction in rate of hydrogenation of 1,3-dichloropropene over 5% rhodium on alumina powder. The effect of catalyst support on the rate of rhodium-catalyzed hydrogenation of 1,3-dichloropropene was as follows: 5% rhodium on alumina powder > 5% rhodium on charcoal powder ≫ 0.5% rhodium on $^1/_8$-in. alumina pellets.

Using cyclohexane as solvent and 5% rhodium on alumina powder it was noticed that the rate of hydrogenation of 1,3-dichloropropene was dependent on the initial concentration and that the rate was faster in the more dilute solutions. This dependency on initial concentration is shown in Fig. 1. This dependency is interpreted as indicating that in this particular system the olefin is more strongly adsorbed on the catalyst surface than hydrogen.

It was also noticed that the rate of hydrogenation of 1,3-dichloropropene using 5% rhodium on alumina powder in cyclohexane was a function of the catalyst concentration. This dependency is shown in Fig. 2.

Experimental

The catalysts used in this work were obtained from Baker and Company, Inc., and were used in the form they were received. Different batches of catalysts (different lot numbers) gave identical results.

Analysis for *cis*- and *trans*-1,3-dichloropropene and 1,3-dichloropropane was done by v.p.c. techniques on an 8 ft. by $^3/_{16}$ in. stainless steel column packed with 30% tricresyl phosphate on Celite operated at 98–100° under 4.0 lb./in.^{2} helium pressure at maximum flow rate of helium through the column under these conditions. The *cis* and *trans* isomers of 1,3-dichloropropene and 1,3-dichloropropane were well separated on this column. Calibration curves were prepared for each of the components to be analyzed. Samples injected into the column were weighed to the nearest 0.1 mg. on an analytical balance and the area of the chromatogram peaks was determined by carefully cutting out the peak and weighing the paper to the nearest 0.1 mg.

Attempted Hydrogenolysis of Haloalkanes.—The following is a typical example for attempted hydrogenolysis of various haloalkanes as reported in Table I. In most cases the formation of hydrogen chloride was the criterion used for hydrogenolysis.

To a 1410-ml. stainless steel rocking autoclave was charged 22.6 g. (0.20 mole) of 1,3-dichloropropane and 0.23 g. of rhodium catalyst (5% Rh on alumina powder). The mixture was heated to 100° and the vessel was pressurized with hydrogen to 860 lb./in.^{2}. After rocking at 100° for 3 hr. the bomb was cooled and vented through two scrubbers containing 1.0 *N* sodium hydroxide solution. The acidified scrubber solution did not give a precipitate with silver nitrate solution. The liquid recovered from the bomb (20.6 g., 91.2% recovery) was shown by infrared analysis to be pure 1,3-dichloropropane.

General Procedure for Hydrogenation.—All of the hydrogenations were carried out in a stainless steel rocking autoclave. The olefin, solvent, and catalyst were charged to the bomb, the

bomb and contents heated to the desired temperature and then pressurized to the desired pressure with hydrogen. The pressure and temperature inside the bomb were recorded automatically *vs.* time. Hydrogenations were always carried out for a period of time after there was no further pressure drop in the system. The bomb and contents were then cooled to room temperature and vented through two gas scrubbers containing 1.0 *N* sodium hydroxide solution. This solution was then analyzed for chloride ion by the Volhard method. The contents of the bomb were then filtered to remove catalyst, weighed, and analyzed by v.p.c. for 1,3-dichloropropane. Propyl chloride was recovered by distillation of the product solution. A typical example of the hydrogenation is given subsequently for the hydrogenation of 1,3-dichloropropene in cyclohexane.

Hydrogenation of 1,3-Dichloropropene.—A mixture of *cis*- and *trans*-1,3-dichloropropene was distilled and the fraction boiling between 103° and 112° collected. This material was shown by infrared analysis to be approximately 50% *cis* isomer and 50% *trans* isomer. To a 1410-ml. stainless steel rocking autoclave was charged 0.334 mole of 1,3-dichloropropene, 150.0 g. of cyclohexane, and 2.40 g. of catalyst (5% Rh on alumina powder). The bomb and contents were heated to 100° and then pressurized with hydrogen to 500 lb/in.^{2}. After about 15 min. there was no further pressure drop. Rocking and heating were continued for an additional 2.75 hr. After this time the bomb was cooled to room temperature and vented through two scrubbers containing 1.0 *N* sodium hydroxide solution. Analysis of this solution revealed that 0.204 mole of hydrogen chloride had been formed.

The liquid obtained from the bomb (178.5 g.) was analyzed by v.p.c. for 1,3-dichloropropane. This solution was found to be 10.1% by weight 1,3-dichloropropane (0.160 mole formed). Fractionation of the solution yielded 9.26 g. of a fraction with b.p. 46.5–48° which was shown to be pure propyl chloride by infrared analysis. This corresponds to a 35.4% yield of propyl chloride and 47.9% yield of 1,3-dichloropropane.

Hydrogenation of *cis*-1,3-Dichloropropene.—A mixture of *cis*- and *trans*-1,3-dichloropropene was fractionated. The fraction boiling at 103–104°, n^{20}D 1.4691 (lit.[7] b.p. 104.3°, n^{20}D 1.4682), was isolated and shown by v.p.c. analysis to be 73% *cis* isomer by weight. This fraction was shown by infrared analysis to be greater than 98% pure *cis*- and *trans*-1,3-dichloropropene. To a 1410-ml. stainless steel bomb was charged 45.0 g. (0.385 mole of 1,3-dichloropropene) of this fraction, 150.0 g. of cyclohexane, and 2.40 g. of catalyst (5% Rh on alumina powder) and the hydrogenation procedure carried out as described previously. There was obtained a 42.9% yield of 1,3-dichloropropene and 31.4% yield of propyl chloride.

Hydrogenation of *trans*-1,3-Dichloropropene.—Distillation of a mixture of *cis*- and *trans*-1,3-dichloropropene yielded a fraction boiling at 111.5–112.0°, n^{20}D 1.4739 (lit.[7] b.p. 112.0°, n^{20}D 1.4730), which was 92% by weight *trans* isomer by v.p.c. analysis. By infrared analysis it was shown that this fraction was greater than 98% pure *cis*- and *trans*-1,3-dichloropropene. Hydrogenation of this fraction was carried out exactly as described for the *cis* isomer. There was obtained a 47.0% yield of 1,3-dichloropropane and 33.5% yield of propyl chloride.

Hydrogenation of 1-Chloropropene.—To a 1410-ml. stainless steel bomb was charged 30.0 g. (0.392 mole) of freshly distilled *cis–trans*-1-chloropropene (b.p. 31–37°), 150.0 g. of cyclohexane, and 2.40 g. of catalyst (5% Rh on alumina powder). Hydrogenation was carried out by the previously described procedure at an initial hydrogen pressure of 610 lb/in.^{2}. There was obtained a 42.4% yield of propyl chloride.

Hydrogenation of Allyl Chloride.—To a 1410-ml. stainless steel bomb was charged 30.0 g. (0.392 mole) of redistilled allyl chloride, 150.0 g. of cyclohexane, and 2.40 g. of catalyst (5% Rh on alumina powder). Hydrogenation was carried out by the previously described procedure at an initial hydrogen pressure of 580 lb./in.^{2}. There was obtained a 57.8% yield of propyl chloride.

Preparation of 5-Chlorohexene-1.—Into a 500-ml. flask fitted with a stirrer and thermometer was placed 50.0 g. (0.608 mole) of biallyl, 100 g. (36 g. of HCl, 1.0 mole) of concentrated hydrochloric acid, and 1.34 g. of zinc chloride. This mixture was stirred at room temperature for 40 hr. The organic layer was then separated, dried over anhydrous potassium carbonate, and distilled. Most of the product was unchanged biallyl. The fraction boiling at 120–123° (5.14 g.) was collected and had a refractive index of n^{25}D 1.4289 (lit.[8] b.p. 121–125°, n^{25}D 1.4279).

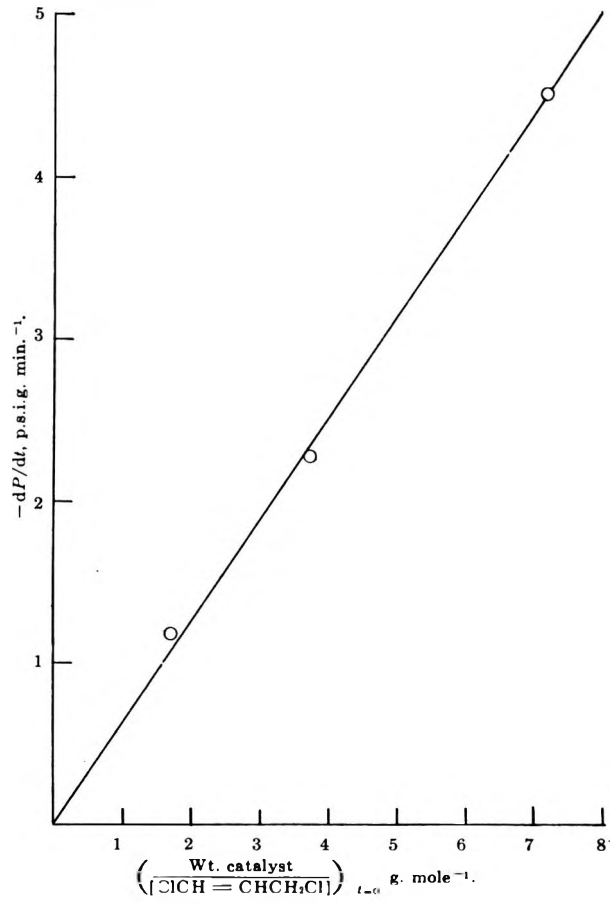


Fig. 2.—Effect of initial catalyst to olefin ratio on rate of hydrogenation of 1,3-dichloropropene.

Hydrogenation of 5-Chlorohexene-1.—To a 110-ml. stainless steel bomb was charged 5.14 g. (0.0433 mole) of 5-chlorohexene-1, 15.4 g. of cyclohexane, and 0.50 g. of catalyst (5% Rh on alumina powder). The bomb and contents were heated to 52° and pressurized to 500 lb./in.^{2} with hydrogen. After rocking and heating at this temperature for 70 min. the bomb was cooled and the gaseous portion vented through two scrubbers containing 1.0 *N* sodium hydroxide solution. A precipitate was not obtained when silver nitrate solution was added to an acidified portion of the scrubber solution. From the bomb was obtained 19.5 g. of product solution. After removal of the cyclohexane by distillation two fractions were collected. The first boiled at 80–120° (5.0 g., n^{25}D 1.4170) and was shown by analysis to be 79% 2-chlorohexane. The second boiled at 120–125° (1.10 g., n^{25}D 1.4153). Literature[9] values for 2-chlorohexane are b.p. 122.5° (754 mm.) and n^{25}D 1.4142. The yield of 2-chlorohexane was 96.9%.

Attempted *cis–trans* Isomerization of 1,3-Dichloropropene over 5% Rh on Alumina Powder in Absence of Hydrogen.—Into a flask fitted with a reflux condenser was placed 20.0 g. of *cis*-rich 1,3-dichloropropene (area % of *cis* and *trans* by v.p.c., 87.4% *cis* and 12.6% *trans*) and 2.00 g. of 5% Rh on alumina powder. The mixture was heated at reflux temperature (about 105°) for 160 min. After this time analysis of the mixture revealed 87.7% *cis* isomer and 12.3% *trans* isomer.

***cis–trans* Isomerization of 1,3-Dichloropropene over 5% Rh on Alumina Powder in Presence of Hydrogen.**—To a Paar apparatus was charged 24.4 g. (0.220 mole) of *cis*-rich 1,3-dichloropropene (analysis by v.p.c., 74.4% *cis* and 25.6% *trans*) and 2.00 g. of 5% Rh on alumina powder. The vessel was pressurized to 50 lb./in.^{2}

(7) E. H. Huntress, "Organic Chlorine Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 653.

(8) F. Cortese, *J. Am. Chem. Soc.*, **52**, 1519 (1930).

(9) E. H. Huntress, "Organic Chlorine Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 1066.

with hydrogen and after about 30 min. shaking at room temperature the pressure had dropped to 47 lb./in.^{2}. The hydrogenation was stopped and analysis of the mixture revealed that 25.0% of the 1,3-dichloropropene had been converted and the remaining 1,3-dichloropropene was 73.0% *cis* and 27.0% *trans*. This corresponds to 1.9 ± 0.4% isomerization of *cis* to *trans* isomer in the unchanged 1,3-dichloropropene.

Acknowledgment.—The authors wish to thank Mr. S. A. Sims for able assistance.

The Microbial Hydroxylation of Tomatidine[1a,b]

YOSHIO SATO AND SHOHEI HAYAKAWA[2]

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare, Bethesda 14, Maryland

Received August 7, 1963

The steroidal alkaloid tomatidine has been hydroxylated by the fungus *Helicostylum piriforme* to yield 7α,11α-dihydroxytomatidine, 7α-hydroxytomatidine, and 9α-hydroxytomatidine. The proofs for their structures are discussed.

With the successful microbial hydroxylation of the steroidal alkaloid solasodine,[3a] it became of interest to study the effect of the fungus *Helicostylum piriforme* on tomatidine (I), the 5,6-dihydro C-25 epimer of solasodine. We previously had observed[3b] that the reduction of the double bond in the steroidal sapogenin, diosgenin, to the 5,6-dihydro derivative, tigogenin, had hindered its hydroxylation entirely.

With tomatidine, however, the hydroxylation proceeded smoothly to give the triol, 7α,11α-dihydroxytomatidine (IIa), in fairly good yields (25–30%). A lesser amount (*ca.* 5%) of the monohydroxylated compound, 7α-hydroxytomatidine (IIB), and a very small amount (*ca.* 0.5%) of 9α-hydroxytomatidine (IIC) also were isolated.

The assignment of a 3β,7α,11α-triol formulation to IIA is based on the degradation of the triol IIA to the known allopregnane derivatives, allopregnane-3β,7α,-11α-triol-20-one triacetate (Va) and allopregnane-3,7,11,20-tetrone (Vc). For the removal of the side chain,[4] the amorphous tetraacetate (IIa) was isomerized with boiling glacial acetic acid to a resinous pseudo-derivative (IIIa) which could not be resolved by alumina chromatography. The reaction product, without further efforts at purification, was oxidized with chromic acid and the acyloxy side chain removed by treatment with boiling acetic acid.[5] Although the products crystallized at this stage, chromatography over alumina failed to resolve them into homogeneous components. The mixture, therefore, was hydrogenated in ethyl acetate over palladium–barium sulfate, whereupon an absorption of about 1.6 moles of hydrogen occurred, and the product became resolvable through alumina chromatography. The purified component agreed in properties with an authentic specimen of 3β,7α,11α-trihydroxyallopregnan-20-one triacetate[6] (Va). For further confirmation, the triol Vb also was oxidized to the known allopregnane-3,7,11,20-tetrone[6] (Vc). In the course of the separation of Va through chromatography, paper chromatographic spot tests of the various fractions indicated the presence of a second component concentrated mainly in the mother liquors after removal of Va. Accordingly the mother liquors were combined, hydrolyzed with base, and chromatographed over Florisil. The crystalline dihydroxyallopregnane (Vd) thus obtained was then oxidized to the known allopregnane-3,11,20-trione[6] (Ve). Apparently, the 7α-hydroxyl moiety in the triol IIA had partially dehydrated during the course of the degradation.

The structure of the diol IIB also was determined by its degradative conversion into the known 3β-acetoxyallopregnane-7,20-dione[7] (Vf) and into 3β,7α-dihydroxyallopregnane-20-one (Vg). For the conversion into Vf, the crude acetate IIb (acetic anhydride–pyridine, 15 hr. at room temperature) was isomerized as usual with glacial acetic acid and the pseudoproduct chromatographed over alumina to yield O,N-diacetylhydroxypseudo- (IIIb) and O,O,N-triacetylpseudotomatidine (IIIc). The 7α-hydroxyl is not completely acetylated under these conditions of acetylation.[8] Barton and Laws[9] have observed the same phenomenon in regard to the acetylation of ergost-22-ene-3β,7α-diol. The subsequent oxidation and acid hydrolysis (acetic acid) of IIIb and the reduction of the resultant 16-dehydro derivative (IVa) affords the known 3β-acetoxyallopregnane-7,20-dione[7] (Vf). For conversion of IIB into 3β,7α-dihydroxyallopregnan-20-one (Vg), the acetylation is conducted under more vigorous conditions (acetic anhydride–pyridine, 1 hr. at steam-bath temperature) to the O,O,N-triacetyl derivative (IIb) and submitted to the usual degradative procedure (IIb → IIIc → IVb → Vh).

The resistance of IIB toward acetylation, its relationship to the triol IIA, and its molecular rotation data[10] (ΔMD −39) all support our assignment of a 7α configuration.

The structure of compound IIC was unequivocally established as 9α-hydroxytomatidine by its degradative conversion in the usual manner (IIc → IIId →

(1) (a) In remembrance of the late Dr. Erich Mosettig of this Institute; (b) a preliminary account of portions of this work was published in *J. Org. Chem.*, **26**, 4181 (1961).

(2) Visiting Scientist (1960–1962), National Institutes of Health.

(3) (a) Y. Sata and S. Hayakawa, *J. Org. Chem.*, **28**, 2739 (1963); (b) S. Hayakawa and Y. Sato, *ibid.*, **28**, 2742 (1963).

(4) Y. Sato, N. Ikekawa and E. Mosettig, *ibid.*, **24**, 893 (1959).

(5) A. F. B. Cameron, K. M. Evans, J. C. Hamlet, J. S. Hunt, P. C. Jones, and A. G. Long, *J. Chem. Soc.*, 2807 (1955).

(6) C. Djerassi, O. Mancera, J. Romo, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 3505 (1953). We thank Dr. P. G. Holton of Syntex, S.A., Mexico, for providing us with an authentic specimen of the triacetate.

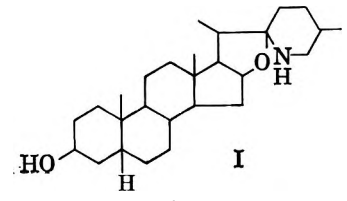
(7) W. Klyne, *J. Chem. Soc.*, 3449 (1951).

(8) L. F. Fieser, J. E. Herz, M. W. Klohs, M. A. Romero, and T. Utne, *J. Am. Chem. Soc.*, **74**, 3309 (1952).

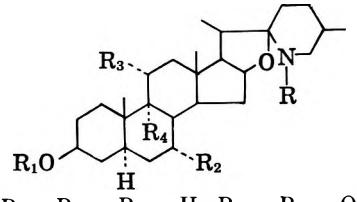
(9) D. H. R. Barton and G. F. Laws, *J. Chem. Soc.*, 52 (1954).

(10) ΔMD = MD (7β-hydroxytomatidine) − MD (tomatidine) = −39. Cited values for 7α-OH, −59, and for the 7β-OH, +110. From L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 179.

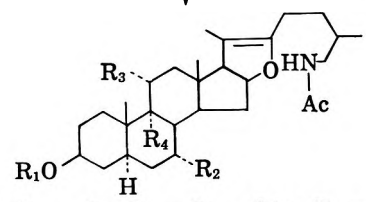
IVc) to 3β,9α-dihydroxyallopregnan-20-one acetate (Vj), the authentic specimen of which was obtained from the catalytic reduction of 5-pregnene-3β,9α-dihydroxy-20-one acetate.[11]



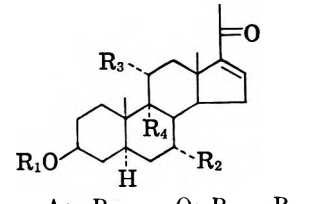
I



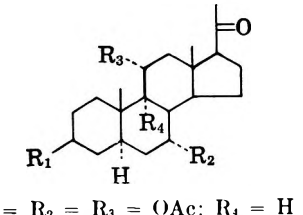
IIA, R = R_1 = R_4 = H; R_2 = R_3 = OH
B, R = R_1 = R_3 = R_4 = H; R_2 = OH
C, R = R_1 = R_2 = R_3 = H; R_4 = OH
a, R = R_1 = Ac; R_2 = R_3 = OAc; R_4 = H
b, R = R_1 = Ac; R_2 = OAc; R_3 = R_4 = H
c, R = R_1 = Ac; R_4 = OH; R_2 = R_3 = H



IIIa, R_1 = Ac; R_2 = R_3 = OAc; R_4 = H
b, R_1 = Ac; R_2 = OH; R_3 = R_4 = H
c, R_1 = Ac; R_2 = OAc; R_3 = R_4 = H
d, R_1 = Ac; R_4 = OH; R_2 = R_3 = H



IVa, R_1 = Ac; R_2 = =O; R_3 = R_4 = H
b, R_1 = H; R_2 = OH; R_3 = R_4 = H
c, R_1 = Ac; R_4 = OH; R_2 = R_3 = H
d, R_1 = Ac; R_2 = R_3 = OAc; R_4 = H
e, R_1 = H; R_4 = OH; R_2 = R_3 = H



Va, R_1 = R_2 = R_3 = OAc; R_4 = H
b, R_1 = R_2 = R_3 = OH; R_4 = H
c, R_1 = R_2 = R_3 = =O; R_4 = H
d, R_1 = R_3 = OH; R_2 = R_4 = H
e, R_1 = R_3 = =O; R_2 = R_4 = H
f, R_1 = OAc; R_2 = =O; R_3 = R_4 = H
g, R_1 = R_2 = OH; R_3 = R_4 = H
h, R_1 = H; R_2 = OH; R_3 = R_4 = H
i, R_1 = R_3 = OAc; R_2 = R_4 = H
j, R_1 = OAc; R_4 = OH; R_2 = R_3 = H

(11) Obtained from the degradation of 9α-hydroxysolasodine; see ref. 3a.

It is of some interest to note that 7α-hydroxylation of steroids in the C-5 allo series is an unique occurrence previously unencountered in this field.

The steroidal alkaloids in recent years have achieved some significance as starting material for the production of biologically active steroid hormones. The hydroxylation of these alkaloids enhances their utility.

Experimental[12]

Fermentation.—The medium was prepared by mixing 20 g. of peptone, 3 g. of corn steep liquor, 50 g. of technical dextrose, and 1000 ml. of tap water. Two hundred-milliliter batches of the sterile medium (pH 4.5) were innoculated with *Helicostylum piriforme* (A.T.C.C. 8992) and agitated for 2 days at 28° on a platform shaker. Forty milligrams of tomatidine in 2 ml. of ethanol was then introduced into each flask and shaking continued for 24 hr.

Isolation of 7α,11α-Dihydroxytomatidine (IIA), 7α-Hydroxytomatidine (IIB), and 9α-Hydroxytomatidine (IIC).—The contents of the flasks were filtered through a bed of Celite to remove the mycelium; the filtrate, after being made basic with alkali, was extracted with chloroform. The extract from a ten-flask run yielded about 420 mg. of crude residue. It was triturated with acetone to afford a crude batch of IIA (yield, 25–30%) which was repeatedly and alternately recrystallized from methanol and ethanol to give rods of 7α,11α-dihydroxytomatidine, m.p. 266–270° dec., $[\alpha]^{20}D$ +23.3° (C_2H_5OH); λ_{max}^{Nujol} 2.94 and 3.33 μ (OH and NH).

Anal. Calcd. for $C_{27}H_{45}O_4N$: C, 72.44; H, 10.13. Found: C, 72.42; H, 10.43.

The mother liquors, after removal of IIA, were combined, evaporated to dryness, and chromatographed over alumina (Woelm neutral, activity I) with the following solvent mixtures: 0.1, 0.2, 0.3, 0.4, 0.5, 1, and 5% methanol in ether. Each fraction was tested by paper chromatography using 30% propylene glycol as the stationary phase and a mixture of toluene–dioxane (7:3 v./v.) as the mobile phase. The compounds were detected by spraying the paper first with an 1% ethanolic cinnamic aldehyde solution, followed by a saturated solution of antimony trichloride in nitrobenzene, and warming over a hot plate. Fractions which gave the same coloration (reddish gray) and having approximately the same R_f values were collected (0.2 ~ 0.3% methanol in ether eluates). The compound, 9α-hydroxytomatidine (0.5%), crystallized as plates, m.p. 188–191°, from acetone. Recrystallization from methanol raised the melting point to 192–195°, $[\alpha]^{20}D$ +2.3° ($CHCl_3$); $\lambda_{max}^{CHCl_3}$ 2.78 and 2.93 μ (OH and NH).

Anal. Calcd. for $C_{27}H_{45}O_3N$: C, 75.13; H, 10.51. Found: C, 74.49; H, 10.44.

Fractions eluted with 0.5 ~1% methanol in ether in the aforementioned chromatogram afforded rods of 7α-hydroxytomatidine (IIB) from methanol. A recrystallized sample from methanol melted at 243–247° dec., $[\alpha]^{20}D$ −3.5° ($CHCl_3$); $\lambda_{max}^{CHCl_3}$ 2.78 and 2.93 μ (OH and NH).

Anal. Calcd. for $C_{27}H_{45}O_3N$: C, 75.13; H, 10.51. Found: C, 75.22; H, 10.68.

O,O,O,N-Tetraacetate of 7α,11α-Dihydroxytomatidine (IIa).—A mixture of 455 mg. of 7α,11α-dihydroxytomatidine, 5 ml. of pyridine, and 2.5 ml. of acetic anhydride was warmed on the oil bath at 70–80° for 20 min. until the solution became clear. It was then allowed to stand at room temperature overnight. After the addition of ice–water, the precipitate was filtered, washed with water, and dried. The resulting amorphous powder (626 mg.) was then chromatographed over alumina (Woelm neutral, activity I) but could not be induced to crystallize. The infrared spectrum of the acetate failed to show any hydroxyl absorption. The amorphous acetate possessed a rotation of +28° in chloroform.

Anal. Calcd. for $C_{35}H_{53}O_8N$: C, 68.26; H, 8.68. Found: C, 68.09; H, 8.91.

Isomerization of IIa to IIIa.—The aforementioned amorphous acetate (459 mg.) was added in small portions to 10 ml. of boiling

(12) Melting points were taken on the Kofler block and are uncorrected. Microanalyses were performed by the Institute's Analytical Service Laboratory under the direction of Mr. Harold G. McCann. The infrared spectra were taken on the Model 21 Perkin-Elmer infrared spectrometer by Mr. H. K. Miller and Mrs. Anne H. Wright of this laboratory.

acetic acid and refluxed for 15 min. The resinous residue, after removal of the solvent, was submitted to alumina chromatography but failed to crystallize.

16-Allopregnene-3β,7α,11α-triol-20-one Acetate (IVd).—A solution of chromic anhydride (210 mg.) in 10 ml. of 80% acetic acid was added dropwise over a period of 15 min. to a stirred solution of IIIa (534 mg.) in 30 ml. of acetic acid with attendant cooling (15°) of the reaction mixture. After the solution had been stirred for 1 hr. at room temperature, water (*ca.* 100 ml.), a small amount of sodium sulfite, and excess salt were added and the saturated mixture extracted with a solution of chloroform–ether (1:9). The residue from the extraction was dissolved in 50 ml. of acetic acid and refluxed for 2 hr. After removal of the acetic acid, the resulting semicrystalline residue crystallized from ether to give 169 mg. of plates, m.p. 180–225°, $[\alpha]^{20}D$ +43.8° ($CHCl_3$); $\lambda_{max}^{C_2H_5OH}$ 236 mμ (log ε 3.98); $\lambda_{max}^{CHCl_3}$ 5.77 (OAc), 5.99 and 6.25 μ (Δ16-20-one). Several attempts at purification proved unsuccessful.

Allopregnane-3β,7α,11α-triol-20-one (Vb) and Its Acetate (Va), Allopregnane-3β,11α-diol-20-one (Vd) and Its Acetate (Vi), and Allopregnane-3,11,20-trione (Ve).—Compound IVd (97.4 mg.) was dissolved in 30 ml. of ethyl acetate with 200 mg. of 10% palladium on barium sulfate and hydrogenated at atmospheric pressure and room temperature. The hydrogen uptake came to about 1.6 moles before it ceased. The product (57.5 mg.) crystallized from ether–pentane to give prisms of m.p. 165–176°. Chromatography over alumina (Woelm neutral, activity I) afforded prisms of m.p. 177–180°, $[\alpha]^{20}D$ +53.4° ($CHCl_3$); $\lambda_{max}^{CS_2}$ 5.75 (OAc), 5.84 (20-ketone). The compound agreed in properties with an authentic specimen of Va.[6]

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.77; H, 8.50.

The alcohol Vb was prepared from the acetate Va by treatment with 1% methanolic potassium hydroxide. It crystallized as prisms from methanol–ether, m.p. 261–263°, $[\alpha]^{20}D$ +88.5° (C_2H_5OH); λ_{max}^{Nujol} 2.76 and 3.01 (OH), 5.72 μ (20-ketone).

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.73; H, 10.11.

The mother liquors, after removal of Va, were combined, hydrolyzed with 1% methanolic potassium hydroxide, and extracted with chloroform. The residue from the extraction was submitted to Florisil chromatography and the fractions eluted with 10% acetone in chloroform crystallized from ether. It yielded rods (2% based on IVd) of Vd, m.p. 186–191°; $\lambda_{max}^{CHCl_3}$ 2.76 and 2.89 (OH), 5.85 μ (20-ketone).

The allopregnanolone (Vd, 16.4 mg.) was acetylated with acetic anhydride–pyridine (1 hr. on steam bath). The diacetate Vi crystallized from acetone–pentane to give 6.4 mg. of crystals of m.p. 164–168°. The compound was identical in properties with an authentic specimen of Vi.[13,14]

A small sample of crude Vd was oxidized with chromic anhydride in acetic acid; the trione Ve crystallized from acetone and then from methanol as plates, m.p. 209–213°. The infrared spectrum of the trione was indistinguishable from an authentic compound of Ve.[6]

Allopregnane-3,7,11,20-tetrone (Vc).—Vb (40 mg.) in 1.5 ml. of acetic acid was oxidized with a solution of 30 mg. of chromium trioxide in 0.3 ml. of 80% acetic acid. Crystallization of the reaction product from acetone–pentane gave 26.9 mg. of plates, m.p. 243–246°, $[\alpha]^{20}D$ +52.5° ($CHCl_3$); $\lambda_{max}^{CHCl_3}$ 5.83 μ (ketone). The tetrone agreed in properties (melting point, mixture melting point, and infrared spectrum) with an authentic sample.[6]

3β-Acetoxyallopregnane-7,20-dione (Vf).—For conversion of IIB into Vf, the acetylation of IIB was conducted at room temperature for 15 hr. and the product without separation submitted to isomerization. At this stage, alumina chromatography (Woelm neutral, activity I) readily separated the products into O,O,N-triacetylpseudotomatidine (IIIc) and hydroxy-O,N-diacetylpseudotomatidine (IIIb). The former was eluted with 0.5% methanol in ether and the latter with 1% methanol in ether. Thus from the acetylation and isomerization of 191 mg. of IIB, 40 mg. of the triacetylpseudoderivative (IIIc) and 110 mg. of the hydroxy diacetylpseudoderivative (IIIb) were obtained. The latter (IIIb) crystallized as rods from aqueous methanol and melted at 88–91°.

Anal. Calcd. for $C_{31}H_{49}O_5N$: C, 72.19; H, 9.58. Found: C, 72.15; H, 9.83.

The pseudoderivative IIIb was oxidized and hydrolyzed in acetic acid in the manner described for IIIa → IVd. The 16-dehydroallopregnan-3β-ol-7,20-dione acetate (IVa) crystallized as plates from aqueous methanol, m.p. 205–208.5°, $[\alpha]^{20}D$ −56.9° ($CHCl_3$).

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.35; H, 8.67.

The 16-dehydro derivative (IVa, 20 mg.) was reduced over 42 mg. of 10% palladium–barium sulfate. The product crystallized as needles from ether–hexane, m.p. 168–170°. It agreed in melting point, mixture melting point, and infrared spectrum with an authentic sample of Vf.[7]

O,O,N-Triacetate of 7α-Hydroxytomatidine (IIb).—7α-Hydroxytomatidine (500 mg.) was dissolved in a mixture of 10 ml. of pyridine and 5 ml. of acetic anhydride and warmed for 1 hr. on the steam bath. The crude resinous acetate (579 mg.) was chromatographed on alumina (Woelm neutral, activity III) and the fractions eluted with hexane and 10% benzene in hexane. IIb was crystallized from methanol–water and then from acetone–pentane to yield plates (194 mg.) of m.p. 186–188°, $[\alpha]^{20}D$ −29.8° ($CHCl_3$); $\lambda_{max}^{CHCl_3}$ 5.80 (OAc), 6.10 μ (NAc). A second crop (97 mg.) of crystals, m.p. 183–187°, also was obtained.

Anal. Calcd. for $C_{33}H_{51}O_6N$: C, 71.06; H, 9.22. Found: C, 70.77; H, 9.47.

16-Allopregnane-3β,7α-diol-20-one (IVb).—The aforementioned acetate (IIb, 184 mg.) was isomerized in 7 ml. of glacial acetic acid in the manner described previously for the preparation of IIIa. It crystallized from acetone–pentane to afford 139 mg. of needles of the so-called O,O,N-triacetylpseudotomatidine (IIIc) of m.p. 169–171°, $[\alpha]^{20}D$ −48.7° ($CHCl_3$); $\lambda_{max}^{CHCl_3}$ 2.89 (NH), 5.79 (OAc), 5.99 and 6.60 μ (HNAc).

Anal. Calcd. for $C_{33}H_{51}O_6N$: C, 71.06; H, 9.22. Found: C, 71.25; H, 9.51.

The isomerized product (IIIc, 125 mg.) was dissolved in 7 ml. of acetic acid and oxidized with 50 mg. of chromic anhydride in 1 ml. of 80% acetic acid. The oxidation product (see IVd for experimental details) was refluxed for 1.5 hr. in a mixture of 4.5 ml. of *t*-butyl alcohol, 0.5 g. of potassium hydroxide, and 0.5 ml. of water. The resinous reaction product (71.3 mg.) was submitted to Florisil chromatography. The 5% acetone in dichloromethane eluants afforded 18.3 mg. of rods of IVb from acetone which melted at 245–251°, $[\alpha]^{20}D$ +25.7° (C_2H_5OH); λ_{max}^{Nujol} 2.91 (OH), 6.04 and 6.31 μ (Δ16-20-one).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.05; H, 9.93.

Allopregnane-3β,7α-diol-20-one (Vg).—The aforementioned crude 16-dehydro derivative (57 mg.) was dissolved in 20 ml. of ethyl acetate and reduced in the presence of 21 mg. of 5% palladium on carbon. The crude hydrogenated product was chromatographed over Florisil and the fraction eluted with 5% acetone in chloroform crystallized from acetone as prisms, m.p. 208–211°, $[\alpha]^{20}D$ +83.6° (C_2H_5OH).

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.47; H, 10.55.

9α-Hydroxytomatidine O,N-Diacetate (IIc).—IIC (545 mg.) was dissolved in a mixture of 10 ml. of pyridine and 5 ml. of acetic anhydride and allowed to stand overnight at room temperature. The crude acetate (635 mg.) was chromatographed over alumina (Woelm neutral, activity I), and the 40% ether in benzene and 0.2% methanol in ether eluates worked up to yield 385 mg. of plates, m.p. 188–201°. Thin layer chromatography (silica gel G, cyclohexane–ethyl acetate, 1:1 v./v.) indicated the presence of a contaminant less polar than the main product. Repeated crystallizations from methanol–ether and then from methanol raised the melting point to 205–209°; the impurity could not be completely eliminated. Compound IIc showed a specific rotation of +4.2° ($CHCl_3$) and possessed infrared absorption bands in carbon disulfide at 2.77 (OH), 5.75 (OAc), and 6.01 μ (N–Ac).

Anal. Calcd. for $C_{31}H_{49}O_5N$: C, 72.19; H, 9.58. Found: C, 72.29; H, 9.78.

16-Allopregnene-3β,9α-diol-20-one (IVc).—IIc (221 mg.) in 5 ml. of acetic acid was isomerized (IIId) and oxidized in 12 ml. of acetic acid with 88 mg. of chromic anhydride in 4.5 ml. of 80% acetic acid in the manner described previously for IVd. The oxidized product (216 mg.) was then hydrolyzed for 2 hr. with a mixture of 9 ml. of *t*-butyl alcohol, 1 g. of potassium hydroxide,

(13) C. Djerassi, E. Batres, J. Romo, and G. Rosenkranz, *J. Am. Chem. Soc.*, **74**, 3634 (1952). We thank Dr. O. Halpern of Syntex, S.A., Mexico, for providing us with 5,16-pregnadiene-3β-11α-diol-20-one diacetate[14] from which Vi was prepared according to their directions.

(14) O. Halpern and C. Djerassi, *ibid.*, **81**, 439 (1959).

and 1 ml. of water. The resulting crude product (98 mg.) was submitted to chromatography over Florisil; the fractions eluted by 5% acetone in chloroform were crystallized from acetone–pentane and then from methanol to yield 33 mg. of prisms, m.p. 206–209°, $[\alpha]^{20}D$ +31.6° ($CHCl_3$); $\lambda_{max}^{CHCl_3}$ 2.79 and 2.91 (OH), 6.02 and 6.29 μ (Δ^{16}-20-one).

The acetate IVc of IVe, which was prepared in the usual manner, crystallized as needles from benzene–pentane, m.p. 181–184°, $[\alpha]^{20}D$ −19.5° ($CHCl_3$); λ_{max}^{Nujol} 2.86 (OH), 5.79 (OAc), 6.01 and 6.29 μ(Δ^{16}-20-one).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.57; H, 9.33.

Allopregnane-3β,9α-diol-20-one Acetate (Vj).—The aforementioned 16-dehydro derivative (IVc, 36 mg.) was dissolved in 4 ml. of ethyl acetate with 32 mg. of 10% palladium–barium sulfate and hydrogenated at atmospheric pressure. Chromatography of the reduction product over alumina (Woelm neutral, activity II) and elution with benzene and 10% ether in benzene afforded a compound (29 mg.) which crystallized as plates, m.p. 187–191°, $[\alpha]^{20}D$ +58.2° ($CHCl_3$); $\lambda_{max}^{CS_2}$ 2.78 and 2.83 (OH), 5.76 (OAc), 5.85 μ (20-ketone).

The substance was identical in properties (melting point, mixture melting point, and infrared spectrum) with an authentic specimen of Vj prepared from 9α-hydroxysolasodine.[3a]

Reactions of Mercaptoamines. II. With Chloroformates and Chlorothiolformates[1]

ARTHUR F. FERRIS AND BEVERLY A. SCHUTZ

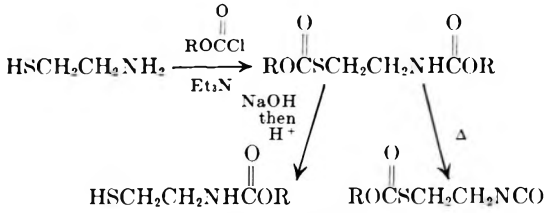
Midwest Research Institute, Kansas City 10, Missouri

Received July 8, 1963

2-Mercaptoethylamine reacted with alkyl chloroformates and chlorothiolformates to give the N,S-disubstituted products, which on basic hydrolysis gave 2-(mercaptoethyl)carbamates in the first case and regenerated 2-mercaptoethylamine in the second. On pyrolysis or treatment with silver nitrate, the S-alkyl N-[2-(alkyldithiolcarbonato)ethyl]thiolcarbamates gave the 2-(alkyldithiolcarbonato)ethyl isocyanates. These reacted with amines to give the corresponding ureas, hydrolyzable to 2-mercaptoethyl ureas.

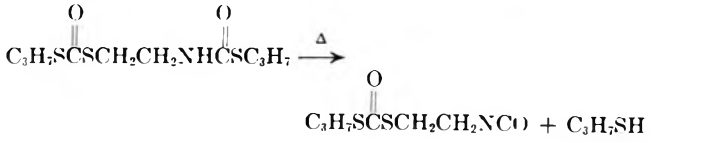
In continuation of studies of the reaction of mercaptoamines with compounds potentially capable of reacting at both the mercapto and amino functions,[2] the reaction of 2-mercaptoethylamine (MEA) with chloroformates and chlorothiolformates has been examined.

In the presence of triethylamine as an acid acceptor, solutions of 2-mercaptoethylamine in dry acetonitrile reacted with ethyl, *n*-propyl, *n*-butyl, and *n*-hexyl chloroformates to give good yields of the N,S-disubstituted products, the O-alkyl N-[2-(alkylthiolcarbonato)ethyl]carbamates. The ethyl and *n*-propyl



compounds could be distilled at reduced pressure, but the higher molecular weight compounds underwent partial pyrolysis when distillation was attempted, giving products with isocyanate absorption in their infrared spectra. The critical temperature for the onset of pyrolysis appeared to be about 150°. All the N,S-disubstituted compounds were hydrolyzed readily at the thiolcarbonato function by sodium hydroxide in aqueous alcohol to give the 2-(mercaptoethyl)carbamates in good yield. The properties of the N,S-disubstituted compounds are reported in Table I and those of the 2-(mercaptoethyl)carbamates in Table II.

Alkyl chlorothiolformates reacted with 2-mercaptoethylamine in the same manner as the chloroformates to give N,S-disubstituted products (Table I). The compounds from methyl and ethyl chlorothiolformate were solids which could be purified by recrystallization, but the product from *n*-propyl chlorothiolformate was a liquid. Like the higher molecular weight chloroformate products, it underwent partial pyrolysis when distillation was attempted. Several repetitions of the distillation completed the pyrolysis, and eventually pure 2-(*n*-propyldithiolcarbonato)ethyl isocyanate was obtained in 30% yield. A number of attempts were



made to hydrolyze the S-alkyl N-[2-(alkyldithiolcarbonato)ethyl]thiolcarbamates to the corresponding 2-(mercaptoethyl)thiolcarbamates, but hydrolysis occurred as readily at the thiolcarbamate function as at the thiolcarbonato function, and it proved impossible to isolate the half-hydrolyzed products.

It is readily apparent that a convenient intermediate for the preparation of 2-mercaptoethylureas would be an S-substituted 2-mercaptoethyl isocyanate wherein the mercapto function was covered by a group easily removed after urea formation. As noted before, pyrolysis of the S-alkyl N-[2-(alkyldithiolcarbonato)ethyl]thiolcarbamates provides one route to such an intermediate. A more convenient route is offered by the metal ion-assisted mercaptan elimination reaction.[3] Treatment of S-methyl N-[2-(methyldithiolcarbonato)ethyl]thiolcarbamate with a solution of silver nitrate in acetonitrile gave a solution of 2-(methyldithiolcarbonato)ethyl isocyanate which reacted with water to give 1,3-bis[2-(methyldithiolcarbonato)ethyl]urea and with amines to give 2-(methyldithiolcarbonato)-ethylureas (Table III). Successful reaction was obtained with aniline, *t*-butylamine, *n*-octylamine, morpholine, and diethyl iminodiacetate. All the products from primary amines, including 1,3-bis[2-(methyldithiolcarbonato)ethyl]urea, underwent basis hydrolysis to give the corresponding 2-mercaptoethylureas. The secondary amine products were completely de-

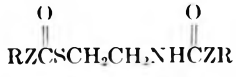
(1) This work was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Contract No. DA-49-193-MD-2174.

(2) Previous paper in this series: A. F. Ferris and B. A. Schutz, *J. Org. Chem.*, **28**, 3140 (1963).

(3) A. F. Ferris and B. A. Schutz, *ibid.*, **28**, 71 (1963).

TABLE I

ALKYL N-[2-(ALKYLTHIOL- AND DITHIOLCARBONATO)ETHYL]CARBAMATES AND THIOLCARBAMATES

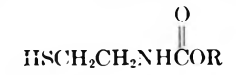


R	Z	Yield, %	M.p. or b.p. (mm.), °C.	Calcd., % C	H	N	S	Found, % C	H	N	S
C_2H_5	O	83	109–110 (0.11)								
			30	43.42	6.83	6.33	14.49	43.21	6.91	6.46	14.32
n-C_3H_7	O	73	140–141 (0.21)[a]	48.17	7.68	5.62	12.86	48.27	7.49	5.76	13.04
CH_3	S	84	44–46	31.98	4.92	6.22	42.68	32.13	5.06	6.13	42.90
C_2H_5	S	65	58–59	37.92	5.97	5.53	37.96	37.86	5.85	5.45	37.75

[a] $n^{27}D$ 1.4729.

TABLE II

ALKYL N-2-(MERCAPTOETHYL)CARBAMATES

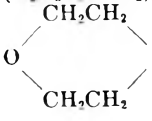


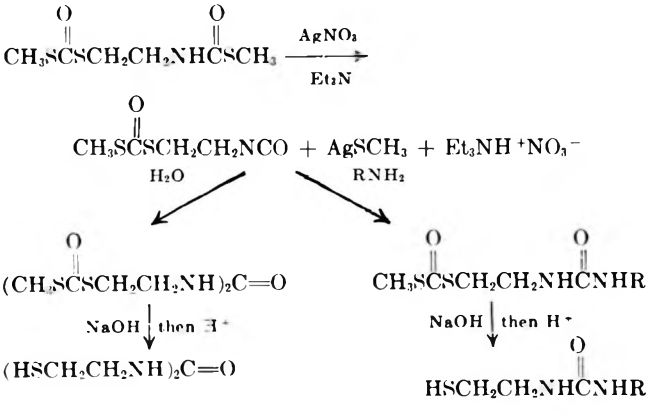
R	Yield, %	B.p. (mm.), °C.	$n^{27}D$	Calcd., % C	H	N	S	Found, % C	H	N	S
C_2H_5[a]	84	75–77 (0.05)	1.4812	40.25	7.43	9.39	21.49	40.22	7.17	9.60	21.44
n-C_3H_7	89	79–80 (0.18)	1.4789	44.15	8.03	8.55	19.64	44.22	8.30	8.61	19.92
n-C_4H_9	83	94 (0.21)	1.4766	47.43	8.53	7.90	18.09	47.24	8.37	7.98	18.18
n-C_6H_{13}	57	105 (0.11)	1.4748	52.65	9.33	6.82	15.62	52.50	9.37	6.92	15.77

[a] This compound was reported by K. Schimmelschmidt, H. Hoffmann, and E. Mundlos, *Ber.*, **96**, 38 (1963); b.p. 96–98° (0.6 mm.).

TABLE III

1-ALKYL OR ARYL 3-[2-(METHYLDITHIOLCARBONATO)ETHYL]UREAS

RR′	Yield, %	M.p., °C.	Calcd., % C	H	N	S	Found, % C	H	N	S
	81	94.5–96	32.91	4.91	8.53	39.04	33.04	5.01	8.67	39.13
t-C_4H_9—, H	77	115–116	43.17	7.25	11.19	25.61	43.25	7.16	11.01	25.79
n-C_8H_{17}—, H	73	76.5–78	50.94	8.55	9.14	20.92	50.71	8.60	8.98	21.04
C_6H_5—, H	81	130.5–132	48.86	5.22	10.36	23.72	48.99	5.31	10.56	23.91
$(C_2H_5O_2CCH_2)_2$—	74	125–127	42.61	6.05	7.65	17.50	42.84	5.82	7.66	17.66
	60	119–120.5	40.89	6.10	10.60	24.25	41.01	6.23	10.67	24.08



composed by aqueous alcoholic sodium hydroxide, and no mercaptoethylureas could be isolated.

Though the literature[4,5] indicates that reaction of isocyanates with carboxylic acids can be used to prepare amides, reaction of 2-(methyldithiolcarbonato)-ethyl isocyanate with acids was not in general a useful route to N-(2-mercaptoethyl)amides. Success was achieved only in one case. Phenylacetic acid reacted with the isocyanate to give a liquid product which was hydrolyzed to N-(2-mercaptoethyl)phenylacetamide, a liquid identified as the 2,4-dinitrophenyl sulfide. Over-all yield was 32%. With other acids the isocyanate either failed to react entirely or reacted with adventitous water to give the bisurea.

Experimental[6]

O-*n*-Propyl N-[2-(*n*-Propylthiolcarbonato)ethyl]carbamate.—To a suspension of 11.4 g. (0.10 mole) of 2-mercaptoethylamine hydrochloride in 50 ml. of dry acetonitrile was added 30.4 g. (0.30 mole) of triethylamine. A new solid came out of solution. The resulting suspension was added in portions, with stirring and cooling, to a solution of 24.4 g. (0.20 mole) of *n*-propyl chloroformate. The temperature was kept below 60°, and when the addition was complete, the mixture was allowed to stand for 1 hr. It was then poured into ice–water and an oil separated. The oil was extracted into three 50-ml. portions of ether, and the solution was dried over magnesium sulfate. Evaporation of the ether left 18.2 g. (73%) of crude O-*n*-propyl N-[2-(*n*-propylthiolcarbonato)ethyl]carbamate. Distillation under reduced pressure gave an analytical sample, b.p. 140–141° (0.21 m.), $n^{27}D$ 1.4729.

Anal. Calcd. for $C_{10}H_{19}O_4NS$: C, 48.17; H, 7.68; N, 5.62; S, 12.86. Found: C, 48.27; H, 7.49; N, 5.76; S, 13.04.

(4) J. von Braun, *Ber.*, **42**, 2743 (1909).

(5) C. L. Agre, G. Dinga, and R. Pflaum, *J. Org. Chem.*, **20**, 695 (1955).

(6) Melting points are corrected and boiling points are uncorrected. Microanalyses by Galbraith Laboratories, Knoxville, Tenn.

O-*n*-Propyl N-(2-Mercaptoethyl)carbamate.—To a solution of 16.5 g. (0.07 mole) of O-*n*-propyl N-[2-(*n*-propylthiolcarbonato)-ethyl]carbamate in 50 ml. of 95% ethanol was added a solution of 13.3 g. (0.33 mole) of sodium hydroxide in 50 ml. of water. The temperature rose from 25° to 42°, and the solution was allowed to stand for 2 hr. A white solid had come out of solution, but dissolved upon the addition of another 100 ml. of water. The solution was made just strongly acid with 5 *N* hydrochloric acid. A gas evolved and an oil separated. The oil was extracted into four 50-ml. portions of ether. After drying over magnesium sulfate, the ether was evaporated under reduced pressure leaving 9.6 g. (89%) of crude O-*n*-propyl N-(2-mercaptoethyl)carbamate. Distillation under reduced pressure gave an analytical sample, b.p. 79–80° (0.18 mm.), $n^{27}D$ 1.4789.

Anal. Calcd. for $C_6H_{13}O_2NS$: C, 44.15; H, 8.03; N, 8.55; S, 19.64. Found: C, 44.22; H, 8.30; N, 8.61; S, 19.92.

S-Methyl N-[2-(Methyldithiolcarbonato)ethyl]thiolcarbamate.—To a suspension of 5.7 g. (0.05 mole) of 2-mercaptoethylamine hydrochloride in 50 ml. of acetonitrile was added 15.2 g. (0.15 mole) of triethylamine. A new solid (triethylamine hydrochloride) came out of solution. The suspension was added in portions, with stirring and cooling, to a solution of 11.0 g. (0.10 mole) of methyl chlorothiolformate in 25 ml. of acetonitrile. The mixture was allowed to stand for an hour and then was poured into ice–water. An oil separated and slowly hardened to a solid. After recovery by suction filtration and drying, the S-methyl N-[2-(methyldithiolcarbonato)ethyl]thiolcarbamate amounted to 9.5 g. (84%), m.p. 34–35.5°. Recrystallization from a mixture of benzene and petroleum ether (b.p. 60–70°) gave an analytical sample, m.p. 44–46°.

Anal. Calcd. for $C_6H_{11}O_2NS_3$: C, 31.98; H, 4.92; N, 6.22; S, 42.68. Found: C, 32.13; H, 5.06; N, 6.13; S, 42.90.

2-(*n*-Propyldithiolcarbonato)ethyl Isocyanate.—To a suspension of 11.4 g. (0.10 mole) of 2-mercaptoethylamine hydrochloride in 50 ml. of acetonitrile was added 30.4 g. (0.30 mole) of triethylamine. A new solid precipitated. The resulting suspension was added in portions, with stirring and cooling, to a solution of 27.6 g. (0.20 mole) of *n*-propyl chlorothiolformate in 50 ml. of acetonitrile. When there was no further rise in temperature, the mixture was allowed to stand for 1 hr. and then was poured into ice–water. An oil separated and was extracted into 150 ml. of ether, and the solution was dried over magnesium sulfate. Evaporation of the ether left 24.2 g. of liquid. Three distillations under reduced pressure with accompanying pyrolysis were carried out on a 10.0-g. sample at a pot temperature of 188–197° and at pressure of 0.7 mm. A fourth distillation gave 2.5 g. (30%) of pure 2-(*n*-propyldithiolcarbonato)ethyl isocyanate, b.p. 108–110° (1 mm.), $n^{27}D$ 1.5299.

Anal. Calcd. for $C_7H_{11}O_2NS_2$: C, 40.95; H, 5.40; N, 6.82; S, 31.23. Found: C, 41.06; H, 5.33; N, 6.72; S, 31.41.

1-[2-(Methyldithiolcarbonato)ethyl]-3-*n*-octylurea.—To a solution of 22.5 g. (0.10 mole) of S-methyl 2-(methyldithiolcarbonato)ethylthiolcarbamate and 10.0 g. (0.10 mole) of triethylamine in 50 ml. of dry acetonitrile was added a solution of 17.0 g. of silver nitrate in 25 ml. of dry acetonitrile. A yellow solid formed, and the temperature rose from 25° to 42°. Then 12.9 g. (0.10 mole) of *n*-octylamine was added, and the temperature rose to 70°. The mixture was allowed to stand until it was at room temperature. Another 100 ml. of acetonitrile was added, and the mixture was heated to boiling and filtered hot. The filtrate was poured into ice–water and a cream colored solid separated. There was thus recovered 22.4 g. (73%) of 1-[2-(methyldithiolcarbonato)ethyl]-3-*n*-octylurea. Recrystallization from 95% ethanol gave an analytical sample, m.p. 76.5–78°.

Anal. Calcd. for $C_{13}H_{26}O_2N_2S$: C, 50.94; H, 8.55; N, 9.14; S, 20.92. Found: C, 50.71; H, 8.60; N, 8.98; S, 21.04.

1,3-Bis[2-(methyldithiolcarbonato)ethyl]urea.—This compound was prepared by the previous procedure through the addition of silver nitrate solution. At this point 20 ml. of water was added. The temperature rose from 40° to 54°. The mixture was allowed to stand until the temperature had dropped back to 25°. Another 100 ml. of acetonitrile was added, the mixture was heated to boiling, and then filtered hot. The filtrate was poured into ice–water, and a white solid formed. The yield of recovered 1,3-bis[2-(methyldithiolcarbonato)ethyl]urea was 13.5 g. (81%). Two recrystallizations from 95% ethanol gave an analytical sample, m.p. 94.5–96°.

Anal. Calcd. for $C_9H_{16}O_3N_2S_4$: C, 32.91; H, 4.91; N, 8.53; S, 39.04. Found: C, 33.04; H, 5.01; N, 8.67; S, 39.13.

1-(2-Mercaptoethyl)-3-*n*-octylurea.—To a suspension of 15.6 g. (0.05 mole) of 1-(2-methyldithiolcarbonatoethyl)-3-*n*-octylurea in 250 ml. of 95% ethanol was added a solution of 8.0 g. (0.20 mole) of sodium hydroxide in 250 ml. of water. The mixture was stirred vigorously for 2 hr. and then made just strongly acid with 5 *N* hydrochloric acid. A gas evolved and a solid formed. The recovered 1-(2-mercaptoethyl)-3-*n*-octylurea amounted to 10.9 g. (92%). Two recrystallizations from acetonitrile gave an analytical sample, m.p. 80.5–82°.

Anal. Calcd. for $C_{11}H_{24}ON_2S$: C, 56.85; H, 10.41; N, 12.06; S, 13.80. Found: C, 57.01; H, 10.24; N, 11.96; S, 13.88.

1-(2-Mercaptoethyl)-3-*t*-butylurea.—Similar hydrolysis of 19.5 g. (0.08 mole) of 1-[2-(methyldithiolcarbonato)ethyl]-3-*t*-butylurea gave 10.3 g (75%) of 1-(2-mercaptoethyl)-3-*t*-butylurea. Three recrystallizations from a mixture of ethanol and water gave an analytical sample, m.p. 115–116.5°.

Anal. Calcd. for $C_7H_{18}ON_2S$: C, 47.69; H 9.15; N, 15.90; S, 18.19. Found: C, 47.86; H, 9.20; N, 15.98; S, 18.29.

1,3-Bis(2-mercaptoethyl)urea.—Similar hydrolysis of 22.7 g. (0.07 mole) of 1,3-bis[2-(methyldithiolcarbonato)ethyl]urea gave 8.8 g. (71%) of 1,3-bis(2-mercaptoethyl)urea. Two recrystallizations from 95% ethanol gave an analytical sample, m.p. 121.5–122°.

Anal. Calcd. for $C_5H_{12}ON_2S_2$: C, 33.51; H, 6.71; N, 15.54; S, 35.57. Found: C, 33.28; H, 6.63; N, 15.55; S, 35.66.

1-(2-Mercaptoethyl)-3-phenylurea.—Similar hydrolysis of 2.7 g. (0.01 mole) of 1-[2-methyldithiolcarbonato)ethyl]-3-phenylurea gave 1.7 g. (87%) of 1-(2-mercaptoethyl)-3-phenylurea, m.p. 140.5–141.5°. The infrared spectrum of this material was identical with that of an authentic sample of 1-(2-mercaptoethyl)-3-phenylurea.[2]

N-[2-(Mercaptoethyl)]phenylacetamide.—To a solution of 22.5 g. (0.10 mole) of S-methyl N-[2-(methyldithiolcarbonato)-ethyl]thiolcarbamate and 10.1 g. (0.10 mole) of triethylamine in 50 ml. of dry acetonitrile was added a solution of 17.0 g. (0.10 mole) of silver nitrate in 25 ml. of acetonitrile. The temperature rose from 20° to 39°, and a yellow solid formed. To this mixture was added a solution of 13.6 g. (0.10 mole) of phenylacetic acid in 20 ml. of dry acetonitrile. When the mixture was heated to 60° a gas evolved vigorously.

The mixture was heated until there was no further evolution of gas and then allowed to cool to room temperature. The yellow solid was filtered out, and the filtrate was poured into ice–water. A yellow semisolid separated and was extracted into two 50-ml. portions of ether, and the solution was dried over magnesium sulfate. Evaporation of the ether left 14.3 g. (53%) of a yellow semisolid which gave an infrared spectrum consistent with that expected for N-[2-(methyldithiolcarbonato)ethyl]phenylacetamide. The semisolid was taken up in 25 ml. of 95% ethanol, and to this solution was added a solution of 8.0 g. (0.20 mole) of sodium hydroxide in 25 ml. of water. The temperature rose from 25° to 47°. The solution was allowed to cool to room temperature. A solid had formed, but dissolved upon adding another 100 ml. of water. This solution was made just strongly acid with hydrochloric acid. A gas evolved and an oil separated. It was extracted with two 50-ml. portions of ether. After drying over magnesium sulfate, the ether was evaporated under reduced pressure. A yellow liquid amounting to 6.5 g. (62%) remained. It gave an infrared spectrum consistent with that expected for N-[2-(mercaptoethyl)]phenylacetamide. A dinitrophenyl sulfide derivative of this product was prepared by dissolving 1.9 g. (0.01 mole) of the product in 25 ml. of 95% ethanol and adding 4 ml. of 10% sodium hydroxide solution (0.01 mole) and a solution of 2.0 g. (0.01 mole) of 1-chloro-2,4-dinitrobenzene in 30 ml. of warm 95% ethanol. The resulting solution was heated to boiling, filtered hot, and the filtrate chilled. A yellow solid formed. The solid was recovered, and a second crop of solid was recovered from the filtrate. The total yield of solid was 2.2 g. (61%). Two recrystallizations from absolute ethanol gave an analytical sample, m.p. 134–137°.

Anal. Calcd. for $C_{16}H_{15}O_5N_3S$: C, 53.18; H, 4.18; N, 11.63; S, 8.87. Found: C, 52.95; H, 3.99; N, 11.77, S, 8.97.

The Preparation of Organic Phosphorus Compounds by Ivanov Reactions. I[1,2]

F. F. BLICKE AND S. RAINES

College of Pharmacy, University of Michigan, Ann Arbor, Michigan

Received June 24, 1963

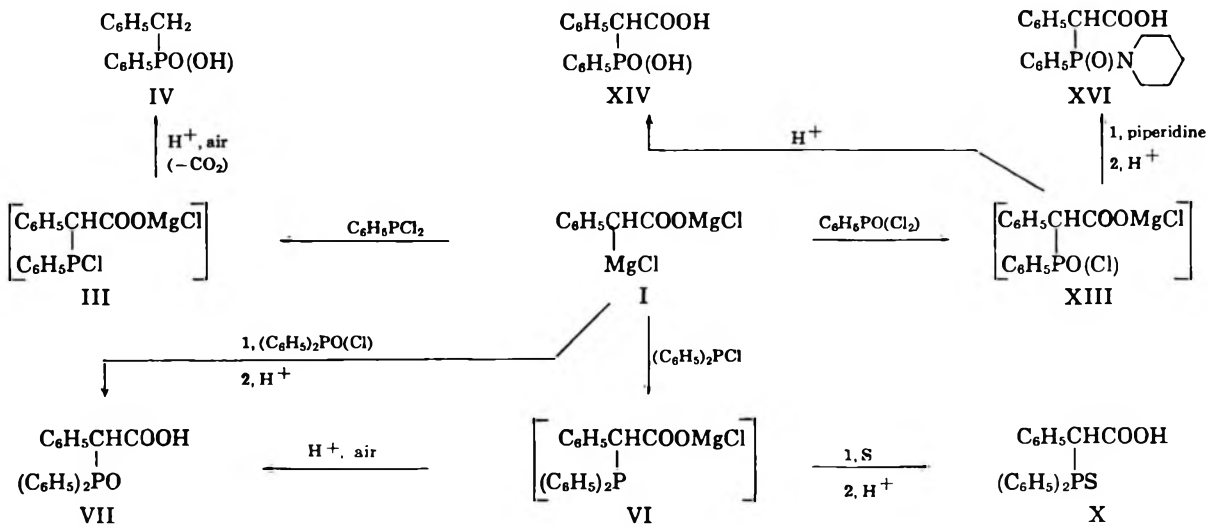
Organic phosphorus compounds have been obtained by reaction of $C_6H_5CH(MgCl)COOMgCl$ and $C_6H_5CH(MgCl)CON(CH_3)_2$ with phenyldichlorophosphine, diphenylchlorophosphine, phenyldichlorophosphine oxide, and diphenylchlorophosphine oxide.

In studies of the scope of the Ivanov reaction with respect to the preparation of organic compounds of phosphorus, reactions were carried out with the use of the Ivanov reagent $C_6H_5CH(MgCl)COOMgCl$ (I) and the Ivanov-like reagent $C_6H_5CH(MgCl)CON(CH_3)_2$ (II). These reagents were prepared by reaction of isopropylmagnesium chloride with phenylacetic acid and with N,N-dimethylphenylacetamide, respectively.

Reagent I reacted with phenyldichlorophosphine to form the unisolated intermediate III which, after treatment with dilute acid, underwent hydrolysis, air oxidation, and decarboxylation to yield phenylbenzylphosphinic acid (IV). The structure of this acid was established by its synthesis from phenyldichlorophosphine oxide and benzylmagnesium chloride in the presence of pyridine.[3] Diazomethane converted IV into methyl phenylbenzylphosphinate (V).

After VI, in the reaction mixture, had been treated with sulfur and the mixture had been acidified, phenyl(diphenylphosphinothioyl)acetic acid (X) was isolated and converted into methyl phenyl(diphenylphosphinothioyl)acetate (XI) by diazomethane. After reaction of the nonisolated VI with methyl iodide and acidification of the reaction mixture, decarboxylation took place and diphenylbenzylmethylphosphonium iodide (XII) was obtained; this product has been synthesized by other procedures.[8,9]

Reagent I and phenyldichlorophosphine oxide reacted to form XIII which, after acidification of the reaction mixture, was converted into phenyl(phenylhydroxyphosphinyl)acetic acid (XIV); diazomethane transformed the acid into methyl phenyl(phenylmethoxyphosphinyl)acetate (XV). The presence of chlorine in the nonisolated, initial reaction product



After reaction of I with diphenylchlorophosphine the reaction mixture, which contained VI, was acidified. Air oxidation took place and phenyl(diphenylphosphinyl)acetic acid (VII) was isolated. This acid was obtained also by interaction of I with diphenylchlorophosphine oxide. When heated above its melting point, VII underwent decarboxylation to form diphenylbenzylphosphine oxide (VIII). Diazomethane converted VII into methyl phenyl(diphenylphosphinyl)-acetate (IX). Other procedures have been used to prepare VII[4] and VIII.[5-8]

XIII was shown by the addition of piperidine to the reaction mixture; after acidification, phenyl(phenylcarboxymethyl)(N,N-pentamethylene)phosphinic amide (XVI) was produced. Diazomethane converted XVI into phenyl(phenylcarbomethoxymethyl)(N,N-pentamethylene)phosphinic amide (XVII).

After reaction of reagent II with diphenylchlorophosphine to form XVIII and then acidification of the reaction mixture, the product was converted by air oxidation into N,N-dimethylphenyl(diphenylphosphinyl)acetamide (XIX). This product was heated with aqueous potassium hydroxide and the reaction mixture, which contained XX, was then acidified whereupon decarboxylation took place and diphenylbenzylphosphine oxide (VIII) was produced. When

(1) Abstracted from the Ph.D. dissertation of S. Raines, University of Michigan, 1962.

(2) This investigation was supported by grants from The Wm. S. Merrell Co. and from the American Foundation for Pharmaceutical Education.

(3) See G. M. Kosolapoff, *J. Am. Chem. Soc.*, **72**, 5508 (1950).

(4) L. Horner, H. Hoffmann, H. G. Wippel, and G. Klahre, *Ber.*, **92**, 2499 (1959).

(5) A. Michaelis and W. La Coste, *ibid.*, **18**, 2109 (1885).

(6) A. Arbuzov, *J. Russ. Phys. Chem. Soc.*, **42**, 395 (1910); *Chem. Abstr.*, **5**, 1397 (1911).

(7) A. E. Arbuzov and K. V. Nikonorov, *Zh. Obshch. Khim.*, **18**, 2008 (1948); *Chem. Abstr.*, **43**, 3801 (1949).

(8) H. Hoffmann, R. Grünewald, and L. Horner, *Ber.*, **93**, 851 (1960).

(9) L. Horner, P. Beck, and H. Hoffmann, *ibid.*, **92**, 2093 (1959).

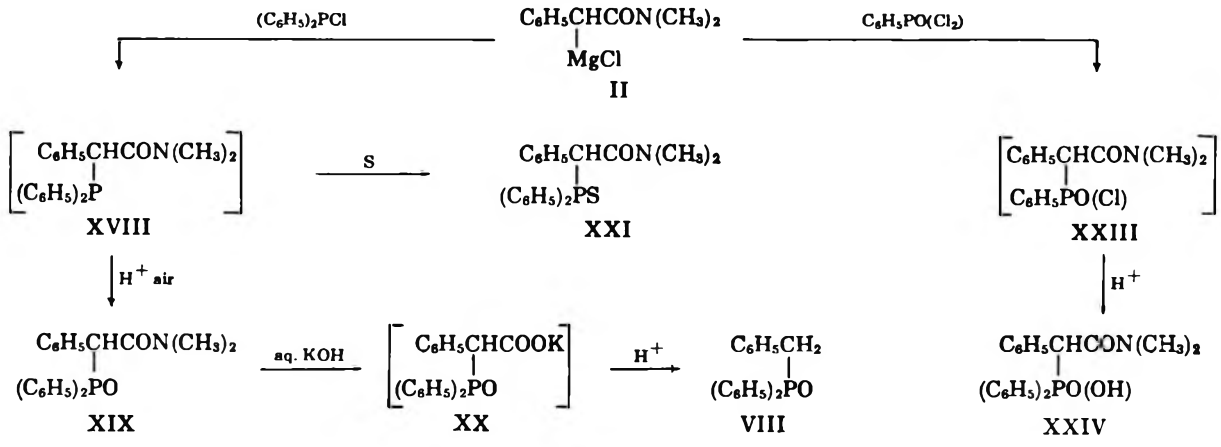


TABLE I

PRODUCTS OBTAINED FROM $C_6H_5CH(MgCl)COOMgCl$

	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Phosphorus, % Calcd.	Phosphorus, % Found
IV	178–180	30	$C_{13}H_{13}O_2P$[a]	67.24	67.53	5.64	5.79	13.34	13.24
V	89–92	59	$C_{14}H_{15}O_2P$	68.29	68.31	6.14	6.33	13.00	12.89
VII	135–137[b]	16[c], 81[d]	$C_{20}H_{17}O_3P$						
IX	205–207	91	$C_{21}H_{19}O_3P$	71.99	72.18	5.47	5.67	8.84	9.10
X	203–205	43	$C_{20}H_{17}O_2PS$[e]	68.16	68.30	4.86	5.02	8.79	8.84
XI	118–120	70	$C_{21}H_{19}O_2PS$[f]	68.84	68.69	5.23	5.27	8.45	8.56
XII	235–237[g]	61	$C_{20}H_{20}PI$	57.43	57.63	4.82	5.02		
XIV	79–81	58	$C_{14}H_{13}O_4P$	60.87	61.12	4.74	4.92	11.21	11.10
XV	86–88	16	$C_{16}H_{17}O_4P$	63.15	63.22	5.63	5.56		
XVII[h]	149–151	12	$C_{20}H_{24}O_3NP$	67.20	67.54	6.77	7.02	8.67	8.50

[a] Calcd. neut. equiv., 232.2. Found, 232.5. [b] Ref. 4, m.p. 136°. [c] Obtained from $(C_6H_5)_2PCl$. [d] Obtained from $(C_6H_5)_2PO(Cl)$. [e] *Anal.* Calcd.: S, 9.11. Found: S, 9.28. [f] *Anal.* Calcd.: S, 8.75. Found: S, 8.81. [g] Ref. 8, m.p. 229–230°. [h] Compounds IV and XII were recrystallized from absolute ethanol; V from petroleum ether (b.p. 90–100°); VII from nitromethane; X from acetic acid; IX from 2-butanone; XI from absolute ethanol after the oil had been triturated with ether; XV, a semisolid, was placed on a porous plate and the solid material was recrystallized from petroleum ether (b.p. 90–100°); XVII, a semisolid, was dissolved in hot petroleum ether (b.p. 90–100°) and the gum which separated from the cold solution was washed with acetone.

TABLE II

PRODUCTS OBTAINED FROM $C_6H_5CH(MgCl)CON(CH_3)_2$

	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Phosphorus, % Calcd.	Phosphorus, % Found
XIX	270–272	41	$C_{22}H_{22}O_2NP$	72.71	72.42	6.10	6.11	8.52	8.75
XXI	189–191	48	$C_{22}H_{22}ONPS$[a]	69.63	69.68	5.83	5.78	8.16	8.16
XXII	237–239	54	$C_{23}H_{25}ONPI$[b]	56.45	56.51	5.15	5.19	6.30	6.17
XXIV	202–204	28	$C_{16}H_{18}O_3NP$	63.36	63.43	5.98	6.06	10.21	10.14
XXV[c]	180–182	63	$C_{17}H_{20}O_3NP$	64.34	64.35	6.35	6.31	9.76	9.65

[a] *Anal.* Calcd.: S, 8.45. Found: S, 8.52. [b] *Anal.* Calcd.: I, 25.93. Found: I, 26.03. [c] Compounds XIX and XXI were recrystallized from nitromethane, XXII from ethanol, XXIV from dioxane, and XXV from 2-butanone.

the original reaction mixture, which contained XVIII, was treated with sulfur the product formed was N,N-dimethylphenyl(diphenylphosphinothioyl)acetamide (XXI). Reaction of XVIII with methyl iodide yielded the methiodide (XXII). The initial, nonisolated reaction product XXIII produced by reaction of II with phenyldichlorophosphine oxide was converted into N,N-dimethylphenyl(phenylhydroxyphosphinyl)acetamide (XXIV) when the reaction mixture was acidified. Diazomethane converted XXIV into N,N-dimethylphenyl(phenylmethoxyphosphinyl)acetamide (XXV).

Experimental

Products obtained from reagents I and II are listed in Tables I and II, respectively.

After a reaction had been carried out, the reaction mixture was hydrolyzed in one of the following ways: (a) the reaction mixture was poured into a mixture of 15 ml. of concentrated hydrochloric acid, 200 ml. of water and ice; (b) a mixture of 18 ml. of concentrated hydrochloric acid and 180 ml. of water was added, dropwise and very slowly, to the stirred reaction mixture which was cooled in an ice bath; (c) 6 g. of ammonium chloride, dissolved in 220 ml. of water, was added, dropwise, to the stirred reaction mixture.

Preparation of $C_6H_5CH(MgCl)COOMgCl$ (I).—Phenylacetic acid (13.6 g., 0.1 mole), dissolved in 100 ml. of sodium-dried benzene, was added, dropwise, to a stirred solution of isopropylmagnesium chloride which had been prepared from 18.0 g. (0.22 mole) of isopropyl chloride, 5.4 g. (0.22 g.-atom) of magnesium, 1 ml. of ethyl bromide, and 150 ml. of ether. The mixture was stirred for 12 hr.

Phenylbenzylphosphinic Acid (IV). A.—The suspension of reagent I was transferred to a dropping funnel and added, dropwise, to a stirred solution of 17.9 g. (0.1 mole) of phenyldichlorophosphine in 25 ml. of benzene. The mixture was stirred for 12 hr., hydrolyzed by method a and the organic layer was extracted with aqueous sodium bicarbonate. After acidification of the alkaline layer, the mixture was extracted with benzene, and the solvent was removed from the dried extract. The oily residue was dissolved in hot chloroform. After some time, the precipitated solid was filtered and triturated with hot petroleum ether (b.p. 60–70°) to remove phenylacetic acid.

B.—Pyridine (7.9 g., 0.1 mole) was added, dropwise, to a stirred mixture of 19.5 g. (0.1 mole) of phenyldichlorophosphine oxide and 200 ml. of ether, and the material was stirred for 4 hr. A solution of benzylmagnesium chloride, which had been prepared from 12.7 g. (0.1 mole) of benzyl chloride, 2.4 g. (0.1 g.-atom) of magnesium, and 100 ml. of ether, was added, dropwise, to the stirred material. After the reaction mixture had been stirred for 4 hr., a mixture of 20 ml. of concentrated hydrochloric acid and 200 ml. of water was added. The organic layer was shaken with aqueous sodium bicarbonate and the alkaline layer was acidified with hydrochloric acid. The precipitated product was recrystallized from absolute ethanol; yield, 5.3 g. (23%); m.p. and m.m.p. 178–180°.

Esters V, IX, XI, XV, XVII, and XXV.—The required acid was dissolved or partially dissolved in a suitable solvent. Methanol was used for the preparation of IX and XXV, and dioxane for the synthesis of the other esters. After the addition of excess diazomethane, dissolved in ether, the solvents were removed and the residue, with two exceptions, was dissolved in benzene; the residues of crude XVII and XXV were dissolved in chloroform. The solution was extracted with aqueous sodium bicarbonate and the solvent was removed from the dried organic layer.

Phenyl(diphenylphosphinyl)acetic Acid (VII). A.—Diphenylchlorophosphine (22.1 g., 0.1 mole) was added, dropwise, to I, the mixture was stirred for 12 hr. and then hydrolyzed by method b. The organic layer was extracted with aqueous sodium bicarbonate, the alkaline solution was acidified, extracted with chloroform, and the solvent was removed from the dried organic layer. The residue was recrystallized from nitromethane. During this process decarboxylation took place to a slight extent. The recrystallized material was treated with aqueous sodium bicarbonate, the mixture was filtered, and the filtrate acidified, whereupon VII precipitated.

B.—Diphenylchlorophosphine oxide (23.7 g., 0.1 mole) was added, dropwise, to the stirred suspension of I. The mixture was refluxed for 3 hr., stirred for 12 hr., and hydrolyzed by method b. The precipitate, which formed between the organic and aqueous layer, was removed by filtration and recrystallized from nitromethane. This material was treated with aqueous sodium bicarbonate and, after filtration, the filtrate was acidified; the product precipitated.

Phenyl(diphenylphosphinothioyl)acetic Acid (X).—Diphenylchlorophosphine (22.1 g., 0.1 mole) was added, dropwise, to the stirred suspension of I and the mixture was stirred for 12 hr. A solution of 6.4 g. (0.2 g.-atom) of sulfur in 75 ml. of carbon disulfide was added dropwise. The mixture was refluxed for 1 hr., stirred for 12 hr. and hydrolyzed by method b. The organic layer was separated and shaken with aqueous sodium bicarbonate. The insoluble material which formed between the organic and alkaline layer was removed by filtration and triturated with dilute hydrochloric acid. After the addition of benzene, which dissolved the material, the organic layer was separated, dried, and the solvent was removed.

Diphenylbenzylmethylphosphonium Iodide (XII).—Diphenylchlorophosphine (22.1 g., 0.1 mole) was added, dropwise, to the stirred suspension of I. After the mixture had been stirred for 12 hr., 21.3 g. (0.15 mole) of methyl iodide was added dropwise; the material was stirred for 12 hr. and hydrolyzed by method a. The solid material which formed between the organic and aqueous layer was removed by filtration and recrystallized.

Phenyl(phenylhydroxyphosphinyl)acetic Acid (XIV).—After 19.5 g. (0.1 mole) of phenyldichlorophosphine oxide had been added to I, the mixture was refluxed for 1 hr. and then hydrolyzed by method b. The organic layer was extracted with aqueous sodium bicarbonate; the alkaline layer was acidified and extracted with chloroform. The solvent was removed from the dried extract. The oily residue became solid and pure after it had been triturated with petroleum ether (b.p. 30–40°) and then with hot petroleum ether (b.p. 60–70°).

Phenyl(phenylcarboxymethyl)(N,N-pentamethylene)phosphinic Amide (XVI).—After the addition of 19.5 g. (0.1 mole) of phenyldichlorophosphine oxide to a stirred suspension of I, the mixture was stirred for 6 hr. Piperidine (17.0 g., 0.2 mole) was added, dropwise, to the mixture which was then stirred for 12 hr. and hydrolyzed by method b. The organic layer was extracted with aqueous bicarbonate; the alkaline layer was acidified and extracted with benzene. After removal of the solvent from the dried benzene layer, the oily residue was triturated with hot petroleum ether (b.p. 90–100°). The solid product was dissolved in hot carbon tetrachloride, and petroleum ether (b.p. 90–100°) was added until the product precipitated. The impure material (20.8 g., 61%) melted at 130–150°. After the carbon tetrachloride–petroleum ether process had been repeated a number of times, 8.8 g. of product was obtained which melted at 145–148°. An analysis showed that this material was still impure.

Preparation of $C_6H_5CH(MgCl)CON(CH_3)_2$ (II).—N,N-Dimethylphenylacetamide (16.3 g., 0.1 mole), dissolved in 150 ml. of sodium-dried benzene, was added, dropwise, to a stirred solution of isopropylmagnesium chloride which had been prepared from 2.7 g. (0.11 g.-atom) of magnesium, 8.7 g. (0.11 mole) of isopropyl chloride, 1 ml. of ethyl bromide, and 200 ml. of ether. The mixture was stirred and refluxed for 1 hr. and then stirred for 12 hr.

N,N-Dimethylphenyl(diphenylphosphinyl)acetamide (XIX).—Diphenylchlorophosphine (22.1 g., 0.1 mole) was added, dropwise, to the stirred suspension of II. The mixture was stirred and refluxed for 12 hr. and then hydrolyzed by method c. The insoluble material was removed by filtration, washed with ether, and recrystallized.

Diphenylbenzylphosphine Oxide (VIII).—Compound XIX (6.0 g.) and 60 ml. of a 15% solution of potassium hydroxide in ethanol were refluxed for 3 hr. The ethanol was removed, the residue (XX) was dissolved in water, and the solution was extracted with benzene. When the alkaline solution was acidified, carbon dioxide was evolved and VIII precipitated. After recrystallization from ethanol to yield was 1.0 g. (20%), m.p. and m.m.p. 190–192°, lit.[5–8] m.p. 192–193°.

N,N-Dimethylphenyl(diphenylphosphinothioyl)acetamide (XXI).—Diphenylchlorophosphine (22.1 g., 0.1 mole) was added, dropwise, to a stirred suspension of II and the mixture was refluxed for 2 hr. Sulfur (6.4 g., 0.2 g.-atom), dissolved in 75 ml. of carbon disulfide, was added, dropwise, to the stirred mixture. The material was refluxed for 1 hr., then stirred for 3 hr. and hydrolyzed by method c. The organic layer was dried, the solvent removed, and the residue was washed with carbon disulfide.

N,N-Dimethylphenyl(diphenylphosphino)acetamide Methiodide (XXII).—Diphenylchlorophosphine (22.1 g., 0.1 mole) was added, dropwise, to a stirred suspension of II. The mixture was refluxed for 2 hr., 28.4 g. (0.2 mole) of methyl iodide was added dropwise, the mixture was stirred for 12 hr. and then hydrolyzed by method c. The insoluble methiodide was removed by filtration, dissolved in ethanol, the solution was decolorized with Nuchar, filtered, and the solvent removed.

N,N-Dimethylphenyl(phenylhydroxyphosphinyl)acetamide (XXIV).—Phenyldichlorophosphine oxide (19.5 g., 0.1 mole) was added, dropwise, to a stirred suspension of II. The mixture was refluxed for 2 hr. and then hydrolyzed by method c. The oil which separated between the organic and the aqueous layer was removed and triturated with hot petroleum ether (b.p. 90–100°). The insoluble solid residue was dissolved in chloroform and the solution was extracted with aqueous sodium bicarbonate. The alkaline layer was acidified, extracted with chloroform, and the solvent was removed from the organic layer.

The Effect of β-Hydrogen Atoms and Hydrocarbon Structure on the Thermal Stability of Sulfones[1]

EDWARD GIPSTEIN, ERIC WELLISCH, AND ORVILLE J. SWEETING

Packaging Division Film Operations, Olin Mathieson Chemical Corporation, New Haven, Connecticut

Received January 30, 1963

The effect of the β-hydrogen atoms and hydrocarbon structure on the thermal stability of sulfones has been investigated. Twelve monomeric sulfones containing from 0 to 18 β-hydrogen atoms and of varying structure were synthesized and then heated at 275° for 1 hr. under vacuum in the absence of solvent. The results indicate that the absence of β-hydrogen atoms, or their substitution by stabilizing groups and by long methylene chains or alicyclic rings, enhances the thermal stability of sulfones. Phenyl groups α to the sulfone group acting as electron-withdrawing groups also have a stabilizing effect. To test these observations, sulfone polymers containing these features were synthesized and their thermal stabilities studied.

It is well known that the sulfone group has an activating influence on the hydrogen atoms at the α-position in sulfones. Two sulfone groups on the same carbon atom make the hydrogen replaceable by alkali metals; three sulfone groups permit the hydrogen atom to ionize.[2]

The precise nature of the effect of the sulfone group on the hydrogen atoms at the β-carbon atoms is not nearly so well known. β-Disulfones appear to exhibit a high degree of instability to basic reagents. Diethyl sulfone, for instance, in the presence of potassium hydroxide decomposes at 200° to give ethylene and potassium ethylsulfinate.[3a] Fenton and Ingold found that dioctyl sulfone is stable under these conditions. This shielding effect of methylene groups on the decomposition of alkyl sulfones by β-elimination in the order of the ease of elimination of olefin was shown to be phenylethyl > ethyl, isopropyl, *sec*-butyl > propyl > *n*-butyl > *n*-amyl, *n*-hexyl, *n*-heptyl, *n*-octyl > isoamyl > isobutyl.[3b] Naylor and Anderson have shown that the decomposition rates of polymers of olefins and sulfur dioxide roughly parallel the total number of hydrogen atoms on the carbon atoms β to the sulfone linkage.[4] Whether a true β-elimination takes place has never been fully established.

The pyrolysis of aromatic sulfones containing methyl groups *ortho* and *para* to the sulfonyl group has been investigated.[5] At least one methyl group was found necessary to produce diarylmethanes by β-elimination.

In general it appears that the thermal stability of sulfones and sulfone polymers may depend on the number of β-hydrogen atoms and the hydrocarbon structures. In the present investigation an attempt was made to correlate these two factors with the thermal properties of sulfones by studying the extent of decomposition of twelve monomeric sulfones at 275° in the absence of solvent (see Table I). For this investigation, sulfones containing 0 to 18 β-hydrogen atoms and of varying structures were prepared and tested. In counting β-hydrogens, we have ignored those of an aromatic ring, since it is quite unlikely that they can participate in hydrogen-bond formation involving an *o*-carbon and a sulfone oxygen.

TABLE I

MODEL MONOMERIC SULFONES

Sulfone	Number of β-hydrogens	M.p. or b.p. (mm.), °C.	Yield, %
Diphenyl[a]	0	127–128	97
Dimethyl[b]	0	109–110	94
Dibenzyl	0	151.0–151.5	17
Isobutyl phenyl[c]	1	126 (1)	87
Benzyl butyl	2	97.0–97.5	78
Diisobutyl[d]	2	265 (750)	62
Dibutyl[e]	4	43.5–44.0	97
Didodecyl[f]	4	92.5–93.0	73
Cyclopropyl phenyl	4	120–124 (0.1)	56
Isopropyl phenyl[g]	6	112–114 (0.5)	47
Diisopropyl[d]	12	128–130 (0.5)	60
Di-*t*-butyl	18	128–129	77

[a] O. Hinsberg, *Ber.*, **43**, 290 (1910). [b] E. Fromm and J. Polma, *ibid.*, **39**, 3315 (1906). [c] *Anal.* Calcd. for $C_{10}H_{14}O_2S$: C, 60.60; H, 7.07; S, 16.16. Found: C, 60.46; H, 7.29; S, 16.29. [d] See ref. 9. [e] N. Grabowsky, *Ann.*, **175**, 348 (1875). [f] P. Allen, Jr., L. S. Karger, J. D. Haygood, Jr., and J. Schresnel, *J. Org. Chem.*, **16**, 767 (1951). [g] See ref. 10.

Discussion

The decomposition of sulfones generally appears to increase with increasing number of β-hydrogen atoms but there are several exceptions. Dibutyl sulfone with four β-hydrogen atoms decomposes to a less extent than isobutyl phenyl, benzyl butyl, and diisobutyl sulfones which contain fewer β-hydrogens. The structural effects of the substituent groups on the thermal stability must therefore be considered. By examining Table II we note that two phenyl groups result in a stable sulfone, perhaps as a result of the type of β-hydrogen atoms and the high energy of activation necessary to produce the highly active phenyl radical formed on scission of the carbon–sulfur bond. Benzyl groups tend to promote instability because the stable benzyl free radical produced on bond scission provides a driving force for decomposition. Alkyl phenyl sulfones show greater stability than alkyl sulfones because of the electron-withdrawing effect of the phenyl group. Stability of alkyl sulfones decreases as the carbon attached to the sulfone group is changed from a primary to a secondary and then to a tertiary carbon atom, corresponding to the increasing stabilities of the primary, secondary, and tertiary alkyl free radicals produced. The shielding effect of a long methylene

(1) Presented before the Division of Organic Chemistry at the 145th National Meeting of the American Chemical Society, New York, N. Y., September, 1963.

(2) C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 740, 754 ff.

(3) (a) G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 3128 (1928); (b) 2338 (1929); 705 (1930).

(4) M. A. Naylor and A. W. Anderson, *J. Am. Chem. Soc.*, **76**, 3962 (1954).

(5) H. Drews, E. K. Fields, and S. Meyerson, *Chem. Ind.* (London), 1403 (1961).

chain or the steric effect of a cyclopropyl group stabilizes the sulfone by making interaction between the sulfone group and the β-hydrogens difficult. Details of a mechanism of decomposition involving β-hydrogen atoms will appear elsewhere.

TABLE II

EFFECT OF β-HYDROGEN ATOMS ON THE THERMAL STABILITY OF SULFONES AT 275° FOR 1 HR.

Sulfone	Number of β-hydrogen atoms	Pressure, mm.	Decomposition, mole %
Dimethyl	0	6	0.03
Diphenyl	0	10	0.14
Dibenzyl	0	25	0.73
Isobutyl phenyl	1	14	1.2
Benzyl butyl	2	22	1.5
Diisobutyl	2	24	3.1
Dibutyl	4	12	0.7
Didodecyl	4	4	0.21
Cyclopropyl phenyl	4	10	0.84
Isopropyl phenyl	6	36	2.8
Diisopropyl	12	76	4.5
Di-*t*-butyl	18	330	85.8

We desired to compare the thermal stability of these simple compounds with the stability of polymeric sulfones and determine whether our structural and mechanistic hypotheses had validity for similar polymers.

Therefore several sulfone polymers with the following structural features were synthesized and examined: polymers without β-hydrogen atoms or with one or more β-hydrogens substituted by stabilizing groups, polysulfones containing long methylene chains or heterocyclic rings, and sulfone polymers containing phenyl groups α to the sulfone groups. In addition, the stability of a polysulfone with three sulfone groups β to one methylene group also was investigated.

We conclude that sulfone polymers of high purity whose β-hydrogens are substituted or shielded by long carbon chains or are sterically hindered ring hydrogens should be thermally stable. Phenyl groups α to the sulfone group acting as electron-withdrawing groups should also aid in the stabilization of such polymers.

Experimental

Preparation and Purification of Sulfones.—The sulfones prepared for this investigation are listed in Table I. They were in most cases prepared by condensation of a mercaptide with a halide in ethanol. The resulting sulfide was oxidized to the sulfone with hydrogen peroxide in acetic acid. The following sulfones were synthesized by other methods.

Dibenzyl sulfone was prepared from benzyl chloride and sodium dithionite.[6] Benzyl chloride, 12.6 g. (0.10 mole) and 9.0 g. (0.50 mole) of sodium dithionite were heated with stirring for 9 hr. in 100 ml. of dimethylformamide at 110°. The product was obtained by pouring the mixture into ice and recrystallizing the crude product from ethyl alcohol, 2.0 g., 17%, m.p. 151.0–151.5° (lit.[7] m.p. 151°).

Benzyl butyl sulfone was synthesized from lithium butylsulfinate, prepared from butyllithium and sulfur dioxide, and benzyl chloride in refluxing ethyl alcohol as solvent. The product, recrystallized twice from isopropyl alcohol, melted at 97.0–97.5°, lit.[8] m.p. 95–97°, 78%.

(6) E. Wellisch, E. Gipstein, and O. J. Sweeting, to be published.
(7) J. Troger and K. Artmann, *J. prakt. Chem.*, **53**, 500 (1896).
(8) S. Archer, U. S. Patent 2,682,544 (June 29, 1954).

Diisopropyl sulfone was prepared from 24.6 g. (0.20 mole) of isopropyl bromide and 11.2 g. (0.20 mole) of sodium hydrosulfide in 100 ml. of water and 100 ml. of ethanol. The mixture was refluxed 4 hr., 300 ml. of water was added, and the fraction extracted with hexane and ether was oxidized with 30% hydrogen peroxide in 100 ml. of acetic acid at 80° for 3 hr. The product, 9.0 g., 60%, was obtained by fractional distillation; it boiled at 128–130° (0.3–0.5 mm.), lit.[9] m.p. 36°.

Anal. Calcd. for $C_6H_{14}O_2S$: C, 48.00; H, 9.30; S, 21.35. Found: C, 48.01; H, 9.39; S, 21.24.

Cyclopropyl phenyl sulfone was prepared by the method of Zimmerman and Thyagarajan[10] by cyclization of 21.9 g. of γ-chloropropyl phenyl sulfone in a solution of sodium *t*-butoxide prepared from 2.76 g. of sodium and 60 ml. of *t*-butyl alcohol. The solution was stirred and refluxed for 6 hr., then cooled, diluted with 200 ml. of water, extracted with ether, dried over sodium sulfate, and concentrated at reduced pressure. Distillation of the residue gave 10.2 g. of a colorless oil, 56%, b.p. 120–124° (0.1 mm.). The product was further purified by fractional crystallization, giving a solid product m.p. 36–37°, lit.[11] m.p. 36–37.5°, b.p. 130–135° (0.5 mm.). The structure of this compound was confirmed by infrared and elemental analysis.

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.33; H, 5.53; S, 17.58. Found: C, 59.04; H, 5.92; S, 17.21.

Di-*t*-butyl sulfone was prepared *via* nucleophilic substitution of *t*-butyl mercaptan on the carbonium ion of *t*-butyl alcohol in sulfuric acid by adapting the method of Fehnel and Carmack,[12] followed by oxidation. A mixture of 225 g. of concentrated sulfuric acid and 65 g. of water was cooled in an ice bath. *t*-Butyl alcohol, 50.4 g. 0.60 mole, was added at such a rate as to control the temperature of the mixture near 10°. After the addition had been completed, 27.0 g. (0.30 mole) of *t*-butyl mercaptan was added dropwise during 30 min. The reaction mixture was allowed to warm to 25°. The product, *t*-butyl sulfide, boiling at 144–149°, was isolated by pouring the mixture over 500 g. of ice, extracting with ether, drying over anhydrous magnesium sulfate, and fractionally distilling the ether solution. The yield was 28.2 g. (88%). The sulfide, 10.2 g., was oxidized to the sulfone in 45 ml. of acetic acid with 30% hydrogen peroxide. The acid was neutralized with aqueous sodium hydroxide and extracted with ether to give 9.5 g. (77%) of sulfone, recrystallized from water, and purified by sublimation, m.p. 128–129°, lit.[13] m.p. 129–130°.

Anal. Calcd. for $C_8H_{18}O_2S$: C, 53.93; H, 10.11; S, 17.97. Found: C, 54.05; H, 10.29; S, 18.09.

Decomposition of Sulfones.—The apparatus used was that already described for the decomposition of sulfinic acids.[14] The thermal decomposition of these sulfones was carried out in tared Pyrex glass tubes containing break-seal capillary joints. Break-seal tubes were used to prevent sublimation and distillation of the sulfones as well as to permit us to determine accurate weight losses of the samples after decomposition. The tubes containing 0.001-mole samples were evacuated at 0.005 mm. for at least 16 hr. and sealed while under vacuum. They were heated to 275 ± 3°.

After 1 hr., the seals were broken by a small iron bar contained in the side arm of the tube, which was manipulated by a magnet outside the tube. The extent of decomposition was determined by the pressures, by the weight loss of the sulfones, and by infrared analysis of the condensible gaseous products collected in the cold finger of an infrared gas cell. The results (Table II) indicate that a dimethyl or a diphenyl sulfone containing no β-hydrogen atoms decomposes least while *t*-butyl sulfone with 18 β-hydrogens decomposes extensively.

Preparation and Characterization of Polysulfones.—**Polymethylene sulfone** was prepared by the oxidation of polymethylene sulfide. The polysulfide was prepared according to the procedure of Lal[15] by the condensation of bis(chloromethyl) sulfide and sodium sulfide nonahydrate in refluxing ethanol. It was oxidized to the polysulfone at 70° in formic acid by use of 30% hydrogen peroxide. The polymer, obtained as a white powder (25%), was washed with hot benzene and dried. The

(9) E. O. Beckmann, *J. prakt. Chem.*, **17**, 439 (1878).
(10) H. E. Zimmerman and B. S. Thyagarajan, *J. Am. Chem. Soc.*, **82**, 2505 (1960).
(11) W. E. Truce and L. B. Lindy, *J. Org. Chem.*, **26**, 1463 (1961).
(12) E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **71**, 84 (1949).
(13) F. G. Bordwell and W. H. McKellin, *ibid.*, **73**, 2251 (1951).
(14) E. Wellisch, E. Gipstein, and O. J. Sweeting, *J. Org. Chem.*, **27**, 1810 (1962).
(15) J. Lal, *ibid.*, **26**, 971 (1961).

polymer did not melt but sublimed with decomposition above 345°. No chloromethyl end groups were found in the polymer.

Anal. Calcd. for $(-CH_2SO_2-)_x$: C, 15.38; H, 2.56; S, 41.02. Found: C, 15.43; H, 2.83; S, 39.96.

Poly-*p*-xylylene sulfone was prepared by the addition of 18 g. (0.10 mole) of sodium dithionite to 18.0 g. (0.10 mole) of *p*-xylylene dichloride in 100 ml. of dimethylformamide at 110°.[6] The polymer was obtained as 10.0 g. of a white amorphous solid (60%), m.p. >360°, by pouring the mixture into ice–water, filtering, and washing with hot ethanol; it was insoluble in most common organic solvents.[16] The structure was confirmed by infrared analysis and found similar to that for dibenzyl sulfone: C–H stretching, 3.45 μ, strong; C–H aromatic, 6.2 and 6.6, strong; C–H deformation, 6.75 and 7.02, very strong; SO_2, 7.6 and 8.95, very strong.

Polytetra-, hexa-, and octamethylene sulfides were prepared from the corresponding dimercaptans and dibromides by condensation in refluxing ethanol in the presence of a basic catalyst. The resulting polysulfides were oxidized to the polysulfones with 30% hydrogen peroxide in formic acid.[17] Melting points and yields of the sulfones were, respectively: 265–269°, 73.0%; 212–215°, 84.5%; 199–204°, 76.7%.

Some precautions were found necessary in the oxidation step and the isolation of product. The polysulfide must be washed free of occluded sodium bromide which interferes with the oxidation of the sulfide by preferential oxidation to bromine. Stirring the polysulfide first in refluxing hot water for several hours was found satisfactory. When the polysulfone was poured into water, a colloidal suspension formed, which was hard to filter and had to be tediously centrifuged, but this could be eliminated by cooling the product in the original formic acid solvent, filtering it, and then washing the polymer free of acid on a Büchner funnel.

All three polysulfones and the *p*-xylylene polysulfone were purified by recrystallization from concentrated sulfuric acid. They were dissolved at 40–70°, recovered by dilution with ice–water, extracted with hot water in a Soxhlet extractor for 24 hr., washed with ether, and dried for 24 hr. at 100° under reduced pressure.

Anal. Calcd. for $(-C_4H_8SO_2-)_x$: C, 40.00; H, 6.72; S, 26.66. Found: C, 39.63; H, 6.63; S, 25.58.

Anal. Calcd. for $(-C_6H_{12}SO_2-)_x$: C, 48.64; H, 8.10; S, 21.62. Found: C, 48.05; H, 8.30; S, 22.03.

Anal. Calcd. for $(-C_8H_{16}SO_2-)_x$: C, 54.54; H, 9.09; S, 18.18. Found: C, 54.77; H, 9.44; S, 18.17.

Polyphenylene octamethylene sulfone was prepared by a modification of the method of Kreuchunas.[18] Bis(*p*-chlorophenyl) sulfone and lithium octamethylene dimercaptide were condensed in quinoline at 175° with copper(I) chloride as catalyst. The polysulfide–polysulfone, m.p. 120–125°, was oxidized to the polysulfone in formic acid at 80° by use of 30% hydrogen peroxide, m.p. 250–255°; yield, 90.0%.

Anal. Calcd. for $(-C_{20}H_{24}O_6S_3-)_x$: C, 52.63; H, 5.26; S, 21.05. Found: C, 52.57; H, 5.32; S, 20.71.

Polyoctamethylene *p*-xylylene sulfide was prepared by the condensation of *p*-xylylene dichloride and octamethylene dimercaptan in refluxing ethanol with sodium. The polysulfide, m.p. 79–81°, was oxidized in the usual way to give the polysulfone, m.p. 245–250°; yield, 90.0%.

Anal. Calcd. for $(-C_{16}H_{24}O_4S_2-)_x$: C, 55.65; H, 7.24; S, 18.56. Found: C, 55.56; H, 7.05; S, 18.87.

Poly-3-oxythiophene 1,1-dioxide was prepared by dissolving 8.5 g. (0.05 mole) of sulfolene chlorohydrin in 100 ml. of tetramethylene sulfone (sulfolane) at 70° and slowly adding 3.2 g. of sodium hydroxide dissolved in 15 ml. of water with stirring for 4 hr. The polymer, 1.6 g. (24%), was isolated from ice–water, extracted with hot water, and dried. A dimeric product which was obtained by Van Lohuizen and Backer[19] by a similar procedure sublimed at 287–290°, whereas our polymer sublimed with decomposition at 355°.

Anal. Calcd. for $(-C_4H_6O_3S-)_x$: C, 35.82; H, 4.47. Found: C, 35.90; H, 4.58.

The infrared spectrum showed strong absorption for SO_2 at 7.7 and 8.8 μ.

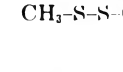
A copolymer of **divinyl sulfone** and **bis(phenylsulfonyl)methane** was prepared in carbon tetrachloride with sodium ethoxide as catalyst by a Michael addition by the procedure of Schoene,[20] m.p. 245–255°; yield, 94.0%. Infrared analysis indicated the structure $[-C(SO_2C_6H_5)_2CH_2CH_2SO_2-]$.

Anal. Calcd. for $(-C_{17}H_{18}O_6S_3-)_x$: C, 48.11; H, 4.24; S, 22.64. Found: C, 47.98; H, 4.95; S, 23.18.

Thermal Decomposition of Polymers.—The polymers were weighed into tared Pyrex glass tubes (a glass-wool plug was inserted to prevent mechanical losses during heating), the tubes were evacuated and the temperature around the samples was raised to 275°. The extent of decomposition determined as described previously is compared in Table III.

TABLE III

THERMAL DECOMPOSITION OF SULFONE POLYMERS AT 275° FOR 1 HR.

Polysulfone	Decomposition products	Decomposition, mole %
	A. No β-hydrogens	
Methylene	SO_2, C_2H_4, CH_4, CO_2, CS_2, CH_3SH, H_2S, CH_3S-CH_3, $CH_3-S-S-CH_3$, 	73
p-Xylylene	SO_2, olefin	10.6
	B. Long methylene chains[a]	
Tetramethylene	SO_2, olefin, hydrocarbon	7.6
Hexamethylene	SO_2, olefin, hydrocarbon	4.8
Octamethylene	SO_2, olefin, hydrocarbon	3.7
p-Xylyleneoctamethylene	SO_2, olefin	7.5
	C. Heterocyclic	
3-Oxythiophene, 1,1-dioxide		No decomposition observed up to 300°
	D. α-Phenyl group	
Phenyleneoctamethylene	SO_2, olefin	2.5
	E. Several β-sulfone groups	
Copolymer of bis(phenylsulfonyl)methane and divinyl sulfone	SO_2, olefin	67

[a] The mechanism of decomposition of polytetra-, hexa-, and octamethylene sulfones is to be published in more detail.

The data of Table III agree with our previous experimental results (Table II) with one exception. The extensive decomposition observed in polymethylene sulfone may be attributed to strong hydrogen bonding between the methylene and sulfone groups associating to give stable six-membered rings within the polymer chain. A disruption of these rings is postulated to occur abruptly at 250°, resulting in rapid decomposition. From the decomposition products of Table III the possibility of a decomposition by C–S scission, occurring at high temperatures and in the absence of β-hydrogens, to produce carbene fragments giving ethylene and episulfide, is reasonable and is being further investigated.

The high instability of the copolymer of bis(phenylsulfonyl)methane and divinyl sulfone containing three sulfonyl groups can be ascribed to their positions β to one $-CH_2-$ group in the polymer repeat unit; the effect of additional sulfone groups appears to be additive.

(16) L. A. Errede and J. M. Hoyt, *J. Am. Chem. Soc.*, **82**, 436 (1960).

(17) H. D. Noether, U. S. Patent 2,534,366 (December 19, 1950); *Textile Res. J.*, **28**, 533 (1958).

(18) A. Kreuchunas, U. S. Patent 2,822,351 (February 4, 1958).

(19) O. E. Van Lohuizen and H. S. Backer, *Rec. trav. chim.*, **68**, 1132 (1949).

(20) D. L. Schoene, U. S. Patent 2,505,366 (April 25, 1960).

Baeyer–Villiger Oxidation of *syn*-7-Chloronorcamphor and *syn*-7-Bromonorcamphor

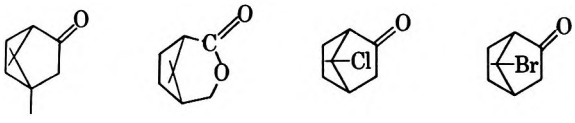
R. R. SAUERS AND J. A. BEISLER

School of Chemistry, Rutgers, The State University, New Brunswick, New Jersey

Received August 7, 1963

Baeyer–Villiger oxidation of *syn*-7-chloronorcamphor and *syn*-7-bromonorcamphor has been investigated. The major products are those formed by methylene migration.

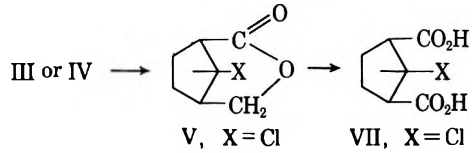
The recent finding that epicamphor (I) is oxidized by peracetic acid to form only β-campholide (II),[1] contrary to predictions based on electronic considerations,[2] has excited our interest in extending the scope of "anomalous" Baeyer–Villiger oxidations. In this communication we describe the results of the reaction of peracetic acid with *syn*-7-chloronorcamphor[3] (III) and *syn*-7-bromonorcamphor[4] (IV) with the expectation that these two ketones would also lead to substantial



amounts of lactones *via* nonelectronically controlled transition states.

Results

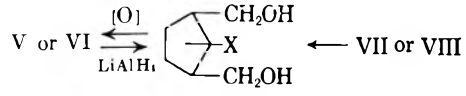
In both bases, the major product was that lactone which arises from migration of the methylene carbon as opposed to the methine carbon at the bridgehead.



V, X = Cl VII, X = Cl
VI, X = Br VIII, X = Br

The structures of these new lactones are assigned as shown on the basis of several lines of evidence. First, they could both be oxidized with nitric acid to the dicarboxylic acids (VII and VIII). Mixture melting points with samples prepared by nitric acid oxidation of the starting ketones were undepressed.

In addition, the lactones were reduced by lithium hydride to the diols (IX and X), both of which were independently synthesized from the dimethyl esters of the acids (VII and VIII). The relatively high yields and close correspondence of physical properties are suggestive of relatively homogeneous lactones initially.



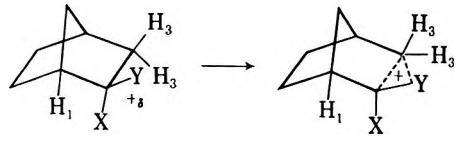
IX, X = Cl
X, X = Br

As a final check on the structure and homogeneity of the lactones, the authentic diols (IX and X) were subjected to mild oxidation.[5] Lactones were formed whose physical properties were very similar, but not quite identical, with those of the Baeyer–Villiger products. Assuming that the Baeyer–Villiger reactions produce only the two possible isomeric pairs of lactones, it is possible to make an estimate of the compositions of the products using the integrated n.m.r. curves since the isomers have different numbers of low-field protons. On this basis, the Baeyer–Villiger lactones are calculated to contain 53% and 71% V and VI, respectively. The figures are probably minimal, considering the other experimental evidence.

Discussion

In addition to what has already been said[1,6] concerning these oxidations with respect to electronic effects *vs.* chair–boat forms in the transition states, we would like to point out a third factor which we believe influences these reactions.

First, we would like to call attention to the results of several rather different kinds of ring-expansion reactions of norbornyl systems of this same general type, *i.e.*, alkyl migrations toward incipient positive centers (eq. 1).



(1)

In addition to Baeyer–Villiger oxidation of norcamphor[6c] (migration toward oxygen), there are five other similar transformations recorded in the literature: reaction of norcamphor with hydrazoic acid[7] (migration to nitrogen), decomposition of norbornyl azide[8] (migration to nitrogen), reaction of norcamphor with diazomethane[9] (migration to carbon), deamination of *exo*-norbornylmethylamine[10] (migration to carbon), and solvolysis of *exo*-norbornylmethyl tosylate[9] (migration to carbon). While these reactions represent a broad spectrum of reaction types, it is intriguing that in the last five cases methylene migration is favored over methine migration despite the generation of boat forms in the transition states. Thus, it appears that it is the Baeyer–Villiger reaction of norcamphor which is exceptional in that it alone is controlled by electronic factors.[11]

(1) R. R. Sauers and G. P. Ahearn, *J. Am. Chem. Soc.*, **83**, 2759 (1961).

(2) M. F. Hawthorne, W. D. Emmons, and K. S. McCallum, *ibid.*, **80**, 6395 (1958).

(3) J. D. Roberts, F. O. Johnson, and R. A. Carboni, *ibid.*, **76**, 5692 (1954).

(4) V. A. Rolleri, Ph.D. thesis, University of Delaware, 1958.

(5) V. I. Stenberg and R. J. Perkins, *J. Org. Chem.*, **28**, 323 (1963).

(6) (a) W. von E. Doering and L. Speers, *J. Am. Chem. Soc.*, **72**, 5515 (1950); (b) M. F. Murray, B. A. Johnson, R. R. Pederson, and A. C. Ott, *ibid.*, **78**, 981 (1956); (c) J. Meinwald and E. Frauenglass, *ibid.*, **82**, 5235 (1960).

(7) R. C. Elderfield and E. T. Losin, *J. Org. Chem.*, **26**, 1703 (1961).

(8) C. L. Arcus, R. E. Marks, and R. Vitterlain, *Chem. Ind.* (London), 1193 (1960).

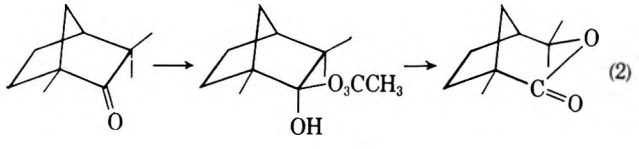
(9) R. R. Sauers and R. J. Tucker, *J. Org. Chem.*, **28**, 876 (1963).

(10) J. Berson and D. Willner, *J. Am. Chem. Soc.*, **84**, 675 (1962).

(11) J. A. Berson and S. Suzuki, *ibid.*, **81**, 4088 (1959), have cogently discussed the relative importance of electronic effects in migrations toward oxygen, nitrogen, and carbon and have concluded that migrations to oxygen should be the most sensitive to electronic differences in the migrating groups.

It seems necessary to consider forces which might work in opposition to both electronic and boat-form interactions in the transition states. The conformation of the leaving residue does not appear to be important since it can readily attain *trans* coplanarity with either of the migrating groups.[2] We believe that the extra factor involved in these reactions is associated with the torsional strain caused by the eclipsed nonbonded interactions between the substituents on C-2 and the hydrogens on C-3.[12] On the other hand, nonbonded interactions between substituents on C-2 and the bridgehead are much less severe since the dihedral angles involved are approximately 44° (H_1 with X) and 79° (H_1 with Y).[13] Thus, migration of the C-2–C-3 bond proceeds with considerable relief of eclipsing strain whereas migration of the C-1–C-2 bond would be expected to involve much less strain relief.

Applied to Baeyer–Villiger reactions of bicyclic ketones, these arguments lead to the conclusion that migration of the C-2–C-3 bond will always be favored regardless of substitution or orientation of the hydroxyperester functions. The results of fenchone oxidation (eq. 2) can now be understood more clearly using these considerations. The electronic effects are essentially equal and the competition is between formation of the boat form and relief of torsional strain. The major product (*ca.* 60%) was the one predicted on the latter basis.



(2)

In those cases where a *syn*-7-substituent is present, these two steric effects operate in the same direction; *i.e.*, chair forms are formed by migration of the C-2–C-3 bond since the hydroxy perester has the opposite configuration from that of the fenchone case.[6c]

Finally, there appears to be a rough correlation between the amount of the "wrong" lactone and the size of the 7-substituent. Assuming that the order of increasing bulk is chlorine < bromine < methyl,[14] one sees an increase in the per cent of methylene migration $< \sim 53\% < \sim 71\% < \sim 100\%$. Presumably, this series also represents the order of increasing importance of boat-form interactions in the transition states.

Experimental

Melting points are uncorrected and were determined on a Mel-Temp apparatus. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrometer. N.m.r. spectra were recorded with a Varian, Model A-60 spectrometer in carbon tetrachloride with tetramethylsilane as internal standard.

syn-**7-Chloronorcamphor**.—*syn*-7-Chloro-*exo*-2-norbornanol was prepared by the procedure of Roberts and co-workers[3] and was oxidized to *syn*-7-chloronorcamphor by the procedure of Brown and Garg.[15] From 27.9 g. (0.19 mole) of alcohol there was obtained 20.6 g. (75%) of a waxy solid, b.p. 67–71° (0.4 mm.), lit.[3] b.p. 105–112° (13 mm.). The 2,4-dinitrophenylhydrazone melted at 191–192, lit.[3] m.p. 192.5–193.5°; the semicarbazone melted at 184–185°, lit.[3] m.p. 183.5–185°. The ketone used in the next step was purified by regeneration from the semicarbazone.[16]

Oxidation of *syn*-7-Chloronorcamphor with Peracetic Acid.—The ketone (10.5 g., 0.073 mole) was dissolved in 100 ml. of glacial acetic acid containing 3.0 g. of sodium acetate. Thirty-five milliliters (*cc.* 0.21 mole) of 40% peracetic acid in acetic acid was added and the solution was kept for 2 weeks in the dark at room temperature. The products were isolated by addition of 500 ml. of water followed by ether extraction. After washing the combined extracts with sodium carbonate and water they were dried over sodium sulfate and evaporated to give 9.2 g. (77%) of crude lactones. All of the starting ketone had been consumed as shown by gas chromatography.

An analytical sample was obtained by gas chromatography on a 5 ft. × 0.25 in. column of silicone (SE-30) at 200° and had m.p. 77–85°, $\lambda_{max}^{CCl_4}$ 5.68 μ.

Anal. Calcd for $C_7H_9ClO_2$: C, 52.33; H, 5.60; Cl, 22.11. Found: C, 52.35; H, 5.69; Cl, 21.86.

The n.m.r. spectrum of this material showed a complex multiplet centered at 5.5 τ which included protons on chlorine- and oxygen-bearing carbons. The ratio of the integrated area of this region to the area of the remainder of the spectrum (between 7 and 8 τ) was 0.39. Assuming that the only two products present are the two isomeric lactones, it can be calculated that lactone V constitutes 53% of the product.

Diacid VII.—Oxidation of the lactonic product was effected by heating 0.978 g. of lactone with 15 ml. of a 70:30 mixture of concentrated nitric acid and water for several minutes. The process was repeated with 10 ml. of the nitric acid solution followed by dilution with water and ether extraction. The acidic products were removed from the combined ether extracts with sodium carbonate solution which was subsequently acidified to liberate the acid fraction. The product was extracted into ether which was dried and evaporated to give 0.14 g. (12%) of *cis*-2-chloro-*cis*-cyclopentane-1,3-dicarboxylic acid after trituration with chloroform. The melting point was 186–189° dec., lit.[3] m.p. 186–187° dec., and was undepressed on admixture with an authentic sample, m.p. 189–191°, prepared similarly in 27% yield by oxidation of *syn*-7-chloronorcamphor.

The **dimethyl ester** of the diacid VII was prepared in 94% yield by heating with BF_3–methanol reagent[17] and had m.p. 108.5–109.5° (needles from cyclohexane), $\lambda_{max}^{CHCl_3}$ 5.80 μ.

Anal. Calcd. for $C_9H_{13}ClO_4$: C, 48.98; H, 5.89; Cl, 16.10. Found: C, 49.24; H, 6.14; Cl, 16.27.

The n.m.r. spectrum showed a sharp singlet at 6.27 τ for the methyl protons and a triplet (J = 4 c.p.s.) at 5.17 τ for the proton on the chlorine-bearing carbon. The relative areas under these peaks was 6:1.

***cis*-1,3-Bis(hydroxymethyl)-*cis*-2-chlorocyclopentane. A. From Diester.**—The diol IX was prepared in 96% yield by reduction of the above diester with lithium aluminum hydride in ether. The melting point of the crude product was 77–80° and was raised to 80–81° by crystallization from benzene, $\lambda_{max}^{CHCl_3}$ 2.92, 9.65 (sh), and 9.80 μ.

Anal. Calcd. for $C_7H_{13}ClO_2$: C, 51.06; H, 7.90; Cl, 21.58. Found: C, 51.29; H, 8.01; Cl, 21.75.

B. From Lactone V.—Lithium aluminum hydride reduction of the Baeyer–Villiger product gave an 81% yield of crude diols whose infrared spectrum was essentially identical with that of the pure diol prepared by procedure A. From a 40-mg. sample of crude diol there was obtained 35 mg. of crystals with m.p. 77–78.5°. The mixture melting point was 78–79°.

Oxidation of Diol IX to Lactone V.[5]—The diol (0.91 g., 5.53 mmoles) was dissolved in 15 ml. of ether and treated with 3.58 g. (12 mmoles) of sodium dichromate dihydrate in 10 ml. of distilled water containing 2.5 ml. of 96% sulfuric acid. After 1 hr. at room temperature, 50 ml. of water was added and the layers were separated. The aqueous phase was extracted further with ether and the combined extracts were washed with sodium carbonate solution. After drying over magnesium sulfate, the ether was evaporated to give 0.27 g. (30%) of lactone V, m.p. 81–92° (sealed capillary). A sample purified by gas chromatography had m.p. 92–99°. Strong absorptions appeared in the infrared

(12) The magnitude of this strain is probably on the order of 2 to 3 kcal./mole. See W. G. Dauben and K. S. Pitzer, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chap. I.

(13) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

(14) See, for example, E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 236.

(15) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

(16) W. G. Woods and J. D. Roberts, *J. Org. Chem.*, **22**, 1124 (1957).

(17) Obtained from Applied Science Laboratories, Inc., State College, Pa. For procedure, see L. D. Metcalfe and A. A. Schmitz, *Anal. Chem.*, **33**, 363 (1961).

spectrum (CCl_4) at 5.70, 8.32, 8.67, and 9.43 μ. The Baeyer–Villiger lactone had some medium intensity bands not found in this spectrum.

The n.m.r. spectrum of this product was slightly simpler than the Baeyer–Villiger product and the ratio of areas of high-field to low-field protons was almost exactly 9:3.

syn-7-**Bromonorcamphor**.—*syn*-7-Bromo-*exo*-2-acetoxynorbornane was prepared by the procedure of Krieger[18] and had b.p. 117–122° (2.5 mm.), lit.[18] b.p. 124–125° (13 mm.), lit.[4] 94–95° (1 mm). Lithium aluminum hydride reduction of this substance in ether gave the corresponding alcohol as a viscous liquid. Oxidation of the crude alcohol by the method of Brown and Garg[15] gave *syn*-7-bromonorcamphor in 70% yield, b.p. 101–106° (1.25 mm.), $n^{20}D$ 1.5349 [lit.[4] b.p. 126–127° (1 mm.), $n^{22}D$ 1.5123]. The 2,4-dinitrophenylhydrazone melted at 202–203°, lit.[4] m.p. 193–194°.

The semicarbazone was prepared in the usual manner, m.p. 187–188°.

Anal. Calcd. for $C_8H_{12}N_3OBr$: C, 39.05; H, 4.92; N, 17.08. Found: C, 38.94; H, 4.89; N, 17.37.

Oxidation of *syn*-7-Bromonorcamphor with Peracetic Acid.—To a solution of 1.52 g. (8.05 mmoles) of ketone (purified by regeneration of the semicarbazone[16]) in 30 ml. of glacial acetic acid containing 0.5 g. of sodium acetate was added 15 ml. (*ca.* 0.09 mole) of 40% peracetic acid. After standing at room temperature in the dark for 15 days, the reaction mixture was diluted with water and extracted with ether. Further processing, as before, gave 1.2 g. (73%) of a viscous oil which was shown to contain no starting material by gas chromatography. This product discolored on attempted molecular distillation and the corresponding n.m.r. spectrum showed two main regions of absorption. One region was centered at 5.5 and the other extended from 7 to 8 τ. The relative areas of these two regions was 0.43 from which it can be calculated that the mixture of lactones is at least 71% VI. The carbonyl stretching frequency appeared at 5.75 μ ($CHCl_3$) and the spectrum in general showed a few weak bands not found in the spectrum of VI prepared later from the diol.

A small sample (0.129 g.) was purified for analysis by crystallization from pentane at −70° to give 0.089 g. of crystalline material which melted at 59.5–61° after sublimation.

Anal. Calcd. for $C_7H_9BrO_2$: C, 40.97; H, 4.39. Found: C, 41.07; H, 4.66.

Diacid VIII.—Oxidation of the bromolactone (0.86 g.) with nitric acid gave 0.2 g. (21%) of crystalline material, m.p. 170–172° dec. The melting point was undepressed on admixture with a sample, m.p. 176.5–177° dec., prepared similarly in 25% yield by nitric acid oxidation of *syn*-7-bromonorcamphor. The diacids were somewhat unstable and did not give good carbon–hydrogen analyses. The dimethyl ester was prepared with BF_3–methanol reagent[17] and could be readily purified by crystallization from pentane, m.p. 86–87°, $\lambda_{max}^{CHCl_3}$ 5.86 μ.

Anal. Calcd. for $C_9H_{13}BrO_4$: C, 40.75; H, 4.91; Br, 30.19. Found: C, 40.78; H, 5.03; Br, 30.10.

The n.m.r. spectrum showed a triplet (J = 4 c.p.s.) at 5.17 and a sharp singlet at 6.22 τ. The relative areas of these two peaks was 1:6.

cis-**1,3-Bis(hydroxymethyl)**-*cis*-**2-bromocyclopentane. A. From Diester.**—The previous diester was reduced with lithium aluminum hydride in ether to give a 78% yield of diol X, m.p. 92–93.5°. The infrared spectrum was identical with that of the sample prepared in procedure B.

B. From Lactone VI.—Lithium aluminum hydride reduction of the lactone (1.55 g.) in ether gave 0.87 g. (55%) of crystalline diol X, m.p. 93–93.5°. The infrared spectrum in chloroform showed O–H absorption at 2.78 (sharp) and 2.92 μ (weak, broad) and C–O absorption at 9.6 and 9.75 μ (strong).

Anal. Calcd. for $C_7H_{13}BrO_2$: C, 40.19; H, 6.22; Br, 38.28. Found: C, 39.97; H, 6.19; Br, 38.52.

Oxidation of Diol X.—Oxidation of diol X (0.17 g.) dichromate as before gave 0.050 g. of an oil which solidified on sublimation at 25 μ, m.p. 61.5–62.5° (sealed capillary). Strong infrared peaks appeared at 5.73, 8.68, 9.22, 9.43, and 9.63 μ (CCl_4).

Acknowledgment.—We wish to thank the National Science Foundation for financial support (G-19143) and for funds toward the purchase of the n.m.r. spectrometer. J. A. B. wishes to acknowledge the National Institutes of Health for a predoctoral fellowship.

(18) H. Krieger, *Suomen Kemistilehti*, **34B**, 24 (1961).

Notes

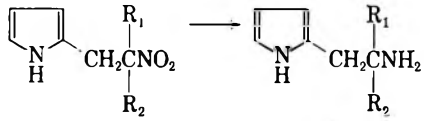
Pyrroles. XV. Some New Alkylations by Means of Pyrrole Mannich Bases[1]

WERNER HERZ AND ULRICH TOGGWEILER

Department of Chemistry, The Florida State University, Tallahassee, Florida

Received July 22, 1963

In order to extend the methods available for the preparation of pyrrolealkylamines, a study of the alkylation[2] of various nitro compounds by the pyrrole Mannich base[3] was undertaken. Reaction of the sodium salts of nitroethane, 1- and 2-nitropropane, nitrocyclohexane, and ethyl 2-nitropropionate with 2-dimethylaminomethylpyrrole by quaternization *in situ* furnished the 2-pyrrolemethyl-substituted nitro derivatives (I) in yields ranging from 23–51%. Alkylations of nitromethane and ethyl nitroacetate were not successful. Catalytic hydrogenation of the condensation products by a special method (see Experimental) resulted in formation of the desired amines.

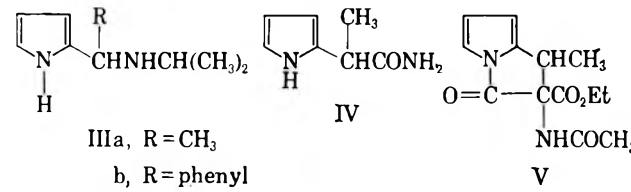


I II

For mechanistic studies of the alkylation reaction we envisaged the synthesis and resolution of Mannich bases carrying a substituent on the carbon atom adjacent to the pyrrole nucleus.[4] Since such bases are not conveniently available from pyrrole by the Mannich reaction,[6] recourse was had to a method involving addition of the substrate to an aldimine.[7,8] In this manner, pyrrole and ethylideneisopropylamine or, more directly, pyrrole, acetaldehyde, and isopropylamine gave the base IIIa in 52% yield. IIIb was formed analogously from pyrrole and benzylideneisopropylamine.

Attempts to quaternize IIIa failed[9] and it was, therefore, necessary to carry out the alkylations with the base itself (elimination–addition conditions), although it has been shown previously[1] that yields in the pyrrole series are much improved when the base is quaternized (substitution conditions). Because of the prolonged time required for completion of the reaction, alkylation of cyanide resulted in formation of the amide (IV, 32%) rather than the nitrile. Similarly, only the lactam V was formed by reaction of IIIa with diethylacetamidomalonate in xylene (*cf.* ref. 3).

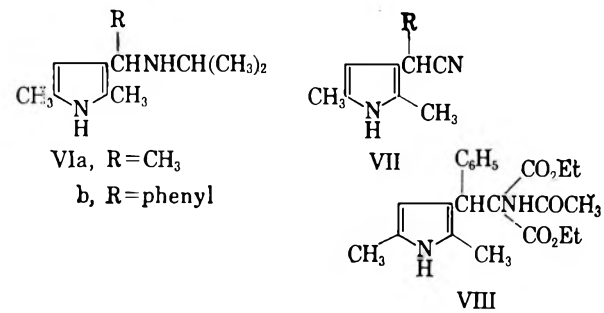
To circumvent this difficulty, the Mannich bases VIa and VIb were prepared from 2,5-dimethylpyrrole and the appropriate aldimine. Reaction of VIa with cyanide ion gave a mixture of the desired nitrile VII (19%) and the corresponding acid (27%). Alkylation of diethyl acetamidomalonate with VIb furnished 60% of the expected product VIII.



IIIa, R = CH_3
b, R = phenyl

IV

V



VIa, R = CH_3
b, R = phenyl

VII

VIII

Experimental[10]

1-(2-Pyrrole)-2-nitrobutane (Ia, R_1 = Ethyl; R_2 = H).—Sodium (4.9 g., 0.21 g.-atom) was added to 250 ml. of absolute ethanol in a flask fitted with stirrer, condenser, drying tube, dropping funnel, and nitrogen inlet. A mixture of 32.4 g. (0.36 mole) of 1-nitropropane and 22.5 g. (0.18 mole) of dimethylaminomethylpyrrole was added followed by 36.5 g. (0.29 mole) of dimethyl sulfate over a period of 30 min. The temperature was not allowed to rise above 35° and stirring was continued until the evolution of trimethylamine (flushed out by nitrogen) had ceased. The solvent was removed at reduced pressure, the residue poured into ice–water and extracted with ether or methylene chloride. The organic extracts were washed, dried, and distilled to yield 14.5 g. (48%), b.p. 102–103° (0.4 mm.), $n^{22}D$ 1.509. The product and its homologs exhibited a tendency to decompose on standing.

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.12; H, 7.19; N, 16.64. Found: C, 57.31; H, 7.38; N, 16.30.

1-(2-Pyrrole)-2-nitropropane (Ib, R_1 = CH_3; R_2 = H).—Reaction of 22.5 g. (0.18 mole) of 2-dimethylaminomethylpyrrole with 27 g. (0.36 mole) of nitroethane in the manner described in the preceding paragraph furnished 8.9 g. (32%) of product, b.p. 97–99° (0.5 mm.).

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.44; H, 6.82; N, 18.40.

2-(2-Pyrrolemethyl)-2-nitropropane (Ic, R_1 = R_2 = CH_3).—Condensation of 22.5 g. (0.18 mole) of 2-dimethylaminomethylpyrrole with 32.4 g. (0.36 mole) of 2-nitropropane gave 15.2 g. (51%) of product, b.p. 90–92° (0.6 mm.).

(1) Previous paper, W. Herz and R. L. Settine, *J. Org. Chem.*, **24**, 201 (1959). Supported in part by the Office of Ordnance Research, U. S. Army, under Contract DA-01-009-ORD-436.

(2) For a review of previously studied alkylations, see H. Hellmann and G. Opitz, "α-Aminoalkylierung," Verlag Chemie, Weinheim, 1960, pp. 285–287.

(3) W. Herz, K. Dittmer, and S. J. Cristol, *J. Am. Chem. Soc.*, **70**, 504 (1948).

(4) This work was begun in 1957 and was interrupted when similar studies using optically active indole derivatives were reported.[5]

(5) J. D. Albright and H. R. Snyder, *J. Am. Chem. Soc.*, **81**, 2239 (1959).

(6) U. Eisner, *J. Chem. Soc.*, 854 (1957).

(7) H. R. Snyder and D. S. Matteson, *J. Am. Chem. Soc.*, **79**, 2217 (1957).

(8) The intramolecular addition of a pyrrolaldimine to the pyrrole nucleus has since been reported: R. B. Woodward, *et al.*, *J. Am. Chem. Soc.*, **82**, 3800 (1960).

(9) For similar observations in the indole series, see ref. 5.

(10) Melting points and boiling points are uncorrected. Analyses by Dr. Weiler and Dr. Strauss, Oxford, England.

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.12; H, 7.19; N, 16.64. Found: C, 56.80; H, 7.48; N, 16.10.

2-(2-Pyrrolemethyl)-1-nitrocyclohexane [Id, $R_1 = R_2 = -(CH_2)_5-$].—Condensation of 22.5 g. (0.18 mole) of 2-dimethylaminomethylpyrrole with 43.5 g. (0.36 mole) of nitrocyclohexane in the usual manner gave 9.3 g. (25%) of the title compound, b.p. 129–131° (0.4 mm.).

Anal. Calcd. for $C_{11}H_{16}N_2O_2$: C, 63.40; H, 7.74; N, 13.45. Found: C, 62.95; H, 7.78; N, 13.70.

Ethyl 2-Nitro-2-(2-pyrrolemethyl)propionate (Ie, $R_1 = CH_3$; R_2 = **Carbethoxy**).—Condensation of 22.5 g. (0.18 mole) of 2-dimethylaminomethylpyrrole with 53 g. (0.36 mole) of ethyl 2-nitropropionate furnished 9.6 g. (23%) of product, b.p. 110–112° (0.3 mm.). This substance decomposed too rapidly for analysis and immediately was reduced to the amine.

1-(2-Pyrrole)-2-aminobutane (IIa).—A solution of 15 g. (0.9 mole) of Ia in 150 ml. of absolute ethanol was refluxed for 0.5 hr. with some Raney nickel, filtered, and reduced in a Parr hydrogenator with 0.2 g. of platinum oxide until hydrogen uptake ceased (when the Raney nickel treatment was omitted, the reduction did not proceed). After removal of solvent, the product was purified through the hydrochloride, regenerated by treatment with base, and distilled to yield 6.8 g. (70%), b.p. 81–82° (0.8 mm.).

Anal. Calcd. for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.70; H, 10.10; N, 19.85.

1-(2-Pyrrole)-2-aminopropane (IIb).—Catalytic reduction of Ib in the same manner gave a 55% yield of IIb, b.p. 80–81° (1 mm.), which decomposed too rapidly for analysis; acetyl derivative, m.p. 93–93.5°; phenylthiourea derivative, m.p. 149–150°. The product was characterized as the acid succinate, m.p. 73–74°.

Anal. Calcd. for $C_{11}H_{18}N_2O_4$: C, 54.52; H, 7.49; N, 11.57. Found: C, 54.11; H, 7.68; N, 11.52.

2-(2-Pyrrolemethyl)-2-aminopropane (IIc).—Prepared from Ic in 73% yield, b.p. 79–79.5°, it decomposed too rapidly to permit analysis. It was characterized as the phenylthiourea derivative, m.p. 125.5–126.5°, and analyzed as the acid succinate, m.p. 145–146°.

Anal. Calcd. for $C_{12}H_{20}N_2O_4$: C, 56.24; H, 7.87; N, 10.93. Found: C, 56.25; H, 7.89; N, 10.90.

Ethyl 2-(2-pyrrolemethyl)-2-aminopropionate (IIe).—This substance, m.p. 72.5–73.5°, was obtained in 58% yield by catalytic reduction of Ie.

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.20; H, 8.00; N, 14.56.

2-(Isopropylaminoethylidene)pyrrole (IIIa).—To a solution of 20.2 g. (0.31 mole) of pyrrole in 150 ml. of acetic acid kept below 15° was added, in an atmosphere of nitrogen, 19.5 g. (0.33 mole) of isopropylamine and then over 1 hr. an ice-cold solution of 14 g. (0.32 mole) of acetaldehyde in 60 ml. of benzene. Stirring was continued for 3 hr. and the flask stored in a refrigerator for 3 days. The contents were poured into 500 ml. of ice water and 50 ml. of ether. The ether layer was separated and washed with sodium bisulfate. The combined aqueous layers were washed with ether and brought to pH 7 with 30% sodium hydroxide solution at a temperature not exceeding 20°. The material which precipitated was filtered and the filtrate made basic. The product was extracted with one 100-ml. and two 30-ml. portions of cyclohexane and the extract chilled in a Dry Ice–acetone bath. There precipitated 24 g. (52%) of IIIa, m.p. 49–51°. Sublimation furnished the analytical sample, m.p. 58–58.5°, whose picrate melted at 163–165° dec.

Anal. Calcd. for $C_9H_{16}N_2$: C, 71.00; H, 10.59; N, 18.42. Found: C, 70.85; H, 10.38; N, 18.55.

2-(2-Pyrrole)propionamide (IV).—A solution of 9.0 g. (0.06 mole) of IIIa and 11.7 g. of potassium cyanide in 900 ml. of 80% ethanol was refluxed with stirring for 130 hr. until the evolution of isopropylamine had ceased, concentrated to 70 ml. on the water pump, and extracted thoroughly with methylene chloride. The organic extracts were washed, dried, and evaporated; yield of amide was 2.5 g. (32%), m.p. 120.5–121°, after recrystallization from benzene and vacuum sublimation.

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.62; H, 7.49; N, 19.88.

The aqueous layer was acidified and extracted with methylene chloride. Purification of the acidic gum, presumably 2-(2-pyrrole)propionic acid, 4 g., by crystallization was unsuccessful; distillation resulted in decomposition.

Preparation of Lactam V.—A solution of 4.5 g. (0.03 mole) of 2-isopropylaminoethylidene pyrrole and 3 g. (0.014 mole) of diethyl acetamidomalonate in 50 ml. of xylene was heated at 90–95° with stirring for 55 hr. About 75% of the theoretical amount of isopropylamine was evolved. Cooling resulted in precipitation of 2.7 g. (51%) of lactam V, which was recrystallized from aqueous ethanol, m.p. 155–155.5°.

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10, N, 10.60. Found: C, 58.75; H, 6.24; N, 10.35.

2-Isopropylaminobenzylidene Pyrrole (IIIb).—To a solution of 7 g. (0.115 mole) of pyrrole in 75 ml. of benzene was added in a nitrogen atmosphere, with cooling and stirring, 25 ml. of acetic acid followed by 15 g. (0.105 mole) of benzylideneisopropylamine in 75 ml. of benzene. The reaction vessel was stored in the refrigerator overnight and the product worked up in the usual manner. It solidified on cooling, yielding 11.5 g. (58%), m.p. 50.5–51.5°, after crystallization from cycloheptane and vacuum sublimation.

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.46; H, 8.46; N, 13.06. Found: C, 78.61; H, 8.50; N, 13.10.

When 10 g. (0.105 mole) of 2,5-dimethylpyrrole was substituted in the above preparation, Mannich base VIb was obtained in 60% yield, m.p. 91–92°, after crystallization from cycloheptane and sublimation.

Anal. Calcd. for $C_{16}H_{22}N_2$: C, 79.29; H, 9.14; N, 11.55. Found: C, 79.03; H, 9.14; N, 11.85.

Diethyl Phenyl-3-(2,5-dimethylpyrrole)methyl-α-acetamidomalonate (VIII).—Reaction of 2.2 g. of VIb with 2.1 g. (0.01 mole) of diethyl acetamidomalonate in boiling toluene for 18 hr. followed by removal of toluene furnished 2.0 g. (60%) of crude VIII, m.p. 179–182°. Two recrystallizations from ethanol raised the melting point to 191.5–192.5°.

Anal. Calcd. for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.05; N, 7.00. Found: C, 65.66; H, 6.96; N, 7.35.

3-(Isopropylaminoethylidene)-2,5-dimethylpyrrole (VIa).—To a solution of 47.5 g. (0.5 mole) of 2,5-dimethylpyrrole in 60 ml. of acetic acid and 100 ml. of toluene–hexane (2:1) kept at 0–10° was added dropwise with stirring 43 g. (0.5 mole) of ethylideneisopropylamine. The temperature was then lowered to −10° which caused precipitation of the acetate of the Mannich base. This was filtered, washed with toluene, dissolved in water, and made basic. There was precipitated 45 g. (50%) of VIa which was sublimed *in vacuo*, m.p. 98–99°. The picrate melted at 138–140°.

Anal. Calcd. for $C_{11}H_{20}N_2$: C, 73.28; H, 11.18; N, 15.54. Found: C, 73.17; H, 11.18; N, 15.41.

2-[3-(2,5-Dimethylpyrrole)]propionitrile.—Reaction of 6.4 g. of VIa with 5 g. of potassium cyanide in aqueous ethanol, until the theoretical volume of isopropylamine had evolved, yielded in the neutral fraction 1 g. of the nitrile, b.p. 112–113° (0.6 mm.), nitrile band at 2250 $mm.^{-1}$.

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.94; H, 8.16; N, 18.90. Found: C, 72.80; H, 8.01; N, 18.58.

The acid fraction furnished 1.5 g. of the corresponding acid, m.p. 96–98°. Sublimation raised the melting point to 99.5–100.5°. The substance exhibited the usual air sensitivity of pyrrole acetic acids.

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 65.04; H, 7.98; N, 8.22.

The Synthesis of C-15 β-Substituted Estra-1,3,5(10)-trienes. II[1]

E. W. CANTRALL, RUDDY LITTELL, AND SEYMOUR BERNSTEIN

Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York

Received July 1, 1963

In part I of the titled paper[1] certain chemical properties of the Δ^{15}-17-one moiety of 3-methoxyestra-

(1) Part I, E. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, **29**, 64 (1964).

TABLE I

MOLECULAR ROTATION ANALYSIS

Compound	$[\alpha]_D$	$[M]_D$	$\Delta[M]_D$
Estrone[3-hydroxyestra-1,3,5(10)-trien-17-one]	+165°[a]	+446°	
15β-Benzyloxy-3-hydroxyestra-1,3,5(10)-trien-17-one	+55°	+207°	−239°
3,15β-Dihydroxyestra-1,3,5(10)-trien-17-one	+174° (pyridine)	+498°	+ 52°
3-Hydroxy-15β-methoxyestra-1,3,5(10)-trien-17-one	+97°[c]	+291°	−155°
15β-Allyloxy-3-hydroxyestra-1,3,5(10)-trien-17-one	+37°[c]	+121°	−325°
15β-(2′-Dimethylamino)ethoxy-3-hydroxyestra-1,3,5(10)-trien-17-one	+61°[c]	+218°	−228°
15β-(2′-Diethylamino)ethoxy-3-hydroxyestra-1,3,5(10)-trien-17-one	+57°[c]	+220°	−226°
15β-Cyano-3-hydroxyestra-1,3,5(10)-trien-17-one	+79°[c] (pyridine)	+233°	−213°
β-Estradiol(estra-1,3,5(10)-trien-3,17β-diol)[a]	+81° (ethanol)[b]	+218°	
15β-Methoxy-estra-1,3,5(10)-trien-3,17β-diol	+27° (pyridine)	+103°	−115°
15β-Cyano-estra-1,3,5(10)-trien-3,17β-diol	±0° (pyridine)	±0°	−218°

[a] V. Deulofeu and J. Ferrari, *Z. Physiol. Chem.*, **226**, 192 (1934). [b] B. Whitman, O. Wintersteiner, and E. Schwenk, *J. Biol. Chem.*, **118**, 789 (1937).

1,3,5(10),15-tetraen-17-one were described. We wish to record in this note the application of these findings to 3-hydroxyestra-1,3,5(10),15-tetraen-17-one (**4**), thus providing a number of novel estrone and β-estradiol intermediates and derivatives.

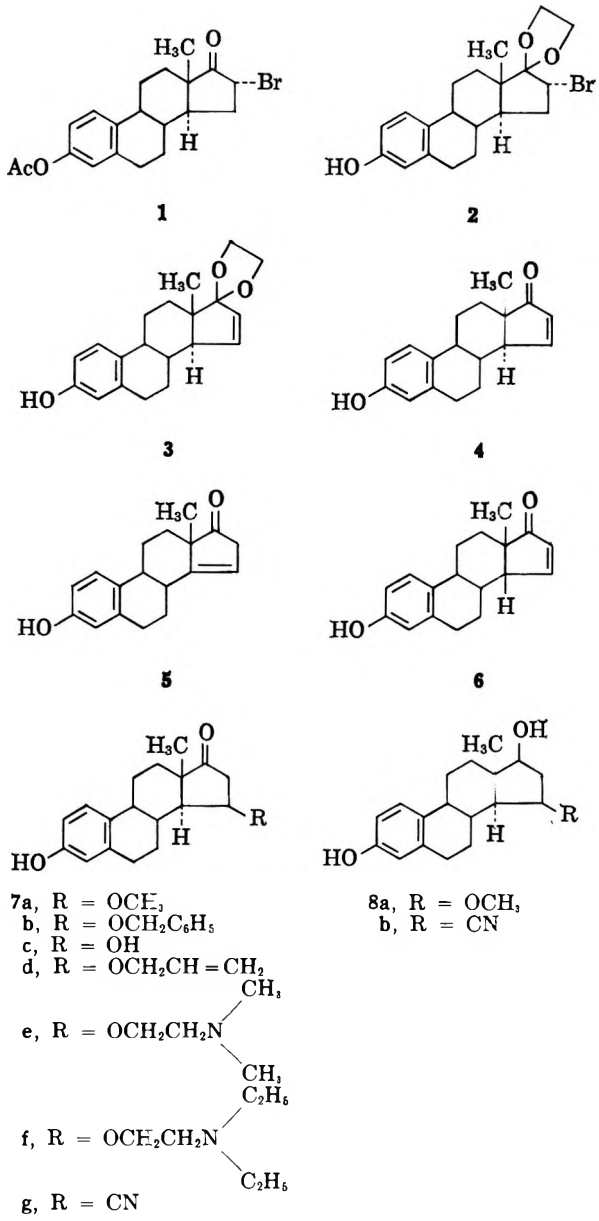
3-Hydroxyestra-1,3,5(10),15-tetraen-17-one (**4**) was synthesized according to the sequence described for the 3-methyl ether.[1] Ketalization of 3-acetoxy-16α-bromoestra-1,3,5(10)-trien-17-one (**1**)[2] in toluene–ethylene glycol with *p*-toluenesulfonic acid over a period of 44 hr. gave a 69% yield of 16α-bromo-17-ethylenedioxyestra-1,3,5(10)-trien-3-ol (**2**). Dehydrobromination of the latter with potassium *t*-butoxide in toluene gave 17-ethylenedioxyestra-1,3,5(10),15-tetraen-3-ol (**3**). Mild acid hydrolysis afforded the desired intermediate, 3-hydroxyestra-1,3,5(10),15-tetraen-17-one (**4**).

Compound **4** on treatment with *p*-toluenesulfonic acid in refluxing benzene afforded a mixture, separated by partition chromatography, which consisted of 3-hydroxyestra-1,3,5(10),14-tetraen-17-one (**5**, 50% yield, ν_{max} 1730 and 1612 cm.$^{-1}$) and 3-hydroxy-14β-estra-1,3,5(10),15-tetraen-17-one (**6**, 19% yield, ν_{max} 1690 and 1620 cm.$^{-1}$, λ_{max} 222 and 280 mμ, ε 15,500 and 2550,. respectively).

Treatment of the 14α-Δ^{15}-17-one (**4**) with potassium hydroxide in aqueous methanol resulted in a quantitative yield of 3-hydroxy-15β-methoxyestra-1,3,5(10)-trien-17-one (**7a**). The corresponding 15β-hydroxy derivative (**7c**) was obtained by hydrogenolysis of 15β-benzyloxy-3-hydroxyestra-1,3,5(10)-trien-17-one (**7b**), in turn prepared from **4** by reaction with benzyl alcohol and potassium hydroxide. Similarly from **4**, the following were prepared by the addition of the appropriate nucleophile: 15β-allyloxy-3-hydroxyestra-1,3,5(10)-trien-17-one (**7d**), 3-hydroxy-15β-(2′-dimethylamino)ethoxyestra-1,3,5(10)-trien-17-one (**7e**), 3-hydroxy-15β-(2′-diethylamino)ethoxyestra-1,3,5(10)-trien-17-one (**7f**), and 15β-cyano-3-hydroxyestra-1,3,5(10)-trien-17-one (**7g**).

In addition, 15β-methoxyestra-1,3,5(10)-trien-3,17β-diol (**8a**) and 15β-cyanoestra-1,3,5(10)-triene-3,17β-diol (**8b**) were prepared by sodium borohydride reduction of the 17-ones, **7a** and **7g**, respectively.

In Table I, the new C-15 substituted estrogens described herein have been submitted to molecular rotational analysis. The solvent effect in several instances has been disregarded with reservation. Generally, with the exception of 3,15β-dihydroxyestra-1,3,5(10)-trien-17-one (**7c**), it can be seen that the compounds conform with the anticipated negative shift in molecular rotation for a C-15 β-substituent.[1] It is believed that the rotational difference of **7c** is exceptional due probably to a solvent effect.



(2) W. S. Johnson and W. F. Johns [*J. Am. Chem. Soc.*, **79**, 2005 (1957)] have reported that a preliminary study of this ketalization was undertaken but was not studied further due to complications resulting from partial solvolysis of the acetoxy group.

Experimental

Melting points are uncorrected. The optical rotations are for chloroform solutions at 25° unless noted otherwise. The infrared absorption spectra were determined in potassium bromide disks, and the ultraviolet absorption spectra were determined in methanol. Petroleum ether refers to the fraction, b.p. 60–70°.

The authors are indebted to William Fulmor and associates for the infrared, ultraviolet, and optical rotation data. We wish also to thank Louis M. Brancone and associates for the analyses.

16α-Bromo-17-ethylenedioxyestra-1,3,5(10)-trien-3-ol (2).—A solution of 16α-bromoestrone acetate (**1**, 1.2 g.)[2] and *p*-toluenesulfonic acid monohydrate (0.220 g.) in toluene (60 ml.) and ethylene glycol (5 ml.) was distilled slowly through a Vigreux column for 44 hr. (total distillate, 45 ml.). The reaction mixture was cooled, neutralized with saturated sodium bicarbonate solution, and extracted with ethyl acetate. Evaporation, and crystallization of the residue from methanol gave 0.825 g. of **2**, m.p. 234–236°. A sample for analysis was recrystallized twice from the same solvent, m.p. 246–247° dec.; $[\alpha]_D$ +20°; ν_{max} 3500 and 1624 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{25}O_3Br$ (393.32): C, 61.06; H, 6.41; Br, 20.31. Found: C, 61.03; H, 6.71; Br, 20.34.

17-Ethylenedioxyestra-1,3,5(10),15-tetraen-3-ol (3).—A solution of potassium (0.4 g.) in *t*-butyl alcohol (20 ml.) was evaporated. Xylene (20 ml.) was added, and the evaporation was repeated. A solution of 16α-bromo-17-ethylenedioxyestra-1,3,5(10)-trien-3-ol (**2**, 0.600 g.) in xylene (40 ml.) was added to the potassium *t*-butoxide, and the mixture was refluxed under nitrogen for 18 hr. The mixture was cooled and extracted with ether. Evaporation gave 0.275 g. of a semisolid which was crystallized from methanol, 0.130 g., m.p. 215–219°. Two additional recrystallizations from acetone–petroleum ether gave the analytical sample, m.p. 218–220°; $[\alpha]_D$ −87°; ν_{max} 3395 and 1616 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{24}O_3$ (312.39): C, 76.89; H, 7.74. Found: C, 77.20; H, 8.11.

3-Hydroxyestra-1,3,5(10),15-tetraen-17-one (4).—A solution of 17-ethylenedioxyestra-1,3,5(10),15-tetraen-3-ol (**3**, 1.0 g.) and *p*-toluenesulfonic acid monohydrate (0.060 g.) in 85% aqueous acetone (82 ml.) was stirred at room temperature for 1.5 hr. The solution was extracted with ether (350 ml.), and the residue obtained upon evaporation was crystallized from methanol to give 0.475 g. of **4**, m.p. 249–251°. A sample for analysis was recrystallized once from ethanol and once from chloroform–methanol, m.p. 250–252°; λ_{max} 222 and 280 mμ (ε 13,700 and 2350); $[\alpha]_D$ −65°; ν_{max} 3380, 1690, and 1612 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{20}O_2$ (268.34): C, 80.56; H, 7.51. Found: C, 80.38; H, 7.63.

Acid-Catalyzed Isomerization of 3-Hydroxyestra-1,3,5(10),15-tetraen-17-one (4).—To a suspension of **4** (1.04 g.) in benzene (100 ml.) was added *p*-toluenesulfonic acid monohydrate (0.700 g.). The steroid completely dissolved upon warming the mixture, and the resulting solution was refluxed for 15 min. The solution was extracted with benzene which on evaporation gave 1.0 g. of a crystalline solid. The latter was subjected to partition chromatography on Celite 545[3] with an *n*-heptane–methanol solvent system. Holdback volumes 3.0 to 5.2, on evaporation, gave 3-hydroxyestra-1,3,5(10),14-tetraen-17-one (**5**, 0.500 g.), m.p. 185–189°. Crystallization once from acetone–petroleum ether and once from ether–petroleum ether gave the analytical sample, m.p. 188–191°; λ_{max} 222 and 280 mμ (ε 8600 and 2260); $[\alpha]_D$ +294°; ν_{max} 3420, 1730, and 1612 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{20}O_2$ (268.34): C, 80.56; H, 7.51. Found: C, 80.00; H, 7.52.

Evaporation of the eluate corresponding to holdback volumes 5.5 to 7.0 gave 3-hydroxy-14β-estra-1,3,5(10),15-tetraen-17-one (**6**, 0.190 g.), m.p. 205–210°. A sample for analysis was recrystallized twice from acetone–petroleum ether and had m.p. 222–224°; λ_{max} 222 and 280 mμ (ε 15,500 and 2550); $[\alpha]_D$ +475°; ν_{max} 3240, 1690, and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{20}O_2$ (268.34): C, 80.56; H, 7.51. Found: C, 80.06; H, 7.79.

3-Hydroxy-15β-methoxyestra-1,3,5(10)-trien-17-one (7a).—A solution of 3-hydroxyestra-1,3,5(10),15-tetraen-17-one (**4**, 0.450 g.) in methanol–tetrahydrofuran (55 ml., 10:1) was treated with 5% aqueous sodium hydroxide (1.2 ml.). The resulting solution was stirred for 0.5 hr., diluted with water, and the product was collected by filtration to give 0.450 g. of **7a**, m.p. 223–227°. Two crystallizations from acetone–petroleum ether gave the analytical sample, m.p. 224–226°; λ_{max} 222 and 278 mμ (ε 8300 and 2100); $[\alpha]_D$ +97°; ν_{max} 3400, 1732, and 1612 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{24}O_3$ (300.38): C, 75.97; H, 8.05; OCH_3, 4.99. Found: C, 75.41; H, 8.08; OCH_3, 4.88.

15β-Benzyloxy-3-hydroxyestra-1,3,5(10)-trien-17-one (7b).—A solution containing 3-hydroxyestra-1,3,5(10),15-tetraen-17-one (**4**, 1.0 g.) and powdered potassium hydroxide (0.600 g.) in benzyl alcohol (20 ml.) was stirred at room temperature for 4 hr. The reaction mixture was treated with ethyl acetate, filtered, steam distilled, and then extracted with ethyl acetate. Evaporation, and crystallization of the crude product from benzene afforded 0.480 g., m.p. 124–127°. A sample for analysis was recrystallized from acetone–benzene and had m.p. 125–128°; λ_{max} 222 and 282 mμ (ε 7600 and 1900); $[\alpha]_D$ +55°; ν_{max} 3390, 1730, 1615, and 734 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{28}O_3$ (376.47): C, 79.75; H, 7.50. Found: C, 79.92; H, 7.37.

3,15β-Dihydroxyestra-1,3,5(10)-trien-17-one (7c).—A solution of 15β-benzyloxy-3-hydroxyestra-1,3,5(10)-trien-17-one (**7b**, 0.300 g.) in acetic acid (4 ml.) containing 10% palladium–charcoal catalyst (0.100 g.) was hydrogenated for 4 hr. at room temperature and atmospheric pressure. The product was extracted with ethyl acetate, and the residue obtained on evaporation was recrystallized three times from acetone–petroleum ether to give the analytical sample, m.p. 224–227°; λ_{max} 222 and 280 mμ (ε 7200 and 2000); $[\alpha]_D$ +174° (pyridine); ν_{max} 3450, 3280, 1722, and 1628 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{22}O_3$ (286.36): C, 75.49; H, 7.74. Found: C, 75.36; H, 7.92.

15β-Allyloxy-3-hydroxyestra-1,3,5(10)-trien-17-one (7d).—A solution of **4** (1.0 g.) in allyl alcohol (50 ml.) containing 5% aqueous sodium hydroxide (2 ml.) was stirred at room temperature for 50 min. The solution was neutralized with acetic acid, and extracted with benzene. The residue obtained on evaporation was crystallized from methanol–water to yield 0.710 g. of **7d**, m.p. 165–168°. Further recrystallization did not alter the melting point; λ_{max} 222 and 282 mμ (ε 10,200 and 2800); $[\alpha]_D$ +37°; ν_{max} 3440, 1735, and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{26}O_3$ (326.42): C, 77.27; H, 8.03. Found: C, 76.77; H, 8.40.

3-Hydroxy-15β-(2′-dimethylamino)ethoxyestra-1,3,5(10)-trien-17-one (7e).—A solution containing **4** (0.300 g.) and 5% aqueous sodium hydroxide (1 ml.) in 2-dimethylaminoethanol (20 ml.) was stirred under a nitrogen atmosphere for 2 hr. at room temperature. Water was added, followed by several drops of acetic acid to give a solid which was collected by filtration, 0.22 g., m.p. 180–184°. Two crystallizations from acetone–petroleum ether gave **7e**, m.p. 185–187° $[\alpha]_D$ +61°.

Anal. Calcd. for $C_{22}H_{31}O_3N$ (357.48): C, 73.91; H, 8.74; N, 3.92. Found: C, 73.51; H, 8.63; N, 4.06.

3-Hydroxy-15β-(2′-diethylamino)ethoxyestra-1,3,5(10)-trien-17-one (7f).—A solution of **4** (0.600 g.) and 5% aqueous sodium hydroxide (2 ml.) in 2-diethylaminoethanol (15 ml.) was stirred at room temperature under a nitrogen atmosphere for 3 hr. The mixture was diluted with water and extracted with ethyl acetate. Evaporation gave an oil (0.6 g.) which by infrared analysis was shown to be a mixture of starting material and desired product. The oil was then subjected to partition chromatography on Celite 545[3] with a *n*-heptane–methanol solvent system. Holdback volume 9.5–10 on evaporation gave 70 mg. of **7b**, m.p. 131–134°. A sample recrystallized from acetone–petroleum ether for analysis had m.p. 131–134°, $[\alpha]_D$ +57°.

Anal. Calcd. for $C_{24}H_{35}O_3N$ (385.53): C, 74.96; H, 9.15; N, 3.63. Found: C, 74.84; H, 9.22; N, 3.66.

15β-Cyano-3-hydroxyestra-1,3,5(10)-trien-17-one (7g).—Treatment of **4** (0.250 g.) with sodium cyanide in refluxing aqueous tetrahydrofuran as described[1] afforded 0.180 g., m.p. 260–65°. Two recrystallizations from methanol gave the analytical sample, m.p. 274–276°; λ_{max} 222 and 280 mμ (ε 8300 and 2100); $[\alpha]_D$ +79° (pyridine); ν_{max} 3390, 2230, 1732, and 1628 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{21}O_2N$ (295.37): C, 77.26; H, 7.17; N, 4.74. Found: C, 77.04; H, 7.24; N, 4.74.

15β-Methoxyestra-1,3,5(10)-triene-3,17β-diol (8a).—A solution of 3-hydroxy-15β-methoxyestra-1,3,5(10)-trien-17-one (**7a**, 0.200 g.) and sodium borohydride (0.200 g.) in methanol (20 ml.) was stirred at room temperature for 1 hr. Water was added,

(3) Celite 545 is a trade-mark of the Johns-Manville Corp. for a grade of diatomaceous earth. That used for partition chromatography was washed with 6 *N* hydrochloric acid, water, and methanol, and was then dried to constant weight.

and the product was extracted with chloroform. Evaporation gave an oil which gave crystals from acetone–petroleum ether, 0.160 g., m.p. 85–95° (containing acetone of crystallization by infrared analysis). Two recrystallizations from ether–benzene gave the analytical sample, m.p. 128–130°, containing 1 mole of benzene of crystallization; λ_{max} 222 and 280 mμ (ε 7600 and 2280); $[\alpha]D$ +27° (pyridine); ν_{max} 3420, 1620, and 678 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{26}O_3 \cdot C_6H_6$ (382.54): C, 78.49; H, 8.96; OCH_3, 3.88. Found: C, 78.19; H, 8.72; OCH_3, 3.82.

15β-Cyanoestra-1,3,5(10)-trien-3,17β-diol (**8b**).—A solution of 15β-cyanoestra-1,3,5(10)-trien-3-ol-17-one (**7g**, 0.280 g.) and sodium borohydride (0.2 g.) in methanol–tetrahydrofuran (7:1, 40 ml.) was stirred at room temperature for 2 hr. Water was added and the product was collected by filtration to give 0.245 g., m.p. 280–282°. A sample for analysis was recrystallized twice from methanol, m.p. 284–286°; λ_{max} 222 and 280 mμ (ε 7500 and 2200); $[\alpha]D$ ±0° (pyridine); ν_{max} 3460, 2250, and 1612 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{23}O_2N$ (297.38): C, 76.73; H, 7.80; N, 4.71. Found: C, 76.43; H, 7.96; N, 4.84.

4-Cyanoformyl-1-methylpyridinium Iodide Oxime and Derivatives

E. J. POZIOMEK,[1] R. H. POIRIER,[2] B. W. FROMM,[1]
D. N. KRAMER,[1] J. A. STOCKINGER,[1] AND M. D. PANKAU[1]

U. S. Army Chemical Research and Development Laboratories, Edgewood Arsenal, Maryland, and Battelle Memorial Institute, Columbus, Ohio

Received May 31, 1963

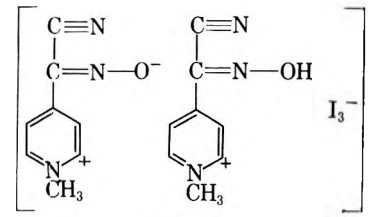
We wish to report on the synthesis of 4-cyanoformyl-1-methylpyridinium iodide oxime (I) and its derivatives, compounds which are more stable to light and oxygen than previously reported pyridinium oximes.

The synthesis of I was accomplished easily by the methylation of 4-pyridylglyoxylonitrile oxime. The glyoxylonitrile oxime was prepared either by isonitrosation of 4-pyridineacetonitrile or by reaction of potassium cyanide with isonicotinohydroxamic chloride.[3]

It was found that I with sodium ethoxide in ethanol or with concentrated ammonium hydroxide gave 4-cyanoformyl-1-methylpyridinium oximate (II). This conjugate base is soluble in water and slightly soluble generally in organic solvents.

4-Cyanoformyl-1-methylpyridinium cadmium triiodide oxime (III) was prepared from I and cadmium iodide in methanol. It was interesting to find that the residue obtained by evaporating the reaction mixture was *soluble* in ethyl ether. This important property may allow future investigations to be performed in other than a hydroxylic solvent.

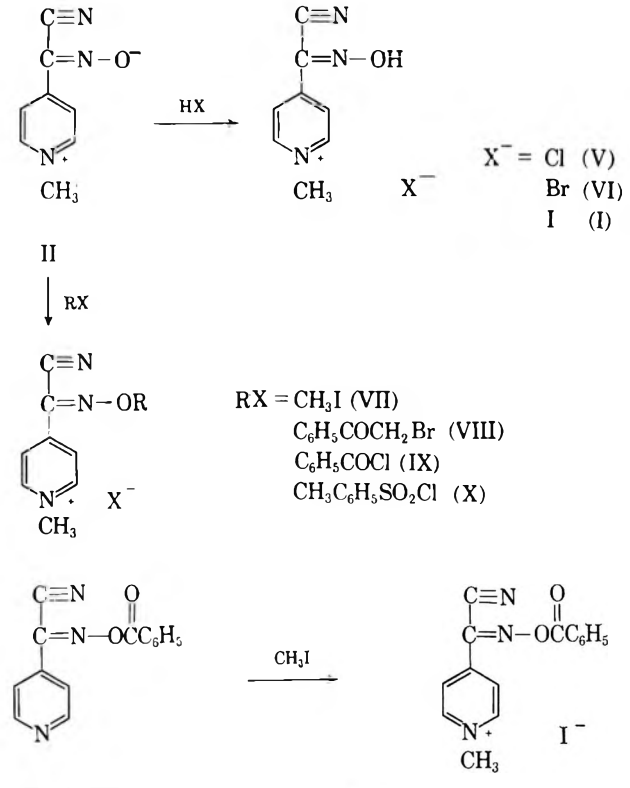
In previous experiences we found that quaternary heterocyclic aldoximes and ketoximes are not stable on exposure to intense ultraviolet light. Pyridinium aldoximates are especially sensitive to both oxygen and light.[4] Comparatively, aqueous solutions of I or II are stable to light and no precautions are needed in handling II in air. A 2% aqueous solution of I stored in quartz tubes for 7 months at 40° under intense ultraviolet light gave a solid which, on the basis of elemental analysis and a comparison of its infrared absorption spectrum to that of an authentic sample, was identified as the triiodide complex IV.



IV

The same complex was isolated when toluene was used in conjunction with methanol (methanol alone is a good solvent for recrystallizing I) in a recrystallization of I. The facile oxidation of iodide undoubtedly reflects a strong association of iodide with the pyridinium ring. It was shown that pyridinium iodide charge-transfer transitions involve an electron transfer to the pyridinium ring.[5] Toluene which is less polar than methanol probably allows a greater contribution of charge-transfer character. Consequently, the iodide should be more prone to radical formation and this would explain the oxidation. Multifold reactivity of tri(*p*-nitrophenyl)methyl derivatives was discussed similarly *vs.* solvent polarity by Kosower.[6] Appropriate light wave length also should promote radical formation.

The reaction of II with hydrochloric, hydrobromic, and hydroiodic acids gave 4-cyanoformyl-1-methylpyridinium chloride (V), bromide (VI), and iodide (I) oximes, respectively. When purifying I we found it more convenient to add hydrogen iodide to II rather than recrystallize crude I a number of times. (This is because of the iodide oxidation.)



(1) U. S. Army Chemical Research and Development Laboratories.
(2) Battelle Memorial Institute.
(3) E. J. Poziomek and A. R. Melvin, *J. Org. Chem.*, **26**, 3769 (1961).
(4) L. Larsson and G. Wallenberg, *Acta Chem. Scand.*, **16**, 788 (1962).
(5) E. M. Kosower, D. Hofmann, and K. Wallenfels, *J. Am. Chem. Soc.*, **84**, 2755 (1962).
(6) E. M. Kosower, *ibid.*, **80**, 3267 (1958).

O-Methyl-4-cyanoformyl-1-methylpyridinium iodide oxime (VII) and O-benzoylmethyl-4-cyanoformyl-1-methylpyridinium bromide oxime (VIII) were prepared from II, and methyl iodide and bromoacetophenone, respectively. Similarly, O-benzoyl-(and O-tosyl-)4-cyanoformyl-1-methylpyridinium chloride oximes, IX (and X) were prepared from II and the corresponding acyl (and sulfonyl) chloride. Also, O-benzoyl-4-cyanoformyl-1-methylpyridinium iodide oxime (XI) was prepared by the methylation of 4-pyridylglyoxylonitrile oxime benzoate.

Charge-transfer absorption bands are very sensitive to small changes in the electron affinity of the ring. In view of the strong electron-withdrawing power of the glyoxylonitrile grouping and the iodide oxidation, the charge-transfer transition response of I and its derivatives to solvent changes should be very interesting.

The conjugate base (II) is only slightly soluble in organic solvents but its solutions vary in color from yellow to blue depending on solvent polarity. Pyridinium cyclopentadienylide solutions are colored similarly and the visible absorption bands were attributed to intramolecular transitions.[7] Electrolytic or chemical reduction of I and its derivatives lead to colors as was also observed in the preparation of stable pyridinyl radicals.[8]

The versatility and stability of I and its derivatives make it attractive to investigate quantitatively the various effects found and we plan to discuss future studies in subsequent publications.

Experimental

4-Cyanoformyl-1-methylpyridinium Iodide Oxime (I). Method A.—To a suspension of 14.7 g. (0.1 mole) of 4-pyridylglyoxylonitrile oxime in methanol was added 42.3 g. (0.3 mole) of methyl iodide. The mixture was refluxed until complete solution occurred (2–3 days). Ether was added to precipitate a yellow-orange solid. Recrystallization from ethanol–ether and drying in a 60° oven for 2 hr. gave 20.6 g. (71.2%) of a bright orange solid, m.p. 183–184° dec.

Anal. Calcd. for $C_8H_6IN_3O$: C, 33.2; H, 2.8. Found: C, 33.4; H, 2.9.

Method B.—To 20.0 g. (0.124 mole) of II suspended in 200 ml. of ethanol was added slowly 20 ml. of 52% hydroiodic acid. The solution was allowed to stir magnetically for 2 hr. and then filtered. The filtrate was allowed to warm on a steam bath and ether was added to the point of cloudiness. On cooling a yellow solid crystallized. One recrystallization from ethanol gave an over-all yield of 18.5 g. (51.6%), m.p. 185–187° dec.

Anal. Calcd. for $C_8H_6IN_3O$: C, 33.2; H, 2.8. Found: C, 33.4; H, 2.8.

The pK_a of I was determined by potentiometric titration to be 4.6. Using the method reported by Rosenblatt[9] and recording absorbance changes of the long wave-length band of maximum absorption with pH (342 mμ; pH, absorbance: 3.86, 0.061; 4.67, 0.231; 5.90, 0.410) we found a pK_a value of 4.59.

4-Cyanoformyl-1-methylpyridinium Oximate (II).—To 19.5 g. (0.07 mole) of I dissolved in the minimum amount of ethanol was added at 5–10° an equimolar solution of freshly prepared sodium ethoxide. In 30 sec. a reprecipitate formed. The mixture was filtered to give 10.1 g. (83%) of a crystalline dusty rose precipitate, m.p. 247–250° dec.

Anal. Calcd. for $C_8H_7N_3O \cdot {}^3/_4H_2O$: C, 55.0; H, 5.0; N, 24.1; neut. equiv., 175. Found: C, 55.0; H, 4.1; N, 24.1; neut. equiv., 180; pK_a 4.6.

The above synthesis was repeated to give a water-free product, m.p. 263–265° dec.

Anal. Calcd. for $C_8H_7N_3O$: C, 59.6; H, 4.4; N, 26.1; neut. equiv., 161. Found: C, 59.9; H, 4.5; N, 25.7; neut. equiv., 162.

Similarly, addition of I (50 g., 0.17 mole) to 200 ml. of concentrated ammonium hydroxide gave a precipitate of II, 24.4 g. (85.3%).

Anal. Calcd. for $C_8H_7N_3O$: C, 59.6; H, 4.4. Found: C, 59.5; H, 4.3.

4-Cyanoformyl-1-methylpyridinium Cadmium Triiodide Oxime (III).—A 150-ml. methanolic solution of 2.9 g. of I and 3.7 g. (0.01 mole) of cadmium iodide was refluxed for 1 hr. on a steam bath. The solution was evaporated to dryness; the residue (completely ether soluble) was recrystallized from methanol to give 1.3 g. (20%) of a yellow solid, m.p. 110°.

Anal. Calcd. for $C_8H_6N_3OCdI_3$: C, 14.7; H, 1.2; N, 6.4; I, 58.1. Found: C, 14.7; H, 1.5; N, 6.3; I, 57.1.

4-Cyanoformyl-1-methylpyridinium Oximate, 4-Cyanoformyl-1-methylpyridinium Triiodide Oxime Complex (IV).—To 1.27 g. (0.005 mole) of iodine in 125 ml. of methanol was added 0.8 g. (0.005 mole) of II and 1.4 g. (0.005 mole) of I. The mixture was heated to boiling on a steam bath and cooled to room temperature. Filtration gave 2.8 g. (76%) of maroon-brown crystals, m.p. 193–195° dec.

Anal. Calcd. for $C_{16}H_{15}I_3N_6O_2 \cdot CH_3OH$: C, 27.7; H, 2.6; I, 51.7. Found: C, 28.2; H, 2.4; I, 51.7.

4-Cyanoformyl-1-methylpyridinium Chloride Oxime (V).—To a mixture of 3.0 g. (0.019 mole) of II in 50 ml. of methanol was added an equimolar amount of aqueous hydrogen chloride. Solution was effected immediately; ether was added to give a yellow oil. The oil was dissolved in methanol; addition of ether precipitated a pale yellow solid, m.p. 225–229° dec. The solid was dissolved in the minimum amount of methanol. The solution was refluxed with activated charcoal. Filtration followed by precipitation with ether gave 1.3 g. (33.6%) of a colorless solid, m.p. 229–233° dec.

Anal. Calcd. for $C_8H_6N_3OCl \cdot {}^1/_3H_2O$: C, 47.5; H, 4.2; N, 20.7. Found: C, 47.8; H, 4.0; N, 20.6.

4-Cyanoformyl-1-methylpyridinium Bromide Oxime (VI).—To a mixture of 1.9 g. (0.012 mole) of II in 50 ml. of methanol was added fuming hydrogen bromide dropwise until complete solution was evident. The colorless product, m.p. 247–252° dec., 1.35 g. (46.6%), was isolated and purified as described for V.

Anal. Calcd. for $C_8H_6BrN_3O$: C, 39.6; H, 3.3; Br, 33.3. Found: C, 40.1; H, 3.4; Br, 32.9.

O-Methyl-4-cyanoformyl-1-methylpyridinium Iodide Oxime (VII).—To 3.22 g. (0.02 mole) of II suspended in methanol was added 13.5 g. (0.096 mole) of methyl iodide. The mixture was allowed to stand (stirred occasionally) until complete solution occurred (2 weeks). Ether was added and an hygroscopic orange solid was filtered. The compound was spread on a porous plate and dried in a vacuum oven at 60°. The color changed to brick red, 5.3 g. (87.4%), m.p. 134–136° dec.

Anal. Calcd. for $C_9H_{10}IN_3O$: C, 35.6; H, 3.3; O, 5.2. Found: C, 35.2; H, 3.4; O, 5.2.

O-Benzoylmethyl-4-cyanoformyl-1-methylpyridinium Bromide Oxime (VIII).—To 3.22 g. (0.02 mole) of II suspended in methanol was added 4.7 g. (0.024 mole) of bromoacetophenone. The mixture was allowed to stir and the product precipitated. More methanol was added and the mixture was warmed on a steam bath until solution took place. Ether was then added to the cooled solution to give 5.5 g. (76.4%) of a tan solid, m.p. 192–193° dec.

Anal. Calcd. for $C_{16}H_{14}BrN_3O_2$: C, 53.4; H, 4.0; Br, 22.2. Found: C, 53.1; H, 4.1; Br, 21.6.

O-Benzoyl-4-cyanoformyl-1-methylpyridinium Chloride Oxime (IX).—To 3.22 g. (0.02 mole) of II suspended in methanol was added 2.8 g. (0.02 mole) of benzoyl chloride. The mixture was stirred until solution occurred, then 30 min. more. Ether was added to precipitate 6.4 g. of a colorless solid, m.p. 148–188° dec. Recrystallization from methanol–ether gave 5.0 g. (69.6%) of a colorless solid, m.p. 187–190° dec.; elemental analysis corresponded to an alcoholate of the desired benzoate ester.

Anal. Calcd. for $C_{15}H_{12}ClN_3O_2 \cdot 1.8CH_3OH$: C, 56.1; H, 5.4. Found: C, 56.1; H, 4.9.

O-Tosyl-4-cyanoformyl-1-methylpyridinium Chloride Oxime (X).—To 3.22 g. (0.02 mole) of II suspended in methanol was added 4.5 g. (0.024 mole) of *p*-toluenesulfonyl chloride. The mixture was stirred until solution occurred, then 30 min. more. Ether was added to precipitate a colorless solid which on recrystallization from methanol–ether gave 3.5 g. (42.5%) of

(7) E. M. Kosower and B. G. Ramsey, *J. Am. Chem. Soc.*, **81**, 856 (1959).

(8) (a) W. M. Schwarz, E. M. Kosower, and I. Shain, *ibid.*, **83**, 3164 (1961); (b) E. M. Kosower and E. J. Poziomek, *ibid.*, **86**, 2035 (1963).

(9) D. Rosenblatt, *J. Phys. Chem.*, **58**, 40 (1954).

colorless crystals, m.p. 169–171° dec. Elemental analyses corresponded to that of an alcoholate of the desired tosylate ester. An infrared absorption spectrum obtained in potassum bromide did not show a peak at 9.1 μ, the major absorption band of 4-cyanoformyl-1-methylpyridinium chloride oxime (V). This would eliminate the possibility that appreciable alcoholysis of *p*-toluenesulfonyl chloride occurred to give V as an impurity.

Anal. Calcd. for $C_{15}H_{14}ClN_3S\cdot1.9CH_3OH$; C, 49.2; H, 5.2. Found: C, 49.2; H, 5.2.

O-Benzoyl-4-cyanoformyl-1-methylpyridinium Iodide Oxime XI.—To 1.0 g. (0.004 mole) of 4-pyridylglyoxylonitrile oxime benzoate[10] in 15 ml. of acetone was added 5 ml. of methyl iodide. The solution was allowed to stand for 2 days, then filtered to give 1.0 g. (63.6%) of orange-red needles, m.p. 137° dec.[1] An infrared absorption spectrum obtained in potassium bromide corresponded closely to that of IX.

Anal. Calcd. for $C_{15}H_{12}IN_3O_2$: C, 45.8; H, 3.1; I, 32.3. Found: C, 45.7; H, 3.2; I, 32.3.

Attempted Recrystallization of 4-Cyanoformyl-1-methylpyridinium Iodide Oxime from Benzene–Methanol and Toluene–Methanol.—To 1.0 g. of I dissolved in the minimum amount of hot methanol was added benzene dropwise until cloudiness was observed. The solution was kept hot during the addition. On allowing the solution to cool to room temperature an orange-brown solid precipitated, m.p. 184–189° dec.

Anal. Calcd. for $C_8H_8IN_3O\cdot C_6H_6$: I, 34.4; N, 11.4. Found: I, 34.4; N, 11.1.

The previous procedure was repeated using toluene to give XI, m.p. 193–196° dec. (an infrared absorption spectrum obtained in potassium bromide corresponded to this of an authentic sample of XI).

Anal. Calcd. for $C_{16}H_{15}I_3N_6O_2$: C, 27.3; H, 2.2; I, 54.1; N, 11.9. Found: C, 27.4; H, 2.4; I, 52.9; N, 11.9.

Synthesis of the benzene solvate was not reproducible and evidence for iodide oxidation also was obtained.

Acknowledgment.—Elemental analyses were performed by the Analytical Research Branch, U. S. Army Chemical Research and Development Laboratory.

(10) E. J. Poziomek, unpublished results.

Pyrano[2,3-*d*]- and Pyrido[2,3-*d*]pyrimidines

HOMER C. SCARBOROUGH

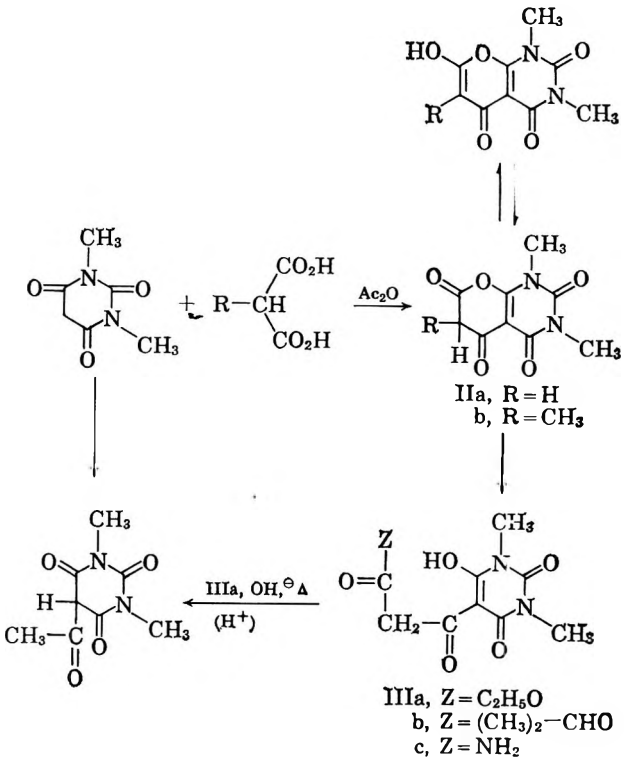
Department of Organic Chemistry, Mead Johnson Research Center, Evansville, Indiana

Received July 22, 1963

Pyrano[2,3-*d*]- and pyrido[2,3-*d*]pyrimidines in which the pyrano or pyrido ring incorporates an enolizable 1,3-dicarbonyl system have been investigated. These compounds were desired because of their acidic hydrogen which might be functionally analogous to that of the imidazole ring of xanthines.

The pyranopyrimidines were prepared by the condensation of malonic acid or methylmalonic acid with 1,3-dimethylbarbituric acid in the presence of acetic anhydride. A related 1,3-diphenyl-2-thiopyrano[2,3-*d*]pyrimidine has been prepared by the condensation of malonyl dichloride with 1,3-diphenyl-2-thiobarbituric acid.[1]

Earlier workers postulated the existence of compound IIa in rationalizing the isolation of IIIa accompanying the synthesis of 1,3-dimethylbarbituric acid.[1] We found that the lactone function of compound IIa was indeed chemically reactive although both IIa and IIb were hydrolytically stable during isolation.



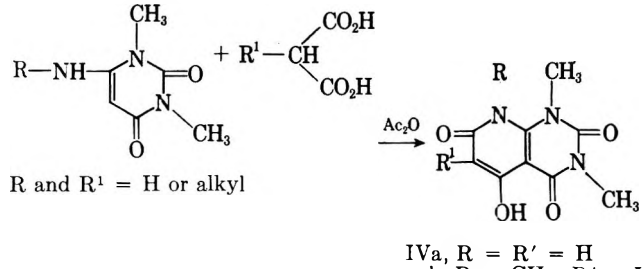
IIa, R = H
b, R = CH_3

IIIa, Z = C_2H_5O
b, Z = $(CH_3)_2$—CHO
c, Z = NH_2

Compound IIa reacted readily with ethanol to form IIIa and with isopropyl alcohol to form IIIb. The isopropyl ester IIIb also was obtained upon attempted recrystallization of IIa from isopropyl acetate. The reaction of IIa with aqueous ammonium hydroxide furnished the amide (IIIc). Compound IIa was precipitated unchanged after standing in 0.1 *N* aqueous sodium hydroxide at 25° for 0.5 hr. The compounds were insoluble in 10% aqueous sodium carbonate solution.

When the ester (IIIa) was heated with aqueous sodium hydroxide and the solution acidified, 5-acetyl-1,3-dimethylbarbituric acid was obtained in 90% yield. The latter was identical with the product obtained from the reaction of 1,3-dimethylbarbituric acid with acetic anhydride.

The pyridopyrimidines were obtained when 4-amino-1,3-dimethyluracils were acylated with malonic acid or alkyl malonic acids in the presence of acetic anhydride. These pyrido[2,3-*d*]pyrimidines (IV) are listed in Table I. Since this work was completed, compound IVa has been reported in 17% yield from a malonic acid preparation using phosphorus oxychloride as condensing agent.[3] No structural proof for IVa was presented.[3]



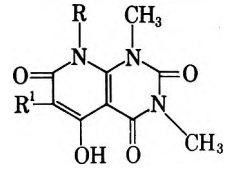
R and R¹ = H or alkyl

IVa, R = R′ = H
b, R = CH_3; R′ = H
c, R = H; R′ = CH_3
d, R = R′ = CH_3

(1) H. Schulte, *Ber.*, **87**, 820 (1954).
(2) J. W. Clark-Lewis and M. J. Thompson, *J. Chem. Soc.*, 1628 (1959).
(3) E. Ziegler and E. Nelken, *Monatsh.*, **92**, 1184 (1961).

TABLE I

5-HYDROXYPYRIDO[2,3-*d*]PYRIMIDINE-2,4,7-1*H*,3*H*,8*H*-TRIONES

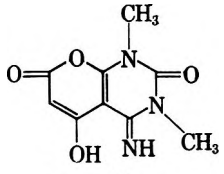


	R	R¹	M.p., °C.	Yield,[a] %	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IVa	H	H[b]	280–282.5[b]	45 (cd, e)	$C_9H_9N_3O_4$	48.43	4.06	18.83	48.48	4.11	18.91
IVb	CH_3	H	220.5–222	46.5 (b, c)	$C_{10}H_{11}N_3O_4$	50.63	4.67	17.72	50.64	4.66	17.68
IVc	H	CH_3	287.5–289.5	58 (d, b)	$C_{10}H_{11}N_3O_4$	50.63	4.67	17.72	50.91	4.76	17.82
IVd	CH_3	CH_3	259.5–260.5	48 (b)	$C_{11}H_{13}N_3O_4$	52.58	5.22	16.73	52.66	5.22	16.90
IVe	H	$CH_3(CH_2)_2CH_2$	195–196	24 (b)	$C_{13}H_{17}N_3O_4$	55.90	6.14	15.05	55.55	6.27	15.19
IVf	CH_3	$CH_3(CH_2)_2CH_2$	119–120	38 (f, ga)	$C_{14}H_{19}N_3O_4$	57.32	6.53	14.33	57.14	6.48	14.21

[a] Yields are of analytically pure material recrystallized from a, heptane; b, acetonitrile; c, butanone; d, dimethylformamide; e, acetic acid; f, methyl alcohol; g, benzene. [b] Reference 3 reports 270°.

That the pyrido[2,3-*d*]pyrimidines had the tautomeric structure IV was shown by examination of the n.m.r. spectra of IVa, b, c, and d in dimethyl sulfoxide. Compounds IVa and IVb exhibit singlets comprising one olefinic proton (358 and 338 c.p.s.)[4] while the 6-methyl groupings of IVc and IVd absorbed as singlets contiguous with a double bond (115 and 113 c.p.s.). All spectra exhibited one hydroxyl proton (745 c.p.s.) that was intramolecularly bonded as shown by the low value for the chemical shift which was unchanged on dilution. The structure represented by IV is the only tautomer capable of intramolecular hydrogen bonding.

An isomeric structure represented by V can be eliminated with consideration of the previously reported N,5-diacetylation of 1,3-dimethyl-4-methylaminouracil.[5]



V

In addition, the chemical shift in dimethyl sulfoxide to 720 c.p.s. establishes the presence of an amide hydrogen for IVa and IVc. The amide hydrogen of these compounds exchanged with trifluoroacetic acid.

Experimental[6]

1,3-Dimethyl-6*H*-pyrano[2,3-*d*]pyrimidine-2,4,5,7-1*H*,3*H*,6*H*-tetrone (Ia).—A mixture of 7.8 g. (0.05 mole) of 1,3-dimethylbarbituric acid,[2] 6.3 g. (0.06 mole) of malonic acid, 11.3 ml. (0.12 mole) of acetic anhydride, and 5 ml. of acetic acid was heated at 80° for 3 hr. to furnish a dark reddish brown solution. The solution was cooled and diluted to 100 ml. with water. The orange solid which separated upon storage at 0° was collected, dried, and recrystallized two times from butanone. There was obtained 4 g. (33%) of lustrous white plates, m.p. 192–194°.

Anal. Calcd. for $C_9H_8N_2O_5$: C, 48.22; H, 3.60; N, 12.50. Found: C, 48.08; H, 3.90; N, 12.89.

1,3,6-Trimethyl-6*H*-pyrano[2,3-*d*]pyrimidine-2,4,5,7-1*H*,3*H*,-6*H*-tetrone (Ib).—A mixture of 7.8 g. (0.05 mole) of 1,3-dimethylbarbituric acid, 7.1 g. (0.06 mole) of methylmalonic acid,[7] 11.3 ml. of acetic anhydride, and 5 ml. of acetic acid was warmed to give a solution which was allowed to stand at 25° for 16 hr. The solution was then heated on the steam bath for 7 hr., a crystalline solid separating from the reaction solution after 3 hr. The solid product collected after cooling the reaction mixture was recrystallized from butanone and from acetonitrile to furnish 5.1 g. (43%) of material, m.p. 236–237.5°. In the 5–7- and 8–9-μ region, absorption peaks were observed at 5.67, 5.80, 5.95, 6.30, 6.60, 6.85 (weak), 8.05 (shoulder), 8.15, and 8.35 μ (0.5% in KBr).

Anal. Calcd. for $C_{10}H_{10}N_2O_5$: C, 50.52; H, 4.23; N, 11.76. Found: C, 50.52; H, 4.34; N, 11.84.

1,3-Dimethyl-5-ethoxycarbonylacetylbarbituric Acid (IIIa).—A solution of 2.24 (0.01 mole) of compound Ia in 75 ml. of absolute ethyl alcohol was concentrated on a hot plate to half volume and then chilled. The product was collected and recrystallized from absolute ethyl alcohol to furnish 2.6 g. (96%) of a white crystalline solid, m.p. 110.5–111°, lit.[2] m.p. 112°.

Anal. Calcd. for $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.22; N, 10.37. Found: C, 48.83; H, 5.23; N, 10.38.

1,3-Dimethyl-5-isopropoxycarbonylacetylbarbituric Acid (IIIb).—A solution of 1.12 g. (0.005 mole) of compound Ia in 15 ml. of isopropyl alcohol was heated to boiling. The solution was cooled and diluted with heptane. The solid which separated upon cooling was collected and recrystallized from cyclohexane to furnish 1.3 g. (92%) of a white crystalline solid, m.p. 73–74.5°. The same material separated when compound Ia was dissolved in hot isopropyl acetate.

Anal. Calcd. for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.86. Found: C, 50.83; H, 5.60; N, 9.66.

5-Aminocarbonylacetyl-1,3-dimethylbarbituric Acid (IIIc).—To 4.5 g. (0.02 mole) of compound Ia was added 50 ml. of concentrated ammonium hydroxide. A bulky white solid was obtained in a few minutes. The solid was collected, rinsed with acetone, and recrystallized from acetic acid and from butanone. There was obtained 3.5 g. (73%) of a white crystalline solid, m.p. 176–178° dec. (gas).

Anal. Calcd. for $C_9H_{11}N_3O_5$: C, 44.81; H, 4.60; N, 17.42. Found: C, 44.73; H, 4.55; N, 17.65.

5-Acetyl-1,3-dimethylbarbituric Acid.—A solution of 1 g. of compound Ia in 20 ml. of 10% aqueous sodium hydroxide was boiled for 10 min. The white solid which precipitated upon acidification of the cooled solution was collected, dried, and recrystallized from cyclohexane to furnish 0.8 g. (90%) of white product, m.p. 96.5–98.5°. A mixture melting point of this product with that prepared by the reaction of 1,3-dimethylbarbituric acid with acetic anhydride showed no depression.

5-Hydroxy-1,3,6,8-tetramethylpyrido[2,3-*d*]pyrimidine-2,4,7-1*H*,3*H*,8*H*-trione (IVd).—A mixture of 8.45 g. (0.05 mole) of 1,3-dimethyl-4-methylaminouracil,[8] 7.1 g. of methylmalonic acid,[7] 11.3 ml. of acetic anhydride, and 10 ml. of acetic acid was heated on the steam bath for 2 hr. During this time the suspended material dissolved and the solution boiled gently. The solution was then cooled in an ice bath and the crystallized product collected

(4) The absorption frequencies were observed at 60 Mc. with respect to internal tetramethylsilane.

(5) W. Pfleiderer and G. Strauss, *Ann.*, **612**, 173 (1958).

(6) Microanalyses were performed by Mr. Clarence Kennedy, Mead Johnson Research Center.

(7) J. N. Norris and H. F. Tucker, *J. Am. Chem. Soc.*, **55**, 4697 (1933).

(8) W. Pfleiderer and K. H. Schundehutte, *Ann.*, **612**, 158 (1958).

by filtration. The method of purification and physical data are listed in Table I.

The other pyridopyrimidines were prepared in a similar manner and are listed in Table I. The compounds are precipitated unchanged by the addition of acid to solutions in 5% aqueous sodium hydroxide. They are insoluble in 10% aqueous sodium carbonate solution.

Attempted Preparation of 6,6-Disubstituted Products.—5-Acetyl-1,3-dimethylbarbituric acid was obtained in 95% yield when diethylmalonic acid and acetic anhydride were heated with 1,3-dimethylbarbituric acid. No discrete products could be isolated from the reaction of diethylmalonic acid and acetic anhydride with 4-amino-1,3-dimethyluracil. The reaction of diethylmalonyl dichloride with 4-amino-1,3-dimethyluracil in dimethylformamide furnished 4-amino-1,3-dimethyl-5-formyluracil. The latter also has been prepared by the reaction of formic acetic anhydride with 4-amino-1,3-dimethyluracil.[5]

Acknowledgment.—The author is indebted to Mr. Charles Combs of the Mead Johnson Research Center for the n.m.r. data. Certain of the intermediates were prepared by Dr. T. A. Martin and Mr. D. H. Causey.

Decomposition of Dimethyl Sulfoxide Aided by Ethylene Glycol, Acetamide, and Related Compounds[1]

VINCENT J. TRAYNELIS AND WILLIAM L. HERGENROTHER[2]

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana

Received July 26, 1963

Dimethyl sulfoxide appears to be thermally quite stable but upon prolonged reflux it does decompose slightly to methyl mercaptan and bismethylthiomethane.[3] This decomposition is aided by acids and retarded by many bases. Nace and Monagle[4] reported the appearance of dimethyl sulfide, methyl mercaptan, and dimethyl disulfide during the reaction of primary halides with dimethyl sulfoxide and, if precautions were not taken to remove the acid produced in this reaction, large amounts of formaldehyde also were formed. The acid-catalyzed cleavage of sulfoxides recently was discussed by Kenney, Walsh, and Davenport[5] and generally results in the reduction of sulfur to a mercaptan and the oxidation of the α-carbon to a carbonyl group. Subsequent reactions of these initial products may result. An alternate path for the decomposition of dimethyl sulfoxide involves disproportionation to dimethyl sulfone and dimethyl sulfide which requires osmium tetroxide as a catalyst.[6]

In our investigations of the dehydration of alcohols in dimethyl sulfoxide,[7] which required elevated temperatures for substantial periods of time, we have noted a number of dimethyl sulfoxide decomposition products. This report summarizes our observations on the thermal decomposition of dimethyl sulfoxide and the effect of certain glycols and amides on this cleavage.

When dimethyl sulfoxide was refluxed for 3 days, 3.7% of volatile material was collected and consisted of paraformaldehyde (1.9%), dimethyl sulfide, dimethyl disulfide, bismethylthiomethane, and water. The dimethyl sulfoxide residue contained a small amount of dimethyl sulfone. These results can be rationalized by the following series of equations.

$$(CH_3)_2SO \longrightarrow CH_3SH + CH_2O \longrightarrow \text{paraformaldehyde}$$

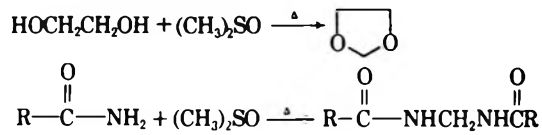
$$2CH_3SH + CH_2O \longrightarrow (CH_3S)_2CH_2 + H_2O$$

$$2CH_3SH + (CH_3)_2SO \longrightarrow CH_3SSCH_3 + CH_3SCH_3 + H_2O$$

$$2(CH_3)_2SO \longrightarrow CH_3SO_2CH_3 + CH_3SCH_3$$

The nature of the initial cleavage reaction is not clear at this time.

A variety of diols when heated in dimethyl sulfoxide undergo dehydration[7b]; however, purified ethylene glycol, heated in refluxing dimethyl sulfoxide for 3 days, promoted the previous cleavage reaction and gave dimethyl sulfide (16% isolated), dimethyl disulfide (19% isolated), and some bismethylthiomethane. The formaldehyde generated reacted with ethylene glycol to produce 1,3-dioxolane (54%). In a similar manner 1,2-propanediol and 1,3-propanediol promoted the cleavage reaction and were converted to 4-methyl-1,3-dioxolane (71% purified) and 1,3-dioxane (64% purified), respectively.



An increase in decomposition products also was observed when acetamide or benzamide was heated in dimethyl sulfoxide at 190° for 36 hr. The formaldehyde liberated combined with these amides to produce methylenebisacetamide (55%) and methylenebisbenzamide (60%). When acetanilide was subjected to the prior reaction conditions, only 7% of volatile materials was collected and 89% unchanged acetanilide was recovered.

The methylenebisamides and the dioxa heterocycles are usually prepared by an acid-catalyzed reaction of formaldehyde with nitriles[8] or amides[9] and with the appropriate diol.[10] The results in this work suggest the possible use of dimethyl sulfoxide in promoting these condensation reactions of formaldehyde and possibly other carbonyl compounds. One experiment in support of this was the reaction of benzamide and paraformaldehyde in dimethyl sulfoxide to form methylenebisbenzamide (63%) in 9 hr.

Although it appeared, in the previous reactions, that dimethyl sulfoxide decomposed into methyl mercaptan and formaldehyde which then reacted with the glycols or amides, we have not excluded the possibility of some interaction of the diols or amides directly with dimethyl

(1) Acknowledgment is made to the donors of the Petroleum Research Fund administered by the American Chemical Society for support of this research.

(2) Abstracted from part of the Ph.D. dissertation of W. L. H., July, 1963.

(3) "Dimethyl Sulfoxide Technical Bulletin," issued by Crown Zellerbach Corp., Camas, Wash.

(4) H. R. Nace and J. J. Monagle, *J. Org. Chem.*, **24**, 1792 (1959).

(5) W. J. Kenney, J. A. Walsh, and D. A. Davenport, *J. Am. Chem. Soc.*, **83**, 4019 (1961). This paper reviews the literature of this cleavage.

(6) H. R. Davis, Jr., and D. P. Sorensen, U. S. Patent 2,870,215 (January 20, 1959); *Chem. Abstr.*, **53**, 11416i (1959).

(7) (a) V. J. Traynelis, W. L. Hergenrother, J. R. Livingston, and J. A. Valicenti, *J. Org. Chem.*, **27**, 2377 (1962); (b) V. J. Traynelis, W. L. Hergenrother, and in part H. T. Hanson and T. A. Valicenti, *ibid.*, **29**, 123 (1964).

(8) E. E. Magat, B. F. Faris, J. E. Reith, and L. F. Salisbury, *J. Am. Chem. Soc.*, **73**, 1028 (1951). Other references cited in this report.

(9) G. Pulvermacher, *Ber.*, **25**, 310 (1892).

(10) H. T. Clarke, *J. Chem. Soc.*, **101**, 1804 (1912).

sulfoxide or some intermediate to produce the dioxa heterocycles or methylenebisamides.

Experimental

Thermal Stability of Dimethyl Sulfoxide.—Dimethyl sulfoxide[11] (78 g., 1.0 mole) was placed in a flask equipped with a Claisen head, condenser, and a receiver cooled in an acetone–Dry Ice bath, and heated at 190° for 72 hr. Paraformaldehyde, 1.5 g. (1.9%), identified by its 2,4-dinitrophenylhydrazone derivative, melting point and mixture melting point with an authentic sample, 165–166° (lit.[12] m.p. 166°), condensed in the Claisen head and 1.40 g. of material collected in the cold trap which consisted of 0.2 g. of ice. The 1.20 g. of liquid was subjected to v.p.c.[13] on a silicone GE-SF-96 column at 100° and with a helium flow rate of 60 cc./min., and was composed of dimethyl sulfide (42 area %), dimethyl disulfide (40 area %), and bismethylthiomethane (18 area %). These compounds were identified by comparison of retention times with authentic material. V.p.c.[13] of the remaining dimethyl sulfoxide under conditions described earlier except at 120° showed the presence of dimethyl sulfone by retention time comparison and peak enhancement with authentic material.

Reaction of Diols in Dimethyl Sulfoxide. A. Ethylene Glycol.—A solution of redistilled ethylene glycol (31 g., 0.50 mole) and dimethyl sulfoxide (158 g., 2.00 mole) was heated for 72 hr. at 190° and produced 64 g. of a distillate collected as in the preceeding experiment. Fractional distillation of this material gave 20 g. (16%) of dimethyl sulfide, b.p. 35–38°, mercuric chloride derivative m.p. 148–149° (lit.[14] b.p. 37.33°, mercuric chloride derivative[15] m.p. 150–151°); 20 g. (54%) of dioxolane, b.p. 73–74°, $n^{20}D$ 1.4000, 2,4-dinitrophenylhydrazone derivative melting point and mixture melting point with formaldehyde 2,4-dinitrophenylhydrazone 165–166°, n.m.r. spectrum[16] singlet 5.22 (2 protons) and singlet 6.24 τ (4 protons) (lit.[10] b.p. 76°, $n^{20}\alpha$ 1.3934, $n^{25}\gamma$ 1.40734, lit.[17] $n^{25}D$ 1.4010); and 12 g. (19%) of dimethyl disulfide, b.p. 104°, $n^{23}D$ 1.5222, n.m.r. spectrum[16] singlet 7.61 τ (lit.[18] b.p. 109.5°, $n^{20}D$ 1.5260). A small amount of bismethylthiomethane was detected by v.p.c. of the initial condensate.

B. 1,2-Propanediol.—The reaction of 1,2-propanediol (15.2 g., 0.200 mole) and dimethyl sulfoxide (109 g., 1.40 moles) at 190° for 48 hr. was processed as above. Fractional distillation of the condensate (32 g.) gave 14.5 g. of 4-methyldioxolane contaminated with dimethyl disulfide. Redistillation of this fraction from sodium produced 12.4 g. (71%) of pure 4-methyldioxolane, b.p. 87–89°, $n^{23}D$ 1.4050 (lit.[10] b.p. 88–89°, $n^{20}\alpha$ 1.40109, $n^{20}\gamma$ 1.41107).

C. 1,3-Propanediol.—A solution of 1,3-propanediol (15.2 g., 0.200 mole) and dimethyl sulfoxide (78 g., 1.0 mole) at 190° for 44 hr. provided 24.5 g. of condensate. The initial distillation gave 13.8 g. of crude 1,3-dioxane which was treated with sodium overnight on a steam bath. Distillation from sodium gave 11.3 g. (64%) of pure 1,3-dioxane, b.p. 104–105°, $n^{20}D$ 1.4168 (lit.[10] b.p. 105°, $n^{20}\alpha$ 1.41652, $n^{20}\gamma$ 1.42730).

Reaction of Amides in Dimethyl Sulfoxide. A. Acetamide.—Using the procedure described under reactions of diols, acetamide (11.8 g., 0.200 mole) and dimethyl sulfoxide (78 g., 1.0 mole) heated at 190° for 36 hr. gave 20 g. of condensate which by v.p.c. (conditions as described in the "Thermal Stability of Dimethyl Sulfoxide") contained dimethyl sulfide, dimethyl disulfide, and bismethylthiomethane. Bismethylthiomethane (4.5 g., 8%), b.p. 148°, $n^{20}D$ 1.5321, disulfone derivative m.p. 144–145° (lit.[19] b.p. 148°, disulfone m.p. 145°), was isolated by distillation. Dimethyl sulfoxide was removed from the reaction mixture and the residue upon crystallization from 95% ethanol gave 7.2 g. (55%) of methylenebisacetamide, m.p. 192–194°, mixture melting point with an authentic sample 194–195° (lit.[9] m.p. 196°). The infrared spectrum was identical with that of an authentic sample.

B. Benzamide.—When a mixture of benzamide (24.2 g., 0.200 mole) and dimethyl sulfoxide (78 g., 1.00 mole) was heated for 34 hr. at 190°, 20 g. of condensate consisting of dimethyl sulfide, dimethyl disulfide, and bismethylthiomethane was isolated. Dimethyl sulfoxide was removed and the residue crystallized from 95% ethanol to give 15.0 g. (60%) of methylenebisbenzamide, melting point and mixture melting point with an authentic sample 217–219° (lit.[9] m.p. 219°). The infrared spectrum was identical with that of an authentic sample.

The product was treated with 2,4-dinitrophenylhydrazine and gave formaldehyde 2,4-dinitrophenylhydrazone, melting point and mixture melting point with an authentic sample 160–163°. When the product was heated with alcoholic potassium hydroxide for 24 hr., benzoic acid (97%) was isolated.

A solution of benzamide (12.1 g., 0.100 mole) and dimethyl sulfoxide (78 g., 1.0 mole) was heated for 9 hr. at 190° while paraformaldehyde (3.0 g., 0.10 mole) was added at 1-hr. intervals until 21.0 g. (0.70 mole) was introduced. After cooling, the reaction mixture was poured into water, filtered, and the solid was recrystallized from 95% ethanol. The yield of methylenebisbenzamide, m.p. 217–219°, was 8.0 g. (63%).

C. Acetanilide.—A solution of acetanilide (27.3 g., 0.200 mole) in dimethyl sulfoxide (78 g., 1.0 mole) was heated at 190° for 24 hr. and processed as before. The condensate (dimethyl sulfide, dimethyl disulfide, and bismethylthiomethane) was 5.5 g., and 24 g. (89%) of unchanged acetanilide, melting point and mixture melting point with an authentic sample 112–114°, was recovered.

Methylenebisbenzamide.—Methylenebisbenzamide, m.p. 217–219°, was prepared in 88% yield from benzonitrile (10.3 g., 0.100 mole), *sym*-trioxane (1.5 g., 0.05 mole), and 38 ml. of 85% sulfuric acid according to the procedure of Magat, Faris, Reith, and Salisbury.[8]

Methylenebisacetamide.—Using the prior procedure,[8] methylenebisacetamide, m.p. 195–196°, was prepared in 46% yield from acetonitrile (0.20 mole) and *sym*-trioxane (0.10 mole) with the following modification. After the reaction mixture was diluted, the acid was neutralized and the solution concentrated before the product crystallized.

(11) The authors wish to thank the Chemical Products Division of the Crown Zellerbach Corp. for making generous samples of this material available for this work.

(12) G. D. Johnson, *J. Am. Chem. Soc.*, **75**, 2720 (1953).

(13) An Aerograph Model A-90P instrument was used.

(14) D. W. Osborne, R. N. Doescher, and D. M. Yost, *J. Am. Chem. Soc.*, **64**, 169 (1942).

(15) W. F. Faragher, J. C. Morrell, and S. Comay, *ibid.*, **51**, 2781 (1929).

(16) N.m.r. spectra were recorded by Mr. R. Daignault on a Varian Associates 60-Mc. high resolution n.m.r. spectrometer, Model V-4300 B, in carbon tetrachloride solution with tetramethylsilane as an internal standard.

(17) H. J. Dauben, Jr., B. Löken, and H. J. Ringold, *J. Am. Chem. Soc.*, **76**, 1362 (1954).

(18) A. I. Vogel and D. M. Cowan, *J. Chem. Soc.*, 18 (1943).

(19) H. Böhme and R. Marx, *Ber.*, **74**, 1667 (1941).

An Attempted Westphalen Rearrangement of a 5β-Hydroxy Steroid[1]

ALEX T. ROWLAND

Department of Chemistry, Gettysburg College, Gettysburg, Pennsylvania

Received July 25, 1963

Numerous studies have been made concerning the Westphalen rearrangement[2] of 5α-hydroxy steroids. These studies have shown that a 6β-substituent is necessary in order for the migration of the C-10 methyl group to C-5 to occur when the alcohol is treated with with an acid catalyst. Recently, Mihina[3] reported the rearrangement of 5α-hydroxy-6β-halo steroids and concluded that a classical carbonium ion intermediate is sufficient to explain the formation of the 5β-methyl-19-nor steroid and by-products. A similar rearrangement of a B-norcholesteryl oxide has been reported by Dauben and co-workers.[4]

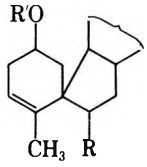
(1) Supported by research grant AM-07105-01 MC from the National Institute of Arthritis and Metabolic Diseases, Public Health Service.

(2) T. Westphalen, *Ber.*, **48**, 1064 (1915).

(3) J. S. Mihina, *J. Org. Chem.*, **27**, 2807 (1962). Pertinent references to the earlier literature are listed in this article.

(4) W. G. Dauben, G. A. Boswell, Jr., W. Templeton, J. W. McFarland, and G. H. Berezin, *J. Am. Chem. Soc.*, **86**, 1672 (1963).

The epimeric system (*i.e.*, 5β-hydroxy steroids) has not been studied in a similar manner. Inspection of a Dreiding model of this system indicates that the C-9 to C-10 bond lies *trans* and backside to the hydroxyl group at C-5. Thus, it might be predicted that rearrangement of this type of steroid would produce a spirane having the interesting structure **1**.



1

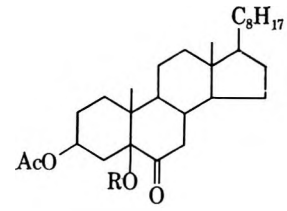
Accordingly, a 5β-cholestane derivative was prepared and treated under conditions which are known to produce rearrangement with the 5α-hydroxy compounds. Reduction of 5β-cholestane-3β,5-diol 6-one 3-monoacetate (Ia)[5] with lithium aluminum tri-*t*-butoxy hydride, followed by acetylation with acetic anhydride–pyridine, yielded 5β-cholestane-3β,5,6β-triol 3,6-diacetate (IIb).[6] It is of interest that the hydroxyl group became *axial* at C-6 instead of *equatorial*, as might have been expected.[7] Saponification of the triol diacetate (IIb) with methanolic potassium hydroxide gave the previously unknown 5β-cholestane-3β,5,6β-triol (IIa).

Treatment of the triol diacetate (IIb) with potassium acid sulfate in acetic anhydride at steam bath temperature for one hour produced a crystalline mixture from which were separated (by chromatography) 43% of cholest-4-ene-3β,6β-diol diacetate (III) and 14% of 5α-cholestan-3β-ol-6-one acetate (IV). The saturated ketone (IV) presumably arose from elimination of the 6α-hydrogen to give the enol acetate, which underwent subsequent hydrolysis and ketonization.

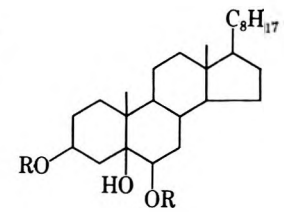
The reaction of 5α-hydroxy-6-keto steroids with acetic anhydride and potassium acid sulfate is known to proceed without a Westphalen rearrangement and to give straightforward acetylation of the 5-hydroxyl function.[8] Treatment of the diolone monoacetate (Ia) under similar conditions gave 5β-cholestane-3β,5-diol-6-one diacetate (Ib) in high yield. The same compound (Ib) was obtained by the acetylation of Ia with an acetic acid–acetic anhydride–*p*-toluenesulfonic acid mixture.

Since neither the 5β-hydroxy-6β-acetoxy nor the 5β-hydroxy-6-keto system promoted a Westphalen rearrangement, Ia was converted by a standard procedure to 5β-cholestane-3β,5-diol-6-one ethylene ketal (V) in order to test this function under the same conditions. When heated in acetic anhydride containing suspended potassium acid sulfate, followed by hydrolysis, infrared analysis indicated that V had been acetylated at the C-3 hydroxyl group and that the C-5 hydroxyl remained unaltered. No evidence was obtained for dehydration of any type.

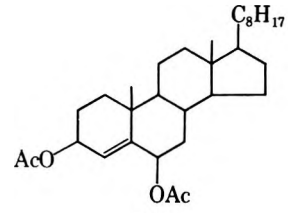
Thus, it appears that 5β-hydroxy steroids do not undergo the Westphalen rearrangement that occurs with the epimeric 5α-hydroxy compounds. The rationale for this probably lies in the internal strain involved in the migration of the C-9 to C-10 bond compared to the elimination of an α-hydrogen from C-4 or C-6.



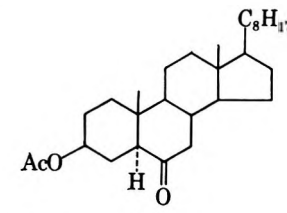
Ia, R=H
Ib, R=Ac



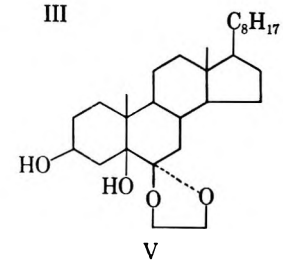
IIa, R=H
IIb, R=Ac



III



IV



V

Experimental[9]

5β-Cholestane-3β,5,6β-triol 3,6-Diacetate (IIb).—To a solution of 500 mg. (1.085 mmoles) of 5β-cholestane-3β,5-diol-6-one 3-monoacetate (Ia)[5a] in 4 ml. of tetrahydrofuran was added 500 mg. of lithium aluminum tri-*t*-butoxy hydride. The solution was stirred magnetically at room temperature for 45 min., at which time the walls of the flask were rinsed with an additional 2 ml. of tetrahydrofuran. After stirring for a further 15 min., the solution was allowed to remain at room temperature for 18 hr. Acidification with 2 *N* hydrochloric acid produced a gelatinous precipitate; water was added, and the product was extracted with three portions of methylene chloride. The combined organic extracts were washed once with water, dried, and evaporated to yield an oil which was treated with 4 ml. of pyridine and 3 ml. of acetic anhydride for 24.5 hr. at room temperature. This solution was added, in portions, to a mixture of 5 ml. of concentrated hydrochloric acid and crushed ice. The precipitated material was filtered, washed well with water, and recrystallized from methanol to give 396 mg. (73%) of IIb, m.p. 157–161°. Recrystallization from acetone–petroleum ether (b.p. 30–60°) yielded 363 mg. of white needles with m.p. 160–162°; $[\alpha]_D$ +9.1° (*c* 1.325), +10.7° (*c* 1.49); λ_{max} 2.79 (w) and 5.74 (s) μ (lit.[10] m.p. 165–167°, $[\alpha]_D$ +16°).

Anal. Calcd. for $C_{31}H_{52}O_5$: C, 73.76; H, 10.38. Found: C, 73.50; H, 10.07.

The homogeneity of IIb was demonstrated by column chromatography (alumina, Merck, acid-washed) and thin layer chromatography (silica gel).

5β-Cholestane-3β,5,6β-triole (IIa).—Five hundred milligrams (0.994 mmole) of IIb was covered with 15 ml. of 0.30 *N* methanolic potassium hydroxide and 13 drops of water. The mixture was heated on the steam bath for 1 hr. (After 0.5 hr., 7 ml. of

(5)(a) A. T. Rowland, *J. Org. Chem.*, **27**, 1135 (1962); (b) Y. Mazur and M. Nussim, *Tetrahedron Letters*, **22**, 817 (1961).

(6) All compounds named according to the Definitive Rules for the Nomenclature of Steroids, *J. Am. Chem. Soc.*, **82**, 5575 (1960).

(7) O. H. Wheeler and J. L. Mateos, *Chem. Ind.* (London), 395 (1957).

(8) B. Ellis and V. A. Petrow, *J. Chem. Soc.*, 1078 (1939).

(9) Melting points are uncorrected. Optical rotations were measured at room temperature in chloroform solutions. Infrared spectra refer to 5% carbon tetrachloride solutions unless otherwise noted. Drying of solutions was accomplished with anhydrous sodium sulfate. Elemental analyses by Micro-Analysis, Inc., Wilmington, Del.

(10) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957). These authors prepared IIb by lithium aluminum hydride reduction of 4β,5-oxido-5β-cholestane-3β,6β-diol, followed by acetylation.

methanol was added and after another 20 min. an additional 10 ml. of the 0.30 *N* base was added.) The resulting solution was acidified to litmus with 2 *N* hydrochloric acid, water was added, and the amorphous material which separated soon crystallized and was collected. Two recrystallizations from acetone–water gave 413 mg. (99%) of IIa (which contained water of crystallization), m.p. 123–126°. A chloroform solution of the product was dried, concentrated, and diluted with carbon tetrachloride to yield 281 mg. of IIa as white plates with m.p. 126–128°; $[\alpha]_D$ +25° (*c* 1.845); $\lambda_{max}^{CHCl_3}$ 2.90 (w, br.) μ.

Anal. Calcd. for $C_{27}H_{48}O_3$: C, 77.08; H, 11.50. Found: C, 77.00; H, 11.49.

Reaction of 5β-Cholestane-3β,5,6β-triol 3,6-Diacetate (IIb) with Potassium Acid Sulfate.—A mixture of 500 mg. (0.994 mmole) of IIb, 150 mg. of powdered potassium acid sulfate, and 5 ml. of acetic anhydride was heated on the steam bath for 1 hr., after which time crushed ice was added to the reaction mixture. After standing for 2.5 hr., the crystallline material was collected and dissolved in methylene chloride. The dried solution was evaporated, and the residue was chromatographed on 25 g. of alumina (Merck, acid-washed). Elution with 40–60% benzene–petroleum ether yielded 308 mg. of semicrystalline material which, upon crystallization from methanol, gave 207 mg. (43%) of cholest-4-ene-3β,6β-diol diacetate (III), m.p. 130–135°, $[\alpha]_D$ −13.5° (*c* 2.07). Recrystallization from methanol gave 170 mg. with m.p. 133–133.5°, λ_{max} 5.74 (s) μ. This material did not depress the melting point of authentic III (m.p. 133–133.5°, $[\alpha]_D$ −13°) prepared by the Darzens' dehydration of 5α-cholestane-3β,5,6β-triol 3,6-diacetate and the infrared spectra of the two samples were identical.

The semicrystalline material (115 mg.) that was eluted with 70% benzene–petroleum ether to 100% benzene mixtures was crystallized from methanol to yield 60 mg. (14%) of 5α-cholestan-3β-ol-6-one acetate (IV) as white rods with m.p. 126–128°, $[\alpha]_D$ −20° (*c* 0.75). Recrystallization from methanol gave 31 mg. with m.p. 128–130°. No depression in melting point was observed upon admixture with authentic IV and the infrared spectra of the two samples were identical.

5β-Cholestane-3β,5-diol-6-one Diacetate (Ib). A.—A mixture of 700 mg. (1.52 mmoles) of 5β-cholestane-3β,5-diol-6-one 3-monoacetate (Ia), 7.5 ml. of acetic anhydride, and 7.5 ml. of glacial acetic acid was warmed on the hot plate until solution was complete. One hundred and forty milligrams of *p*-toluenesulfonic acid monohydrate was added to the cooled solution, which was allowed to remain overnight at room temperature. The flask was then cooled in an ice–water mixture as water was added in portions. The precipitated product was collected, washed with water, and recrystallized from methanol containing a small amount of chloroform to yield 700 mg. (92%) of Ib, m.p. 190–193°. Recrystallization from chloroform–petroleum ether gave 653 mg. of small white needles with m.p. 192–193.5°; $[\alpha]_D$ −26° (*c* 1.25), −23° (*c* 1.30); λ_{max} 5.73 (s) and 5.79 (s, sh) μ.

Anal. Calcd. for $C_{31}H_{50}O_5$: C, 74.06; H, 10.02. Found: C, 74.02; H, 9.88.

B.—A mixture of 300 mg. (0.652 mmole) of Ia, 80 mg. of powdered potassium acid sulfate, and 2.5 ml. of acetic anhydride was heated on the steam bath for 80 min. Crushed ice was added to precipitate the product, which was collected, washed with water, and recrystallized from acetone–petroleum ether to give 285 mg. (87%) of Ib, m.p. 191–193°. No depression of the melting point occurred upon admixture with Ib prepared by method A.

5β-Cholestane-3β,5-diol-6-one Ethylene Ketal (V).—To a solution of 1.000 g. (2.17 mmoles) of the diolone monoacetate (Ia) in 80 ml. of toluene were added 10 ml. of redistilled ethylene glycol and 80 mg. of *p*-toluenesulfonic acid monohydrate. The mixture was boiled under reflux for 6.75 hr. (constant water separation) with magnetic stirring, cooled, stirred for a few minutes after the addition of 1 g. of anhydrous potassium carbonate, and diluted with water. The layers were separated and the aqueous phase was saturated with sodium chloride and extracted twice with ether. The combined organic phases were washed with a saturated saline solution and dried. Evaporation of the solvents gave an oil [λ_{max} 2.79–2.89 (w, br), 5.75 (m, sh), 5.84 (m) μ] which was treated with 10 ml. of 0.34 *N* methanolic potassium hydroxide by warming on the hot plate for 0.5 hr. The cooled solution was diluted with water and extracted three times with methylene chloride. The combined extracts were washed with water and dried. Evaporation of the solvent yielded an orange oil which crystallized slowly (upon seeding with V from another run) from cold 95% ethanol to give 576 mg. (57%) of the ketal (V) as pale yellow crystals, m.p. 136–140°. Recrystallization from methanol yielded 501 mg. of pure V, m.p. 140–142°; $[\alpha]_D$ +23.5° (*c* 1.41); λ_{max} 2.82 (w, br.) μ.

Anal. Calcd. for $C_{29}H_{50}O_4$: C, 75.27; H, 10.89. Found: C, 75.33; H, 10.67.

Hydrolysis of the Ethylene Ketal (V).—A solution of 50 mg. (0.108 mmole) of V and 12 mg. of *p*-toluenesulfonic acid monohydrate in 3 ml. of acetone containing 3 drops of water was allowed to stand at room temperature for 22.5 hr. Three milliliters of water was added, most of the acetone was removed by an air stream, and the resulting suspension was extracted three times with methylene chloride. The dried extracts were evaporated to yield an oil whose infrared spectrum was identical to that of 5β-cholestane-3β,5-diol-6-one.[5a]

The oil was dissolved in 0.5 ml. of glacial acetic acid and 0.5 ml. of acetic anhydride and treated with 10 mg. of *p*-toluenesulfonic acid monohydrate for 21 hr. at room temperature. Crushed ice was added to the green solution and, after precipitation was complete, the product was collected and recrystallized from acetone–petroleum ether to give 45 mg. (83%, calculated from V) of the diolone diacetate Ib,[11] m.p. 190–192°. The mixture melting point with Ib prepared from Ia was 191–192.5°.

Reaction of the Ethylene Ketal (V) with Potassium Acid Sulfate.—A mixture of 143 mg. (0.309 mmole) of V, 50 mg. of potassium acid sulfate, and 4 ml. of acetic anhydride was heated on the steam bath for 70 min. Crushed ice was added to the green solution and, after standing overnight, the orange oil that had separated was redissolved by the addition of *ca.* 25 ml. of acetone. The resulting solution was heated on the steam bath for 1.5 hr., as acetone was added periodically to maintain solution. Cooling, followed by the addition of water and two extractions with chloroform gave an oil whose infrared spectrum [λ_{max} 2.82 (w), 2.89 (w), 5.75 (s), and 5.85 (m) μ] indicated incomplete removal of the ketal group and significant acetylation at C-3. The oil was treated in the manner used for the hydrolysis of the ketal (V) and gave another oil whose infrared spectrum [λ_{max} 2.89 (w), 5.75 (s), and 5.85 (s) μ] was identical with that of Ia.[5a] Upon treatment with 80 mg. of potassium acid sulfate in 2 ml. of acetic anhydride on the steam bath for 1 hr., this material yielded a brown oil which, upon two recrystallizations from methanol, gave 35 mg. (23%) of the diolone diacetate (Ib) as brown crystals, m.p. 185–187° (previous softening).

Acknowledgment.—The author is indebted to Thomas Green and Steven Dressner for technical assistance.

(11) The facile hydrolysis of V and subsequent conversion to Ib indicated that no unusual rearrangement occurred in the formation of V from Ia: *cf.* S. Bernstein, M. Heller, and W. S. Allen, *J. Org. Chem.*, **26**, 1333 (1961).

Heterocyclic Derivatives of 3-Aminopropanethiol

E. CAMPAIGNE AND P. K. NARGUND

Department of Chemistry, Indiana University, Bloomington, Indiana

Received July 22, 1963

2-Aminoethanethiol, 3-aminopropanethiol, and their substituted derivatives[2] are known to protect experi-

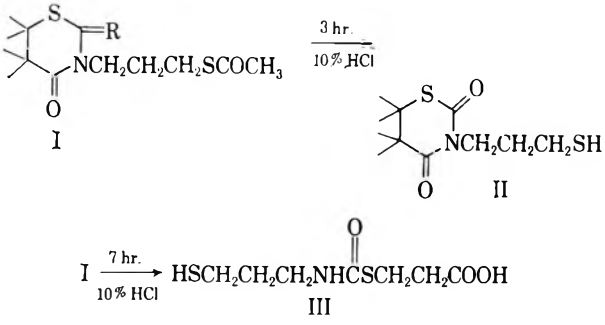
(1) Contribution No. 1156, from this laboratory. This investigation was supported by the U. S. Army Research and Development Command (Contract No. DA-49-193-MD 2096).

(2)(a) D. G. Doherty and W. T. Burnett, Jr., *Proc. Soc. Exptl. Biol. Med.*, **89**, 312 (1955); (b) S. Akerfeldt, *Acta Chem. Scand.*, **14**, 1980 (1960); D. P. Jacobus, B. Ramsay, R. E. Spalding, and D. C. Dittmer, Abstracts of Papers, presented at the 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962; (c) T. P. Johnston and A. Gallagher, *J. Org. Chem.*, **26**, 3780 (1961), and references cited therein; (d) H. Bretschneider, *Monatsh.*, **81**, 372 (1950); Holmberg and B. Sörbo, *Nature*, **183**, 832 (1959); B. Sörbo, *Acta Chem. Scand.*, **12**, 1990 (1958); (e) A. Kaluszyner, P. Czerniak, and E. D. Bergmann, *Radiation Res.*, **14**, 23 (1961).

mental animals against ionizing radiation. In the course of attempts to synthesize effective drugs with lower toxicity and longer duration of protective action, 3-(β-aminoethyl)-1,3-thiazane-2,4-dione hydrochloride was found to be an active compound.[3] We were therefore interested in synthesizing N-mercaptoalkyl derivatives of 1,3-thiazane-2,4-dione and thiazolidine-2,4-dione, which are derivatives of aminoalkanethiols.

3-(γ-Acetylthiopropyl)-1,3-thiazane-2,4-dione (I, R = O) was obtained in 60% yield by refluxing a mixture of thiolacetic acid and 3-allyl-1,3-thiazane-2,4-dione in carbon tetrachloride over an ultraviolet lamp in a nitrogen atmosphere. 3-(γ-Acetylthiopropyl)thiazolidine-2,4-dione (IV) was prepared in a similar way.

Studies on the acid hydrolysis of (I, R = O) showed that it was possible to effect the complete hydrolysis of the acetylthio group to thiol (II) in 3 hr., but that prolonged hydrolysis resulted in cleavage of the amide linkage of the thiazane ring as well, affording the mercapto acid (III). Mild acid hydrolysis of IV gave 3-(γ-mercaptopropyl)thiazolidine-2,4-dione (V).



It is remarkable that attempts to prepare the anti-Markovnikov thiolacetic acid adducts of 3-allyl-1,3-thiazane-2-thione-4-one (I, R = S) and 3-allylrhodanine with or without benzoyl peroxide as a catalyst and ultraviolet light as a radical promoter failed to give the desired products. The starting thiones were partially recovered in these reactions. It seems that, in some way, the thione moieties are acting to inhibit the free-radical addition reaction, possibly by inhibiting radical formation from thiolacetic acid.

The n.m.r. spectrum of I was in accord with the assigned structure, in particular showing a quartet resonance due to the four ring protons at 6.93 and a singlet resonance for the methyl of the acetyl group at 7.70 τ. The N-methylene protons occurred as a triplet at 6.18, whereas the S-methylene protons were observed as a triplet at 7.22 τ. The methylene protons flanked by the two adjacent methylene groups were seen as a multiplet in the range of 7.88 to 8.42 τ. The n.m.r. spectrum of II showed the quartet of four ring protons at 6.93 and triplet for the N-methylene protons at 6.17 τ. A multiplet due to the middle methylene protons and the thiol proton was present at 8.00 to 8.58, whereas the S-methylene protons appeared as a multiplet at 7.37 to 7.70 τ. The assignment of τ-values for the middle methylene, S-methylene, and thiol protons is supported by the τ-values of 1,3-propanedithiol[4] which shows a triplet resonance for the thiol proton at 8.65, a multiplet for the middle methylene protons at 8.22, and a multiplet for the S-methylene protons at 7.32 τ.

The n.m.r. spectrum of IV was in agreement with the assigned structure, showing a singlet at 5.93 due to the two ring protons and a singlet at 7.70 τ due to the methyl protons of the acetyl group. A triplet for the N-methylene protons was shown at 6.40 and a triplet for the S-methylene protons appeared at 7.05 τ. A multiplet for the methylene protons flanked by the two adjacent methylene groups was observed at 7.97 to 8.33 τ. The structure of V was confirmed by the n.m.r. spectrum, showing a singlet resonance at 5.97 and, in agreement with the spectrum of the thiazanedione, a triplet resonance for the N-methylene protons at 6.33 τ. The multiplet for the middle methylene protons and the thiol was shifted to 7.97 to 8.75, whereas the S-methylene protons were observed as a multiplet in the range of 7.42 to 7.68 τ.[5] The structure of III was confirmed by the infrared spectrum, which showed all the characteristic peaks for the NH, CH, SH (very weak), amide carbonyl, carboxyl carbonyl, and C–N stretches; the first and last, being shifted from their usual positions, are in the characteristic absorptions for monoalkyl dithiocarbamates.[6]

Experimental[7]

3-Allyl-1,3-thiazane-2,4-dione.—The synthesis consisted of two steps: (1) preparation of O-ethyl allylthiocarbamate, and (2) its reaction with β-chloropropionic acid in acetic anhydride to give 3-allyl-1,3-thiazane-2,4-dione.

(1) **Preparation of O-ethyl Allylthiocarbamate.**—Allyl isothiocyanate (59.5 g., Aldrich Chemical Co.) and ethanol (120 ml.) were refluxed for 60 hr. on a steam bath and the excess solvent was removed under reduced pressure. The liquid was distilled and the fraction boiling at 64–65° (0.3 mm.), 71.5 g. (82%), was collected. Vladzimirskaya[8] obtained this compound in 70.7% yield.

(2) **Reaction of O-Ethyl Allylthiocarbamate and β-Chloropropionic Acid.**—A mixture of O-ethyl allylthiocarbamate (145 g., 1 mole), β-chloropropionic acid (108.5 g., 1 mole), acetic anhydride (350 ml.), and 2 drops of concentrated sulfuric acid was refluxed for 4–5 hr., after which the excess acetic anhydride was removed under reduced pressure. The fraction distilling at 108–111° (1.1 mm.) was collected and weighed 100 g. (59%). The infrared spectrum showed by the absence of an NH band at 3–3.1 and C–N stretch at 6.6, and by the presence of amide carbonyl peak at 5.9 and carbamoyl carbonyl peak at 6.15 μ that the product was the ring-closed thiazanedione. The boiling point of 3-allyl-1,3-thiazane-2,4-dione is reported[8] as 82–87° (0.7 mm.).

Anal. Calcd. for $C_7H_9NO_2S$: C, 49.12; H, 5.26; N, 8.71. Found: C, 49.00; H, 5.50; N, 18.67.

β-(Allyldithiocarbamoyl)propionic Acid.—Sodium allyldithiocarbamate, prepared from 28.5 g. (0.5 mole) of allylamine, carbon disulfide, and sodium hydroxide in the usual way, was dissolved in 250 ml. of water, cooled to 0°, and 36 g. (0.5 mole) of β-propiolactone added dropwise, with stirring, at such rate as to keep the temperature below 5°. One-half hour after addition was complete, the solution was acidified with 18% hydrochloric acid, and the oil which separated was extracted with ether, and the ether extracts dried over anhydrous sodium sulfate. Removal of ether left a yellow solid which was recrystallized from

(3) E. Campagine, L. Fedor, and M. C. Wani, Abstracts of Papers, 141st Meeting of the American Chemical Society, Washington, D. C., March, 1962, p. 32N.

(4) High Resolution N.M.R. Spectra Catalog, Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 47.

(5) Proton magnetic resonance spectra were determined in carbon tetrachloride at concentrations between 6–8% w./v. at 25°, using a Varian A-60 spectrometer, and tetramethylsilane as an internal standard.

(6) L. J. Bellamy, "Infrared Spectra of Complex Molecules," 2nd Ed., Methuen, London, 1960, p. 357.

(7) All melting points are corrected. Analyses were performed by the Midwest Microlab, Inc., Indianapolis, Ind. The assistance of Mr. Rod Hamilton in determination of the n.m.r. spectra is acknowledged.

(8) E. V. Vladzimirskaya, *J. Gen. Chem. USSR*, **32**, 528 (1962).

benzene to give 30 g. (29%) of yellow needles melting sharply at 69.7°, and showing infrared absorption at 5.9 μ.

3-Allyl-1,3-thiazane-2-thion-4-one.—Following the procedure of Gresham,[9] 20.5 g. (0.1 mole) of β-(allyldithiocarbamoyl)-propionic acid was dissolved in 25 ml. of acetic anhydride containing 2 drops of concentrated sulfuric acid, and the mixture stirred for 2 hr. at 55–70°, until the solution became clear. After filtering, the cooled clear solution was poured into 150 ml. of ice water, stirred, and let stand overnight. The oil which separated was extracted with ether, and, after drying over anhydrous sodium sulfate, the ether was removed. The resultant yellow oil, $n^{20}D$ 1.6383, was collected between 145–147° at 0.5 mm., and weighed 12 g. (64%). The presence of a peak at 5.9, but none at 6.1–6.2 μ, confirmed the assignment of amide and carbamoyl CO peaks in 3-allyl-1,3-thiazane-2,4-dione.

Anal. Calcd. for $C_7H_9NOS_2$: C, 44.91; H, 4.81; N, 7.48; S, 34.20. Found: C, 45.05; H, 5.22; N, 7.06; S, 33.30.

3-(γ-Acetylthiopropyl)-1,3-thiazane-2,4-dione (I).—Thiolacetic acid (22.8 g., 0.3 mole, Aldrich Chemical Co.) was added to 3-allyl-1,3-thiazane-2,4-dione (51 g., 0.3 mole) dissolved in carbon tetrachloride (120 ml.), and the mixture was refluxed over a ultraviolet lamp (140-w.) for 22 hr. under a nitrogen atmosphere in a quartz flask. Excess solvent was removed under reduced pressure; distillation of the crude product gave a forefraction boiling in the range of 60–116° (0.3–0.8 mm.) which was discarded and a second fraction, boiling at 195–196° (0.4 mm.) which weighed 42 g. (60%). The infrared spectrum of this fraction showed the amide carbonyl peak at 5.84, carbonyl of the acetyl group at 5.92, and the carbamoyl carbonyl peak at 6.05 to 6.07 μ.

Anal. Calcd. for $C_9H_{13}NO_3S_2$: C, 43.70; H, 5.30; S, 25.90. Found: C, 43.57; H, 5.44; S, 25.61.

3-(γ-Mercaptopropyl)-1,3-thiazane-2,4-dione (II).—A mixture of I (18.4 g.) and 10% hydrochloric acid (300 ml.) was heated with stirring on a steam bath for 3 hr. under nitrogen. At the end of 3 hr. the reaction mixture was cooled and extracted with ether. The ether extract was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the product distilled at 153–154° (1 mm.) as a pale yellow liquid weighing 11 g. (70%). The infrared spectrum showed thiol absorption at 3.9, amide carbonyl absorption at 5.9, and carbamoyl carbonyl absorption at 6.15 μ.

Anal. Calcd. for $C_7H_{11}NO_2S_2$: C, 40.97; H, 5.37; N, 6.83; S, 31.22. Found: C, 40.69; H, 5.65; N, 6.68; S, 31.40.

β-(3-Mercaptopropylthiocarbamoyl)propionic Acid (III).—A mixture of I (12.1 g.) and 10% hydrochloric acid (150–200 ml.) was heated with stirring on a steam bath for 7 hr. under nitrogen. The reaction mixture was cooled and extracted with ether, and the ether extract dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the solid recrystallized from benzene as colorless needles. It weighed 7 g. (64%) and melted at 100°. The infrared spectrum showed the shifted NH absorption at 3.06,[6] amide carbonyl absorption at 5.95, carbamoyl carbonyl absorption at 6.18, and shifted C–N stretch[6] at 6.6 μ. A very weak peak for thiol was present at 3.91 μ. The compound gave a positive potassium iodide–iodine solution test for free thiol.

Anal. Calcd. for $C_7H_{13}NO_3S_2$: C, 37.65; H, 5.83; N, 6.28; S, 28.70. Found: C, 37.96; H, 6.02; N, 6.27; S, 29.00.

3-Allylthiazolidine-2,4-dione.—This compound was prepared according to the procedure described under 3-allyl-1,3-thiazane-2,4-dione using chloroacetic acid instead of β-chloropropionic acid. It distilled at 81–83° (0.7 mm.) and weighed 125 g. (79.6%). E. V. Vladzimirskaya[10] reports b.p. 81–85° (0.7 mm.). The infrared spectrum of the compound showed, by the presence of amide carbonyl peak at 5.75, the carbamoyl carbonyl peak at 6.0 μ, and the absence of NH and C–N stretches, that the product was ring-closed thiazolidinedione. 3-Allylthiazolidine-2-thion-4-one (3-allylrhodanine, Aldrich) showed a single amide carbonyl peak at 5.75 μ, thus confirming the band assignments for amide and carbamoyl carbonyl peaks.

3-(γ-Acetylthiopropyl)thiazolidine-2,4-dione (IV).—The reaction of the thiolacetic acid and 3-allylrhodanine was carried out according to the procedure described for the preparation of I. The product (40 g., 57%) distilled as a yellow liquid boiling at 162–163° (0.5 mm.) and 168–171° (1 mm.). The infrared spectrum showed two peaks for carbonyl absorptions, one at 5.7 and the other a broad peak at 5.9 and 5.98 μ. The peak at 5.7 is due to amide carbonyl of the thiazolidine ring, but the two carbonyl peaks of the acetyl and carbamoyl groups result in a single broad peak at 5.9 to 5.98 μ.

Anal. Calcd. for $C_8H_{11}NO_3S_2$: C, 41.20; H, 4.72; N, 6.01; S, 27.47. Found: C, 41.60; H, 4.96; N, 5.41; S, 27.59.

3-(γ-Mercaptopropyl)thiazolidine-2,4-dione (V).—A mixture of IV (23.3 g.) and 10% hydrochloric acid (350 ml.) was heated on a steam bath for 3 hr. while stirring under nitrogen. The reaction mixture was then cooled and extracted with three 100-ml. portions of ether. The combined ether extract was dried over anhydrous sodium sulfate and the solvent removed. The yellow liquid boiling at 139–141° (1 mm.) was collected and weighed 13 g. (68%). The compound gave a positive potassium iodide–iodine solution test for thiol. The infrared spectrum showed the amide carbonyl absorption at 5.7 and carbamoyl carbonyl absorption at 5.95–6.0 μ.

Anal. Calcd. for $C_6H_9NO_2S_2$: C, 37.70; H, 4.71; N, 7.33; S, 33.53. Found: C, 37.38; H, 4.83; N, 7.14; S, 33.65.

(9) T. L. Gresham, J. E. Jansen, and F. W. Shaver, *J. Am. Chem. Soc.*, **70**, 1001 (1948).

(10) E. V. Vladzimirskaya, *J. Gen. Chem. USSR*, **32**, 2000 (1962).

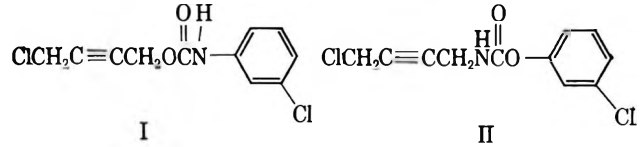
Study of 4-Amino-2-butyn-1-ol and Preparation of the Reverse Carbamate of the Selective Herbicide, Barban

ERIC C. JUENGE[1] AND PAUL SPANGLER[2]

The Department of Chemistry, Kansas State College of Pittsburg, Pittsburg, Kansas, and Spencer Chemical Company, Merriam, Kansas

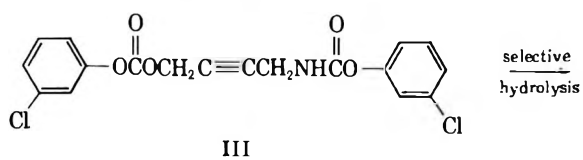
Received August 1, 1963

The successful preparation of barban, 4-chloro-2-butynyl *N*-(3-chlorophenyl)carbamate (I), and application as a selective herbicide[3,4] suggested the preparation of the reverse carbamate of barban, 3-chlorophenyl *N*-(4-chloro-2-butynyl)carbamate (II), starting with 4-amino-2-butyn-1-ol.

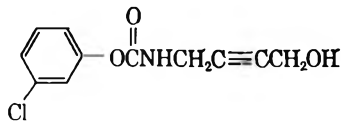


I II

Attempted reaction of 3-chlorophenyl chloroformate with 4-amino-2-butyn-1-ol to initiate the preparation of the reverse carbamate (II) failed when substitution occurred at both amino and hydroxy groups yielding 3-chlorophenyl *N*-[4-(3-chlorophenylcarbonyldioxy)-2-butynyl]carbamate (III). Good yields of the bis-



III



IV

(1) Kansas State College of Pittsburg, Pittsburg, Kan.

(2) National Science Foundation Undergraduate Research Participant, Kansas State College, Pittsburg, Kan.

(3) T. R. Hopkins, R. D. Neighbors, P. D. Strickler, and L. V. Phillips, *J. Org. Chem.*, **24**, 2040 (1959).

(4) T. R. Hopkins and J. W. Pullen, U. S. Patent 2,906,614 (1959).

substituted product were obtained despite reactant ratio and solvent dilution favoring formation of the monosubstituted product. Selective hydrolysis of the carbonate group in compound III was accomplished by refluxing with aqueous alcoholic hydrochloric acid yielding 3-chlorophenyl *N*-(4-hydroxy-2-butynyl)-carbamate (IV). Refluxing concentrated hydrochloric acid, in which the compound was insoluble, failed to hydrolyze the compound. Compound III showed a carbonyl peak at 5.69 and one at 5.90 μ, while the hydrolyzed compound (IV) showed a carbonyl peak at 5.78 μ.

The hydroxy carbamate (IV) was converted to the reverse carbamate (II) of barban by treatment with thionyl chloride. The reverse carbamate does not show a broad region for associated hydroxyl in the infrared as shown by all of the other butynyl hydroxides studied here, but shows a sharp NH peak for NH stretching frequency of the carbamate.

Experimental[5]

Starting Material.—4-Chloro-2-butyn-1-ol (51% yield of pure product) was synthesized by established procedures.

4-Amino-2-butyn-1-ol Hydrochloride from 4-Chloro-2-butyn-1-ol.—Chloro-2-butyn-1-ol (41.82 g., 0.4 mole) was mixed with 1400 ml. of concentrated ammonium hydroxide and the homogeneous mixture was stirred overnight. The mixture was evaporated by stirring on a steam bath until no appreciable ammonia fumes were detectable. As the reaction cooled, the entire material formed a brown crystalline mass. Recrystallization from methanol yielded 30.4 g. (63% yield) of pure product, m.p. 177–178°, with signs of sublimation just before melting.

Anal. Calcd. for C_4H_8ClNO: C, 39.52; H, 6.63; Cl, 29.17. Found: C, 39.71. H, 6.56; Cl, 28.96.

4-Amino-2-butyn-1-ol.—To 30.37 g. (0.25 mole) of 4-amino-2-butyn-1-ol hydrochloride was added 40 ml. of distilled water (not quite enough water to dissolve it). The mixture was neutralized to pH 13, which required about 25 ml. of 10 *N* sodium hydroxide, and was extracted with diethyl ether in a continuous extractor. A water layer formed below the ether layer. The water was removed from this layer by azeotropic distillation with benzene. The residue solidified as it cooled to room temperature. The crude material was purified by crystallization from ethyl acetate. Last traces of solvent were removed under vacuum to avoid exposure to air. The yield was 13.5 g. (63.6%), m.p. 59–60°. The analytical sample was prepared by distillation, b.p. 121–123° (3 mm.), as a colorless liquid which solidified to white crystals with a slight yellow tinge, m.p. 60–61°.

Anal. Calcd. for C_4H_7NO: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.58; H, 8.23; N, 16.57.

***N*-3-Chlorophenyl-*N'*-4-hydroxy-2-butynylurea.**—4-Amino-2-butyn-1-ol (10.00 g., 0.118 mole) was dissolved in about 270–300 ml. of dry ethyl acetate and kept at 40–50° to maintain solution. At this temperature, 18.1 g. (0.118 mole) of 3-chlorophenylisocyanate dissolved in 20 ml. of dry ethyl acetate was added dropwise. The mixture was stirred at room temperature over the weekend. After collection and an ethyl acetate wash, the product, which was insoluble in dilute hydrochloric acid, melted at 126–127° and weighed 13.0 g. Two recrystallizations from ethanol yielded a product, m.p. 129–130°, which was analyzed.

Anal. Calcd. for $C_{11}H_{11}ClN_2O_2$: C, 55.35; H, 4.65; Cl, 14.86; N, 11.74. Found: C, 55.30; H, 4.90; Cl, 14.42; N, 11.46.

***N*-Phenyl-*N'*-4-hydroxy-2-butynylthiourea.**—The above procedure was followed through the addition step. In this reaction, 11.84 g. (0.088 mole) of phenyl isothiocyanate and 7.46 g. (0.088 mole) of 4-amino-2-butyn-1-ol were used. The reaction mixture was refluxed for 4 hr. and filtered while hot. The filtered solution was set in the ice box over the weekend to allow crystallization. The yield, after collection and an ethyl acetate wash, was 6.98 g., m.p. 150–151°. The product was insoluble in dilute hydrochloric acid. An analytical sample was prepared by recrystallization from ethanol followed by sublimation at 145° (1 mm.). The pure material melted at 154–156°.

Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found: C, 59.94; H, 5.25; N, 12.26.

3-Chlorophenyl Chloroformate.—To 200 ml. of toluene about 80 ml. of phosgene (0.60 mole) was added. 3-Chlorophenol, 76.8 g. (0.60 mole) in 100 ml. of toluene, and then 47.4 g. (0.60 mole) of pyridine was added dropwise with stirring at 0–10°. After the reaction mixture was hydrolyzed by slow addition of water, the product was extracted with toluene, and the toluene solution was then dried over anhydrous calcium chloride. The toluene solvent was removed, and the residue was then fractionated with a 1-ft. column yielding 77.4 g. (67.6%) of product, b.p. 98–100° (13 mm.). Infrared spectra was consistent for this compound. A middle fraction was analyzed.

Anal. Calcd. for $C_7H_4Cl_2O_2$: C, 44.01; H, 2.11; Cl, 37.12. Found: C, 43.79; H, 2.22; Cl, 36.89.

3-Chlorophenyl Carbonate.—The residue from the preceding distillation solidified, m.p. 77–80°. This solid, 20.64 g., was crystallized from benzene, and the analytical sample was prepared by further recrystallization from ethanol to a constant m.p. 84–85°. The same carbonate (shown by mixture melting point and identical infrared spectra) was obtained on long exposure of a small sample of the previous 3-chlorophenyl chloroformate to moist air or by treatment with aqueous sodium hydroxide. The infrared spectrum was consistent with that expected for the product.

Anal. Calcd. for $C_{13}H_8Cl_2O_3$: C, 55.15; H, 2.85; Cl, 25.05. Found: C, 54.93; H, 2.65; Cl, 25.10.

3-Chlorophenyl *N*-[4-(3-Chlorophenylcarbonyldioxy)-2-butynyl]carbamate (III).—To 30.0 g. (0.353 mole) of 4-amino-2-butyn-1-ol, dissolved in 1400 ml. of ethyl acetate, 27.8 g. (0.353 mole) of pyridine was added. 3-Chlorophenyl chloroformate (67.4 g., 0.353 mole) dissolved in 200 ml. of ethyl acetate was added dropwise over a 2.5-hr. period. A white precipitate formed immediately. The pyridine hydrochloride (39.6 g., theoretical 40.8 g.) was removed by filtration. The ethyl acetate was removed from the filtrate by evaporation under slight vacuum. The remaining oil was extracted with dry ether, and the product was precipitated by addition of hexane. Despite the fact that equimolar quantities of reactant, high dilution, and an order of addition providing excess 4-amino-2-butyn-1-ol were used, the bis-substituted compound (58 g., m.p. 73–74°) was obtained. Recrystallization from ethanol gave a product melting at 76–77°. Traces of 3-chlorophenyl carbonate, present in some runs, were removed by sublimation of the carbonate at 55° (1 mm.) leaving analytically pure product, m.p. 78–79°.

Anal. Calcd. for $C_{18}H_{13}Cl_2NO_5$: C, 54.84; H, 3.32; N, 3.55; Cl, 17.99. Found: C, 54.76; H, 3.42; N, 3.52; Cl, 17.95.

3-Chlorophenyl *N*-(4-Hydroxy-2-butynyl)carbamate (IV).—Selective hydrolysis of 3.94 g. (0.01 mole) of 3-chlorophenyl *N*-[4-(3-chlorophenylcarbonyldioxy-2-butynyl)]carbamate was accomplished by a 0.5-hr. reflux with 40 ml. of concentrated hydrochloric acid to which was added 78.8 ml. of ethanol to solubilize the mixture. After refluxing, water and hydrochloric acid were removed by azeotropic distillation with benzene. The benzene solution was concentrated to 20–30 ml. The product was separated as a light orange oil (possibly a supercooled liquid) by addition of 200 ml. of hexane. The mixture was allowed to stand overnight to complete the separation, and the mixed solvent was then decanted. After drying for 3 hr. at 50° (1 mm.), the product (2.87 g., 67%) was obtained. The infrared spectrum of the product taken on a Model 137 Infracord showed only one carbonyl peak at 5.78 as opposed to two carbonyl peaks 5.69 and 5.90 μ, for the carbonate–carbamate compound (III).

Anal. Calcd. for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21. Found: C, 55.16, 55.40; H, 4.40, 4.31.

3-Chlorophenyl *N*-(4-Chloro-2-butynyl)carbamate (II) from 3-Chlorophenyl *N*-(4-Hydroxy-2-butynyl)carbamate (IV).—The dropwise addition of 0.75 g. (0.0063 mole) of thionyl chloride, in 5 ml. of benzene, to 1.3 g. (0.0054 mole) of 3-chlorophenyl *N*-(4-hydroxy-2-butynyl)carbamate was completed in a 15–20-min. period. The temperature was then maintained between 58–62° for 4 hr. The product was separated by addition of about 50 ml. of hexane. After removal of trace amounts of solvent at reduced pressure (1 mm.), 0.89 g. (64% yield) of product was obtained. The same yields were obtained using larger runs. Analysis of this crude product indicated at least 95% content of

(5) All melting points are uncorrected.

halogenated product (II), on the bases of increased chlorine percentage. A small sample was placed in a microevaporative still. A colorless oil collected at 64° (0.5–1 mm.). After standing overnight the oil crystallized to a white solid which was washed with hexane leaving the analytical sample, m.p. 69–70°. Alternatively, chromatography on activated alumina with a hexane–ether eluent gave 80% recovery of an oil which required several weeks to crystallize. The infrared spectrum of the compound showed a sharp peak at 2.8 μ with disappearance of the broad O–H band found in the starting material.

Anal. Calcd. for $C_{11}H_9Cl_2NO_2$: C, 51.19; H, 3.52. Found: C, 51.30; H, 3.72.

Acknowledgment.—We are pleased to acknowledge the support of this work by the National Science Foundation Undergraduate Participation Program. The authors also wish to thank Dr. T. R. Hopkins, Mr. Paul D. Strickler, and Dr. L. V. Phillips for their many helpful suggestions in the development of this work.

The Hydrogenation of Dihydrolanosteryl and Dihydroagnosteryl Acetates[1]

J. D. CHANLEY AND T. MEZZETTI

Department of Chemistry, The Mount Sinai Hospital, New York, New York

Received July 25, 1963

We wish to report that both dihydrolanosterol, 3β-hydroxy-5α-lanost-8-ene, and dihydroagnosterol, 3β-hydroxy-5α-lanost-7:8,9:11-diene, acetates are hydrogenated to an easily separable mixture of the saturated acetate, 3β-acetoxy-5α-lanostane (67% yield), and saturated ether, 3β-ethoxy-5α-lanostane (24% yield). The identity of these products was established by a comparison of their melting points and mixture melting points, specific rotation, and infrared spectra with authentic samples.[2]

The hydrogenations proceed slowly at atmospheric pressure, when relatively large amounts of Adams, catalyst (PtO_2) are employed and a few drops of perchloric acid have been added to the solvent, acetic acid. These findings are in contrast to the numerous reports concerning the nonhydrogenability, under a variety of conditions, of either the Δ7- or Δ8-lanosten-3-ol, and dihydroagnosterol.[3] The hydrogenation of the 9:11 double bond of 3β-acetoxy-5α-lanost-9-ene has been accomplished[4] (PtO_2, acetic acid, 60°), albeit with some difficulty. The stereochemistry of the hydrogens at C-8 and C-9, β and α, for both the saturated acetate and the saturated ether has been established.[4-7] These observations coupled with the known stability[8] of the 9:11 double bond as contrasted to the ready intraconvertibility[9] of the 7:8 and 8:9 double bond isomers of 3β-acetoxy-5α-lanostene under acid conditions indicate that addition of hydrogen to the 9:11 and 7:8 double bonds take place at the α and β faces, respectively, and, in fact, it is the isomer (7:8-ene) derived from dihydrolanosterol which is hydrogenated.[10] The last consideration follows from the steric course of the hydrogenation of dihydrolanosterol. The relative rates of saturation of the double bonds has not as yet been investigated.

The catalytic reduction of an ester to an ether under the conditions employed is striking. The recently reported[11] catalytic hydrogenation of succinic anhydride to butyrolactone and butyric acid bears a formal resemblance to our findings. The role of the solvent and acidity as well as possible intermediates in the conversion of the acetate to an ether remains to be elucidated.

Experimental[12]

3β-Acetoxy-5α-lanost-8-ene, dihydrolanosteryl acetate, m.p. 120–121°, lit.[14] m.p. 120–121°, prepared by hydrogenation, over PtO_2, of crude lanosteryl acetate dissolved in ethyl acetate–acetic acid mixture, was recrystallized from methanol–petroleum ether (b.p. 30–60°). 3β-Acetoxy-5α-lanost-7:8,9:11-diene, dihydroagnosteryl acetate [m.p. 164–165°; λ_{max} 236 mμ (ϵ 12,500), 244 (14,830), and 252 (9800)], was prepared by oxidation of dihydrolanosteryl acetate with N-bromosuccinimide, according to Dorée, *et al.*,[15] and recrystallized several times from acetone and methanol (lit.[3] m.p. 168–169°).

3β-Acetoxy-5α-lanostane and 3β-Ethoxy-5α-lanostane. A.—Dihydroagnosteryl acetate (340 mg.) dissolved in glacial acetic acid (200 ml.) containing 12 drops of perchloric acid (70%) was hydrogenated, at atmospheric pressure and room temperature in the presence of PtO_2 (300 mg.). After 48 hr. fresh catalyst (200 mg.) was added and the hydrogenation continued for *ca.* an additional 48 hr.[17] After removal of spent catalyst, the hydrogenation mixture was poured into ice–water, and the precipitated solid collected by filtration and dried *in vacuo* over phosphorus pentoxide. The dried material, dissolved in petroleum ether (b.p. 30–60°), was chromatographed on Woelm alumina (34 g.). The alumina, initially of activity I, had been partially deacti-

(1) This work was supported by National Science Foundation Grant G-24019, Office of Naval Research Contract NR-107543, and National Institutes of Health Grant A-6180.

(2) We wish to thank Professor George Petit for supplying us with these samples.

(3) L. Ruzicka, R. Denss, and O. Jeger, *Helv. Chim. Acta*, **29**, 204 (1946); H. Wieland and W. Benend, *Z. Physiol. Chem.*, **274**, 215 (1942); J. F. Cavalla, J. F. McGhie, and M. K. Pradham, *J. Chem. Soc.*, 3142 (1951); D. H. R. Bart, J. S. Fawcett, and B. R. Thomas, *ibid.*, 3147 (1951); *cf.* L. J. Bellamy and C. F. Dorée, *ibid.*, 172 (1941).

(4) W. Voser, M. Montavon, H. S. H. Gunthard, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **33**, 1893 (1950).

(5) M. V. Mijovic, W. Voser, H. Heusser, and O. Jeger, *ibid.*, **35**, 964 (1952).

(6) D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 903 (1954).

(7) G. R. Petit and T. R. Kasturi, *J. Org. Chem.*, **26**, 4553 (1961).

(8) H. R. Bentley, J. A. Henry, D. S. Irvine, and F. S. Spring, *Chem. Ind.* (London), 217 (1953); *J. Chem. Soc.*, 3673 (1953).

(9) R. E. Marker, E. L. Wittle, and L. M. Mixon, *J. Am. Chem. Soc.*, **59**, 1368 (1937).

(10) Dihydrolanosteryl acetate was hydrogenated under the same conditions as are given in the Experimental section, except that perchloric acid was omitted. As shown by infrared analysis and chromatography, 80% of final product consisted of a 70/30 mixture of the acetates of lanost-8-en-3-ol and lanost-7-en-3-ol, respectively, while 20% was identified as the fully hydrogenated lanostanyl acetate. In the absence of catalyst, a solution (acetic acid + perchloric acid, *cf.* Experimental) of the acetate of lanost-8-en-3-ol, after standing for 2 days at room temperature, is converted, as shown by infrared analysis and chromatography, into a 60/40 mixture of the Δ7- and Δ8-ene, respectively.

(11) (a) R. McCrindle, K. H. Overton, and R. A. Raphael, *Proc. Chem. Soc.*, 313 (1961); (b) Professor John T. Edward (private communication) has informed us that in his laboratories a number of lactones derived from steroids have been hydrogenated (PtO_2) to the corresponding ethers.

(12) All melting points were taken on a Fisher-Johns melting point apparatus. Rotations were determined in chloroform; ultraviolet spectra were determined in ethanol (95%), and infrared spectra of solutions in carbon disulfide and carbon tetrachloride, employing a Beckman DU and Perkin Elmer 421 infrared spectrophotometer, respectively.

(13) L. Ruzicka, R. Denss, and O. Jeger, *Helv. Chim. Acta*, **28**, 759 (1945).

(14) L. Ruzicka, E. Rey, A. C. Muhr, R. Denss, and O. Jeger, *ibid.*, **28**, 759 (1945).

(15) C. F. Dorée, J. F. McGhie, and F. Kurzer, *J. Chem. Soc.*, 570 (1949).

(16) R. G. Curtis, *ibid.*, 1017 (1950).

(17) The uptake of hydrogen was in great excess over that calculated for 2 moles of hydrogen. Subsequently it was shown that acetic acid also is hydrogenated when perchloric acid is present.

vated by the addition of 4% of its weight of acetic acid (10%). Elution was effected with petroleum ether (b.p. 30–60°), 50-ml. fractions, followed by petroleum ether (b.p. 72–78°). The course of the chromatography was followed by noting the presence or absence of an acetyl band in the infrared, as indicated in Table I. Recrystallization of the combined fractions, 2 and 3 (negative tetranitromethane test), from ethyl acetate and methanol yielded 3β-ethoxy-5α-lanostane (56 mg.) as plates, m.p. 133.5–135°, $[\alpha]^{25}D$ 44.7°; lit.[7] m.p. 133.5°, $[\alpha]^{25}D$ 53.2°. Mixture melting point with an authentic sample, m.p. 133.5°, showed no depression while their infrared spectra in carbon tetrachloride were superimposable, with the strong characteristic ether band at 1101 cm.$^{-1}$.

TABLE I

Fraction	Solvent	Infrared band at 1733	Material	Weight, mg.
1	Pet. ether (b.p. 30–60°)	Neg.	Oil	*ca.* 10
2,3	Pet. ether	Neg.	Ether	75
4	Pet. ether			
5–12	Pet. ether	Pos.	Lanostanyl acetate	
13–21	Pet. ether (b.p. 72–78°)	Pos.	Lanostanyl acetate	210

Recrystallizations of the combined fractions, 5–21, from petroleum ether–methanol mixture afforded pure 3β-acetoxy-5α-lanostane (180 mg., negative tetranitromethane test) of $[\alpha]^{25}D$ +41.2°. The saturated acetate so prepared exhibits a double melting point. It melts at 151–152°, resolidifies, and remelts at 156.5–157°. The authentic sample exhibited the same behavior on melting and mixture melting point gave no depression. The infrared spectra (carbon tetrachloride and carbon disulfide) of both samples were identical in all respects (lit.[4] m.p. 151–152°, $[\alpha]^{20}D$ 41°; lit.[18] m.p. 156–157°, $[\alpha]^{20}D$ 46°).

B.—Dihydrolanosteryl acetate was hydrogenated and worked up as for dihydroagnosteryl acetate. 3β-Acetoxy- and 3β-ethoxylanostane were isolated in essentially the same proportions, as above.

(18) J. F. McGhie, M. K. Pradham, J. F. Cavalla, and S. A. Knight, *Chem. Ind.* (London), 1165 (1951).

17-Oxa-5α-Androstan-3-one[1]

SUMANAS RAKHIT AND MARCEL GUT

The Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts

Received July 11, 1963

The study of the effects of structural modifications of natural steroid hormones upon their biological activities has received much attention in the last few years and has led to a number of highly active synthetic modifications. A review of the publications in this field reveals examples of the insertion of oxygen in the D-ring,[2,3] although no steroid analog has been prepared in which that ring remained five-membered. This paper describes the synthesis of a 17-oxa compound with a five-membered D-ring. Our interest in such a compound is due to the fact that a modification of the procedure could lead to 17-aza steroids.[4]

This paper describes two routes leading to the elimination of C-17, followed by ring closure to a five-membered lactone and reduction to a diol which, in turn, could be ring-closed to the desired 17-oxa steroid.

The required lactone II, possessing an oxygen function at C-16, and thereby readily amenable to oxidative degradation, was obtained by a Baeyer–Villiger oxidation of the known 3β,16β-diacetoxy-5α-androstan-17-one[5] (I). Its reduction with lithium aluminum hydride gave the tetrol III which was oxidized with periodic acid to the aldehyde IV, with the desired oxygen function at C-13 and the C-17 eliminated. The crude aldehyde was oxidized with chromic acid to its acid which lactonized spontaneously to V. Attempts to reduce the lactone directly to the desired ether with either lithium aluminum hydride and boron trifluoride or with sodium borohydride and boron trifluoride led[6] only to the triol. Therefore, the lactone V was transformed to the 3-ketal and then reduced with lithium aluminum hydride to give 13α,16-dihydroxy-13,16-seco-17-nor-5α-androstane 3-ethylene ketal (VII). Ring closure with *p*-toluenesulfonyl chloride–pyridine, followed by hydrolysis of the ketal function gave the desired 17-oxa-5α-androstan-3-one (VIII).

An alternative approach to the preparation of VIII starts with the readily available lactone[7] IX, which was formylated to the 3β-hydroxy-16-hydroxymethylene-17α-oxa 5α-D-homoandrostan-17-one[8] (X). Acetylation of the lactone X furnished the diacetate XI and the latter was ozonized to yield, after decomposition of the ozonide and usual work-up, 3β-acetoxy-17-oxa-5α-androstan-16-one. Hydrolysis[6] of the acetate with sodium carbonate and oxidation[6] of the resulting alcohol with chromic acid gave 17-oxa-5α-androstane-3,16-dione, identical in all respects with V obtained previously.

Experimental[9]

3β,16β-Diacetoxy-17a-oxa-5α-D-homoandrostan-17-one (II).—To a solution of 5 g. of 3β,16β-diacetoxy-5α-androstan-17-one[5] (I) in 80 ml. glacial acetic acid, 500 mg. of *p*-toluenesulfonic acid and 30 ml. of 40% peracetic acid were added; the mixture was stored at room temperature in the dark for 24 hr. The solution was then poured into cold water and the precipitate collected and thoroughly washed with water. Upon drying 5.05 g. (96.5% yield) of II, m.p. 212–215°, was obtained. Thin layer chromatography of the crude product showed it to be a single compound. An analytical sample was crystallized from dichloromethane–ether to yield needles, m.p. 217–219°; $[\alpha]^{22}D$ −39° (*c* 1.0, chloroform); ν_{max} 1760 (16-acetoxy), 1745 (δ-lactone), and 1730 cm.$^{-1}$ (3-acetoxy).

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.72; H, 8.26.

13,17-Seco-5α-androstane-3β,13α,16,17-tetrol (III).—A solution of 5 g. of the lactone II in 100 ml. of absolute tetrahydrofuran was added with stirring over a period of 20 min. to a slurry of 5 g. of lithium aluminum hydride in 350 ml. of absolute tetrahydrofuran. The mixture was refluxed for 18 hr., then cooled, and the excess reagent decomposed by ethyl acetate. A saturated solution of sodium sulfate was added and the precipitated inorganic material filtered off. The inorganic material was thoroughly extracted with ethyl acetate, the extracts were

(1) Supported, in part, by National Institute of Health Grant H-5266.

(2) J. F. Bagli, *Can. J. Chem.*, **40**, 2032 (1962).

(3) G. R. Petit, V. R. Ghatak, B. Green, T. R. Kasturi, and D. M. Piatak, *J. Org. Chem.*, **26**, 1685 (1961).

(4) S. Rakhit and M. Gut, manuscript in preparation.

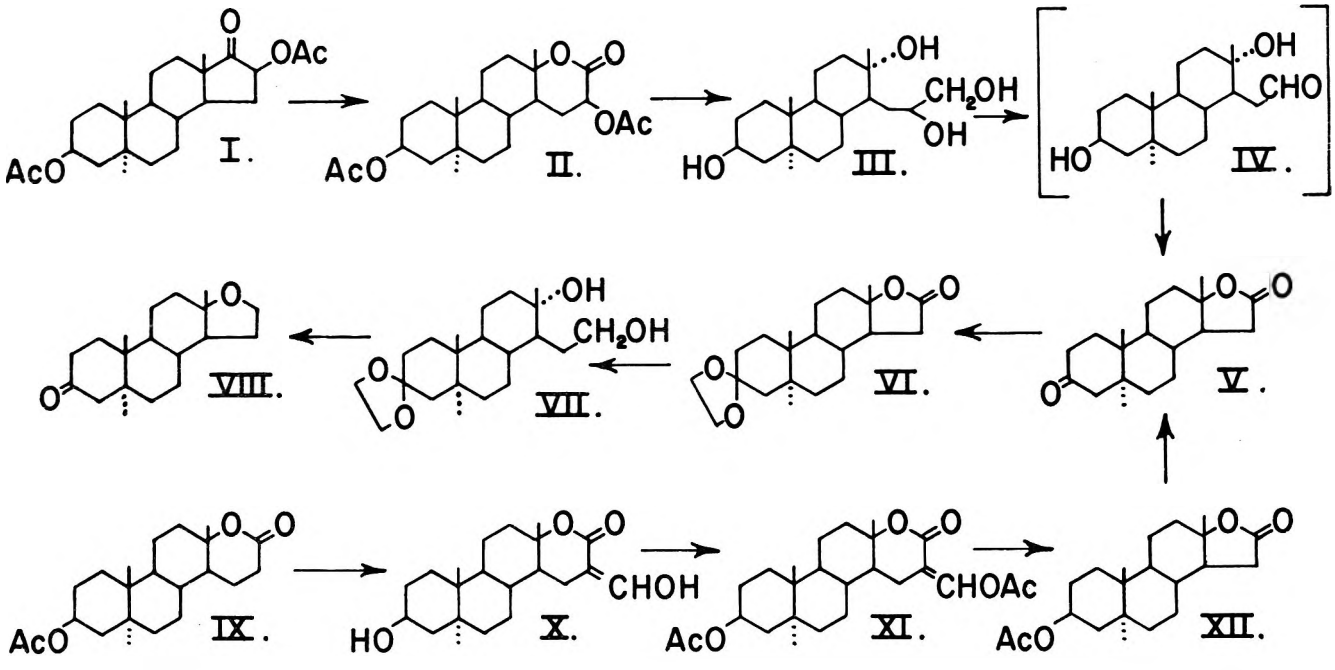
(5) W. S. Johnson, B. Gastambide, and R. Pappo, *J. Am. Chem. Soc.*, **79**, 1991 (1957).

(6) Not described in Experimental.

(7) H. Levy and R. P. Jacobsen, *J. Biol. Chem.*, **171**, 71 (1947).

(8) L. H. Knox, R. Villoti, F. A. Kincl, and H. J. Ringold, *J. Org. Chem.*, **26**, 501 (1961).

(9) Melting points were determined on a Fisher-Johns apparatus and are not corrected. The ultraviolet absorption spectra were taken in methanol and the infrared spectra in a potassium bromide pellet (Infracord). For chromatographic purifications, the silica gel used was Davison Type 923, 100–200 mesh. Analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.



added to the original filtrate, and the combined solutions dried over sodium sulfate. Removal of the solvents gave 3.9 g. (97%) of the tetrol III, m.p. 201–203°. The infrared spectrum of the crude material showed no absorption in the carbonyl region. Recrystallization from methanol–ether furnished an analytical sample of prisms, m.p. 207–208°; $[\alpha]^{22}D$ −13° (*c* 1.0, dioxane).

Anal. Calcd. for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 69.73; H, 10.73.

17-Oxa-5α-androstane-3,16-dione (V).—To a solution of 4 g. of the tetrol III in 200 ml. of dioxane was added 8 g. of periodic acid in 20 ml. of water. The solution was allowed to stand at room temperature in the dark for a period of 23 hr. The solution was then neutralized with sodium hydrogen carbonate solution and most of the solvent was removed *in vacuo*. The residue was poured into cold water and the precipitate was extracted with ether. The ether extract was washed with water and dried over sodium sulfate. Removal of solvent yielded 3.5 g. of oily aldehyde IV, demonstrated by the presence of a carbonyl absorption at 1730 cm.$^{-1}$ in the infrared spectrum. This oil resisted all attempts at crystallization, and was, therefore, directly oxidized to the lactone IX as described subsequently.

The crude aldehyde IV, *vide supra*, was dissolved in 100 ml. of absolute acetone and cooled to 0–5°. A solution of chromic acid[10] was added until the brown color persisted. The mixture was stirred for 5 min. at 0–5° and then for another 5 min. at room temperature. Excess reagent was decomposed by adding a few ml. of methanol and then the mixture was poured into water. The precipitate was extracted with methylene chloride; the organic layer was washed with a solution of sodium hydrogen carbonate and with water, and dried over sodium sulfate. Removal of solvent yielded 3.35 g. of an oil. Upon trituration with ether, 1.0 g. of the lactone V, m.p. 165–167°, was obtained. The mother liquors were adsorbed on a column of silica gel. Elution with ethyl acetate–benzene mixtures (1:9 and 1:7) yielded another 800 mg. of V, m.p. 168–169°. Total yield of lactone was 1.8 g. (50.7%). Further elution of the column with solvent mixtures of higher polarity failed to yield any clearly defined product. A portion of the lactone was crystallized for analysis three times from dichloromethane–ether to give needles, m.p. 170–171°; $[\alpha]^{22}D$ −24° (*c* 1.0, chloroform); ν_{max} 1775 (γ-lactone) and 1705 cm.$^{-1}$ (3-ketone).

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.60; H, 8.88.

17-Oxa-5α-androstan-16-one 3-Ethylene Ketal (VI).—To a solution of 1.0 g. of 17-oxa-5α-androstane-3,16-dione (V) in 200 ml. of 2-methyl-2-ethyl-1,3-dioxolane was added 18 mg. of *p*-toluenesulfonic acid and the solution refluxed for 5 hr. Ether was added after cooling and the organic phase was washed with sodium hydrogen carbonate solution and with water, and finally dried over sodium sulfate. Removal of solvent under reduced pressure (benzene being added to remove last traces of dioxolane by codistillation), gave 1.1 g. of an oil which upon trituration with ether yielded 950 mg. of 17-oxa-5α-androstan-16-one 3-ethylene ketal, m.p. 179–181° (82% yield). An analytical sample was obtained by successive recrystallizations from ether to give colorless needles, m.p. 187–188°; $[\alpha]^{22}D$ −44° (*c* 1.0, chloroform); ν_{max} 1775 cm.$^{-1}$ (γ-lactone).

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 72.03; H, 9.16. Found: C, 71.82; H, 9.04.

13,16-Seco-17-nor-5α-androstane-13α,16-diol 3-Ethylene Ketal (VII).—To a slurry of 500 mg. of lithium aluminum hydride in 300 ml. of absolute tetrahydrofuran was added with stirring over a period of 20 min. a solution of 520 mg. of 17-oxa-5α-androstan-16-one 3-ethylene ketal (VI) in 50 ml. tetrahydrofuran, and the mixture refluxed for 20 hr. After cooling, the excess reagent was decomposed by ethyl acetate, a saturated solution of sodium sulfate was added, and the precipitated inorganic material filtered off. The residue was then thoroughly washed with ethyl acetate and the washings were added to the original filtrate. The solution was dried over sodium sulfate, and the solvent removed under reduced pressure to yield 500 mg. of crystalline 13α,16-dihydroxy-13,16-seco-17-nor-5α-androstane 3-ethylene ketal (VII), m.p. 144–146° (95% yield). A portion of this was crystallized twice from methanol–ether for analysis to give needles, m.p. 152–153°; $[\alpha]D$ −7° (c 1.0, chloroform).

Anal. Calcd. for $C_{20}H_{34}C_4$: C, 70.97; H, 10.13. Found: C, 71.28; H, 10.18.

17-Oxa-5α-androstan-3-one (VIII).—To 350 mg. of 13α,17-dihydroxy-13,16-seco-17-nor-5α-androstane 3-ethylene ketal (VII) in 10 ml. of dry pyridine was added 500 mg. of *p*-toluenesulfonyl chloride. The solution was stored at room temperature for 24 hr. and then heated on a steam bath for 3 hr. Pyridine was removed under reduced pressure and the oily residue taken up in ether and washed with cold 2 *N* hydrochloric acid, water, sodium hydrogen carbonate solution, and with water, and then dried over sodium sulfate. Removal of solvent yielded 300 mg. of an oil, which showed in the infrared absorption spectrum no hydroxyl band and a weak carbonyl band indicating partial hydrolysis of the ketal function. The oil was dissolved in 40 ml. of acetone and refluxed with 50 mg. of *p*-toluenesulfonic acid for 1 hr. Most of the solvent was removed under reduced pressure and the residue diluted with water. The precipitate was extracted with ether. The ether extract was washed with water and dried over sodium sulfate. Removal of the solvent gave 250 mg. of crystalline 17-oxa-5α-androstan-3-one (VIII), m.p. 100–102°, 87% yield. An analytical sample, obtained by a recrystallization from hexane, gave plates, m.p. 109–110°; $[\alpha]D$ +42° (*c* 1.0, chloroform); ν_{max} 1700 cm.$^{-1}$ (3-ketone).

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.47; H, 10.25.

3β-Acetoxy-17a-oxa-5α-D-homoandrostan-17-one (IX).—This

(10) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **39** (1946).

substance was prepared from 3β-acetoxyandrost-5-en-17-one as described by Levy and Jacobsen[7] in an over-all yield of 85%. The melting point of the lactone was found to be 169–170°, lit. m.p. 169.7–169.9°.

3β-Hydroxy-16-hydroxymethylene-17a-oxa-5α-D-homoandrostan-17-one[8] (X).—A mixture of 2.5 g. of IX, 150 ml. of dry thiophene-free benzene, 10 ml. of ethyl formate, and 2 g. of sodium hydride (50% in oil) was stirred in an atmosphere of nitrogen for a period of 5 hr. Excess reagent was decomposed by a few milliliters of methanol, and water added to the mixture. The aqueous alkaline layer was separated and the organic phase washed with water. The aqueous washing and the alkaline extract were mixed and acidified with cold 2 *N* hydrochloric acid. The precipitate was collected and dried to yield 2.55 g. of X, m.p. 291–292°, lit. m.p. 292–294°; ν_{max} 3340 (OH), 1690 (δ-lactone carbonyl), and 1610 cm.$^{-1}$ (hydroxymethylene); λ_{max} 250 mμ (log ε 4.05).

3β-Acetoxy-16-acetoxymethylene-17α-oxa-5α-D-homoandrostan-17-one (XI).—A solution of 2 g. of X in 25 ml. of pyridine and 5 ml. of acetic anhydride was kept at room temperature for 18 hr. Excess acetic anhydride was decomposed by adding a few ml. of methanol and the solution was poured into ice–water. The precipitate was collected and dried to give 2.4 g. of the diacetate XI, m.p. 105–105°. A sample was crystallized three times from ether–hexane for analysis to give needles, m.p. 108–110°; $[\alpha]^{22}D$ −122° (*c* 1.0, chloroform); λ_{max} 237 mμ (log ε 4.12); ν_{max} 1760 (16-acetoxy), 1740 (3-acetoxy), 1708 (conjugated δ-lactone), and 1630 cm.$^{-1}$ (double bond of acetoxymethylene).

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.02; H, 8.45.

3β-Acetoxy-17-oxa-5α-androstan-16-one (XII).—A solution of 2 g. of XI in a mixture of 30 ml. of ethyl acetate and of 30 ml. of acetic acid was cooled to −10° and then ozonized for a period of 75 min. After addition of 5 ml. of a 30% solution of hydrogen peroxide and 5 ml. of water the mixture was stored at 25° for 24 hr. It was then diluted with ether, washed with water, with sodium hydrogen carbonate solution, and water, and dried over sodium sulfate. Removal of solvent gave 2 g. of an oil which was dissolved in 10 ml. of benzene and adsorbed on a column of silica gel. Elution with mixtures of ethyl acetate, benzene (5% and 10%) yielded fractions melting in the range of 139–142°. These fractions were combined to give a total of 1.42 g. of XII (85%). No other compound of definite nature could be isolated by further elution of the column. An analytical sample was prepared by crystallizing from dichloromethane–hexane to give prisms, m.p. 146–148°; $[\alpha]^{23}D$ −59° (c 1.0, chloroform); ν_{max} 1776 (γ-lactone), 1730 (3-acetate), and 1236 cm.$^{-1}$ (3-acetate).

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.68; H, 9.17.

Quinazolines and 1,4-Benzodiazepines. XVI.[1] Synthesis and Transformations of 5-Phenyl-1,4-benzodiazepine-2-thiones

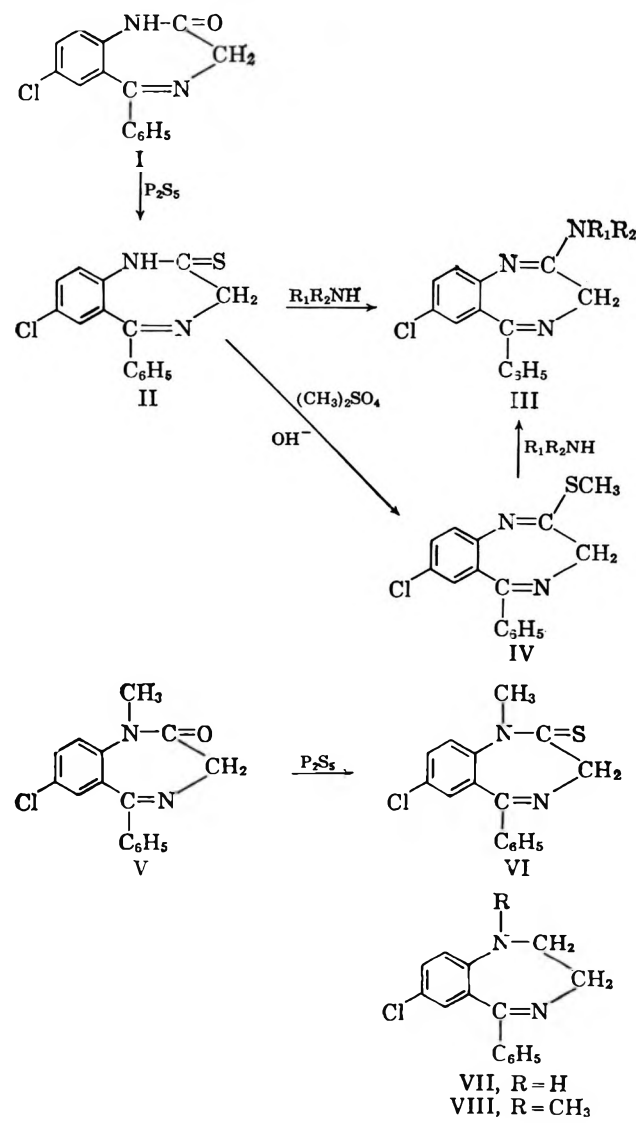
G. A. ARCHER AND L. H. STERNBACH

Department of Chemical Research, Research Division, Hoffmann-La Roche, Inc., Nutley, New Jersey

Received July 17, 1963

In continuation of our studies of the chemistry of 5-phenyl-1,4-benzodiazepin-2-ones, we examined methods for effecting transformations of the carbonyl grouping in position 2. Firstly we turned our attention to the synthesis and reactions of the thiolactam II. We expected the thione group in II to undergo nucleophilic replacement, when treated with a primary or secondary amine, to give aminobenzodiazepines of type III. This type of reaction has been used for the preparation of amino compounds from the corresponding thionamides, in the pyrimidine,[2] purine,[3] and quinazoline,[4,5] series, but had not been applied to 1,4-benzodiazepines.

Thiation of the lactam I was readily achieved by treatment with phosphorus pentasulfide in refluxing pyridine, to give the desired thiolactam II. Reaction of II with primary or secondary aliphatic amines, or with secondary heterocyclic amines, resulted in formation of compounds of type III, with evolution of hydrogen sulfide. Since it has been reported[6] that S-alkylthiopyrimidines react with amines more readily than do the corresponding thiopyrimidines, we were led to methylate II to the methylmercapto derivative (IV). That the product was in fact the S-methyl derivative, and not the isomeric N-methylthiolactam (VI), was proved by its ready acid hydrolysis to I and also by the unequivocal synthesis of VI from the N-methylbenzodiazepinone (V).



(1) Paper XV, L. H. Sternbach, G. A. Archer, and E. Reeder, *J. Org. Chem.*, **28**, 3013 (1963).

(2) (a) F. E. King and T. J. King, *J. Chem. Soc.*, 726 (1947); (b) F. H. S. Curd, M. I. Davis, E. C. Owen, F. L. Rose, and G. A. P Tuey, *ibid.*, 370 (1946).

(3) L. B. Townsend and R. K. Robins, *J. Am. Chem. Soc.*, **84**, 3008 (1962).

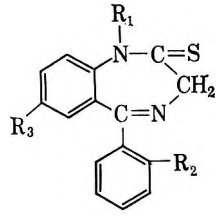
(4) N. S. Leonard and D. Y. Curtin, *J. Org. Chem.*, **11**, 349 (1946).

(5) S. S. Berg, *J. Chem. Soc.*, 4041 (1961).

(6) D. J. Brown, "The Chemistry of Heterocyclic Compounds," Vol. XVI, A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1962, p. 283.

TABLE I

1,3-DIHYDRO-2*H*-1,4-BENZODIAZEPINE-2-THIONES

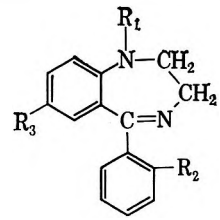


R_1	R_2	R_3	M.p., °C.[a]	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
H	H	H	256–257	9	$C_{15}H_{12}N_2S$	71.40	71.35	4.79	4.65	12.70	12.54
H	H	Br	255–256	30	$C_{15}H_{11}BrN_2S$	54.39	54.29	3.35	3.24	9.68	9.71
H	H	Cl	245–247	40	$C_{15}H_{11}ClN_2S$	62.82	62.55	3.87	3.95	11.19	11.22
H	H	CH_3	260–261	28	$C_{16}H_{14}N_2S$	72.14	72.25	5.30	5.52	12.04	12.07
H	H	NO_2	209–214	13	$C_{15}H_{11}N_3O_2S$	60.59	61.07	3.73	4.27	10.78	10.69
H	Cl	Cl	251–253	40	$C_{15}H_{10}Cl_2N_2S$	56.08	56.43	3.14	3.25	9.98	9.81
H	F	Cl	229–232	29	$C_{15}H_{10}ClFN_2S$	59.12	58.88	3.30	3.52	10.52	10.12
H	OCH_3	Cl	222–224	38	$C_{16}H_{13}ClN_2OS$	60.66	60.49	4.13	4.36		
CH_3	H	Cl	162–164	73[c]	$C_{16}H_{13}ClN_2S$	63.88	63.96	4.36	4.55	10.66	10.86
CH_3	Cl	Cl	160–163	75	$C_{16}H_{12}Cl_2N_2S$	57.32	57.66	3.61	3.45	9.56	9.75
CH_3	F	Cl	144–146	48	$C_{16}H_{12}ClFN_2S$	60.28	60.24	3.79	3.77	10.06	9.80
CH_3[b]	CF_3	H	133–136	83	$C_{17}H_{13}F_3N_2S$	61.07	61.01	3.92	4.08	9.59	9.47

[a] The compounds described were crystallized from ethanol. [b] The starting material, 1,3-dihydro-1-methyl-5-(2-trifluoromethylphenyl)-2*H*-1,4-benzodiazepin-2-one, was made by methylation of the corresponding desmethyl compound [G. Saucy and L. H. Sternbach, *Helv. Chim. Acta*, **45**, 2226 (1962)] by treatment with sodium methoxide and methyl iodide. The product crystallized from aqueous ethanol as colorless rhombs, m.p. 135–137°. *Anal.* Calcd. for $C_{17}H_{13}F_3N_2O$: C, 64.14; H, 4.12. Found: C, 64.45; H, 3.84. [c] The thiation of 1-substituted benzodiazepinones generally gave better yields of thiolactams than in the case of the unsubstituted lactams.

TABLE II

2,3-DIHYDRO-1*H*-1,4-BENZODIAZEPINES



R_1	R_2	R_3	Crystd.[a] from	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
H	H	CH_3	Aqueous alcohol	130–132	$C_{16}H_{16}N_2$	81.32	81.38	6.82	6.93				
H	OCH_3	Cl	Aqueous alcohol	190–191	$C_{16}H_{15}ClN_2O$	67.00	67.32	5.27	5.36				
H[b]	OCH_3	Cl	Methanol–ether	254–255 dec.	$C_{16}H_{15}ClN_2O \cdot HCl$	59.45	59.82	4.99	5.12			21.93	21.94
CH_3[b]	F	Cl	Methanol–acetone	245–247 dec.	$C_{16}H_{14}ClFN_2 \cdot HCl$	59.09	59.24	4.65	5.14	8.61	8.57		
CH_3	CF_3	H	Hexane	83–85	$C_{17}H_{15}F_3N_2$	67.09	67.25	4.97	4.86	9.21	9.16		
CH_3[b]	CF_3	H	Alcohol–ether	251–252	$C_{17}H_{15}F_3N_2 \cdot HCl$	59.91	59.97	4.73	4.68	8.22	8.19		

[a] Yields obtained were comparable with those obtained for the examples reported in the Experimental section. [b] Hydrochloride. The base was dissolved in the calculated amount of methanolic hydrogen chloride and the crystalline salt was precipitated by the addition of ether.

Compound IV reacted readily with primary or secondary amines to give aminobenzodiazepines of formula III. Reaction of IV with monomethylamine gave the methylaminobenzodiazepine III (R_1 = CH_3, R_2 = H), which was identical with that previously obtained[7] by deoxygenation of 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (Librium®).

Reaction of II or IV with piperidine gave the piperidinobenzodiazepine (III, R_1R_2N = piperidino).[8]

Another reaction of the thiolactams II and VI was their desulfurization, by treatment with Raney nickel in boiling acetone, to give the dihydrobenzodiazepines (VII and VIII). Both these compounds have been obtained by other methods; the former by reduction of I with lithium aluminum hydride,[9] the latter by methylation of VII[9] and also by a four-step synthesis from 2-chloro-5-nitrobenzophenone.[10,11]

A number of analogs of the thiolactams II and VI were made by the method described in the Experimental section; their properties are given in Table I. The 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones used as starting materials have been described in the literature.[10,11]

(7) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).

(8) Benzodiazepines having a tertiary amino group in position 2 were not previously accessible by the route described[7] for preparation of benzodiazepines having a primary or secondary amino group in position 2. See also S. C. Bell, C. Gochman, and S. J. Childress, *J. Med. Pharm. Chem.*, **5**, 63 (1962).

(9) L. H. Sternbach, E. Reeder, and G. A. Archer, *J. Org. Chem.*, **28**, 2456 (1963).

(10) L. H. Sternbach, R. Ian Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *ibid.*, **27**, 3788 (1962).

(11) L. H. Sternbach, R. Ian Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *J. Med. Chem.*, **6**, 261 (1963).

Some of the thiolactams listed in Table I were desulfurized by treatment with Raney nickel, as described in the Experimental section, to give the 2,3-dihydrobenzodiazepines shown in Table II.

Experimental

All melting points are corrected. The infrared and ultraviolet absorption spectra of starting materials and reaction products were compared in order to establish structural changes. The infrared spectra were determined in 3% chloroform solutions or in potassium bromide pellets, using a Perkin-Elmer Model 21 spectrophotometer; the ultraviolet absorption spectra were determined in isopropyl alcohol and in 0.1 *N* hydrochloric acid.

7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (II).—A solution of 271 g. of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (I)[12] and 242 g. of phosphorus pentasulfide in 2 l. of anhydrous pyridine was stirred and heated under reflux for 45 min., with protection from atmospheric moisture. The mixture was then rapidly chilled in an ice bath and poured slowly into 5 l. of a well stirred, ice-cold saturated sodium chloride solution. The resulting precipitate was separated by filtration, washed with water, dried *in vacuo*, and dissolved in methylene chloride. The solution was filtered through a bed of activated alumina and concentrated. Addition of petroleum ether (b.p. 40–60°) gave compound II which was recrystallized from alcohol and obtained as pale yellow prisms (40%), m.p. 244–246°.

Anal. Calcd. for $C_{15}H_{11}ClN_2S$: C, 62.82; H, 3.87; S, 11.19. Found: C, 62.55; H, 3.95; S, 11.22.

7-Chloro-2-methylmercapto-5-phenyl-3*H*-1,4-benzodiazepine (IV).—To a stirred solution of 2.87 g. of II in a mixture of 12 ml. of aqueous 1 *N* sodium hydroxide and 15 ml. of methanol was added within 30 min. a solution of 1.39 g. of dimethyl sulfate in 5 ml. of methanol. Stirring was continued for 10 min., then the mixture was diluted with water and made strongly basic with sodium hydroxide solution. The precipitated product was separated by filtration, washed with water, and recrystallized from alcohol, to give pale yellow prisms, m.p. 132–134° (76%).

Anal. Calcd. for $C_{16}H_{13}ClN_2S$: C, 63.88; H, 4.36; S, 10.66. Found: C, 63.52; H, 4.39; S, 10.86.

Acid Hydrolysis to I.—A solution of 1 g. of IV in a mixture of 100 ml. of alcohol and 20 ml. of 1 *N* hydrochloric acid was kept at 20–25° for 6 days. Methyl mercaptan was evolved (detected by its characteristic odor, and yellow coloration with lead acetate paper). The solution was diluted with 100 ml. of water and neutralized (pH 7) with dilute sodium hydroxide. The resulting precipitate was filtered and recrystallized from methylene chloride–hexane to give 0.63 g. (70%) of I, identical[13] with an authentic sample.

7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (VI).—A solution of 14.3 g. of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one[12] (V) and 11.1 g. of phosphorus pentasulfide in 100 ml. of anhydrous pyridine was stirred and heated under reflux for 1 hr., with protection from atmospheric moisture. The solution was evaporated *in vacuo*, the resulting tarry residue was dissolved in methylene chloride and filtered through a bed of activated alumina. Concentration of the filtrate and addition of petroleum ether gave the product, which was recrystallized from alcohol and formed pale yellow prisms (73%), m.p. 162–164°.

Anal. Calcd. for $C_{16}H_{13}ClN_2S$: C, 63.88; H, 4.36; S, 10.66. Found: C, 63.96; H, 4.55; S, 10.86.

7-Chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (III, $R_1 = CH_3$; $R_2 = H$).—Monomethylamine gas was bubbled slowly through a refluxing solution of 25 g. of IV in a mixture of 300 ml. of alcohol and 50 ml. of dimethyl sulfoxide. After the evolution of methyl mercaptan had ceased (18 hr.), the solution was concentrated *in vacuo*, and the residue dissolved in dilute hydrochloric acid. The aqueous acidic layer was extracted with ether, made basic with sodium hydroxide, and extracted with methylene chloride. The methylene chloride solution was concentrated to give the nearly pure product, which was recrystallized from acetone and formed colorless prisms (91%), m.p. 238–240°, identical[13] with an authentic sample.[7]

7-Chloro-5-phenyl-2-piperidino-3*H*-1,4-benzodiazepine (III, NR_1R_2 = Piperidino). **A. From II.**—A solution of 28.7 g. of II and 17 g. of piperidine in a mixture of 250 ml. of methanol and 50 ml. of dimethyl sulfoxide was refluxed on the steam bath until evolution of hydrogen sulfide ceased (after 1.5 hr.). The solution was concentrated and the product isolated in the manner described in the previous experiment. Recrystallization from aqueous alcohol gave colorless prisms (60%), m.p. 115–116°. The yield was not increased by longer reaction periods.

Anal. Calcd. for $C_{20}H_{20}ClN_3$: C, 71.12; H, 5.96; N, 12.44. Found: C, 71.47; H, 6.23; N, 12.47.

B. From IV.—A mixture of 3.01 g. of IV and 21 g. of piperidine was refluxed until evolution of methyl mercaptan ceased (after 1.5 hr.). The resulting solution was concentrated, and the product isolated as previously, to give colorless prisms (89%), m.p. 115–116° (from alcohol), identical[13] with the authentic sample prepared by method A. The yield was unaffected by prolongation of the reaction time.

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (VIII).—A mixture of 20 g. of VI, 500 ml. of acetone, and 160 g. of wet Raney nickel was stirred and refluxed for 2 hr. Filtration and evaporation of the filtrate gave the crude product, which was purified by dissolving it in dilute hydrochloric acid and extracting the solution with ether to remove nonbasic impurities. The acidic solution was then made basic with dilute sodium hydroxide and extracted with methylene chloride, to give VIII (69%), which was identical[13] with an authentic sample.[9]

7-Chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (VII).—Desulfurization of II with Raney nickel, followed by purification of the product in the manner described previously, gave VII as yellow plates (52%), m.p. 166–167° (from aqueous ethanol), identical[13] with an authentic sample.[9]

Acknowledgment.—We are indebted to Dr. A. Motchane, Mr. S. Traiman, and Dr. V. Toome for the infrared and ultraviolet spectra, and to Dr. Al Steyermark and his staff for the microanalyses. Mr. L. A. Dolan was helpful in the preparation of larger amounts of starting materials and intermediates.

(12) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).

(13) Identity was established by comparison of melting points, infrared spectra, and mixture melting point.

Autoradiolysis of 6,7,8,9,10,10-Hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepine 3-Oxide-5a,9a-C^{14}

SYLVAN E. FORMAN AND JACK R. GRAHAM[1]

The FMC Corporation, Chemical Divisions, Central Research and Development Center, Princeton, New Jersey

Received June 13, 1962

The autoradiolysis of compounds containing radioactive isotopes is a well known phenomenon.[2] We wish to report a new and interesting observation of this sort of behavior with C^{14}-labeled samples of the insecticide Thiodan (I).

The infrared spectra of samples of Thiodan-5a,9a-C^{14} (6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepine 3-oxide-5a,9a-C^{14}) taken shortly after preparation[3] showed no indication of the presence of Thiodan ether (II) (4,5,6,7,8,8-hexachloro-1,3,3a,4,7,7a-hexahydro-4,7-methanoisobenzofurane). The radio-Thiodan was stored in vials kept in a desiccator which was placed in a darkened cabinet. About 2.5 years later new infrared spectra showed the presence of Thiodan ether.

(1) Niagara Chemical Division, Middleport, N. Y.

(2) A. Murray, III, and D. L. Williams, "Organic Syntheses with Isotopes," Part I, Interscience Publishers, Inc., New York, N. Y., 1958, p. 19.

(3) S. E. Forman, B. L. Gilbert, G. S. Johnson, C. A. Erickson, and H. Adelman, *J. Agr. Food Chem.*, **8**, 193 (1960).

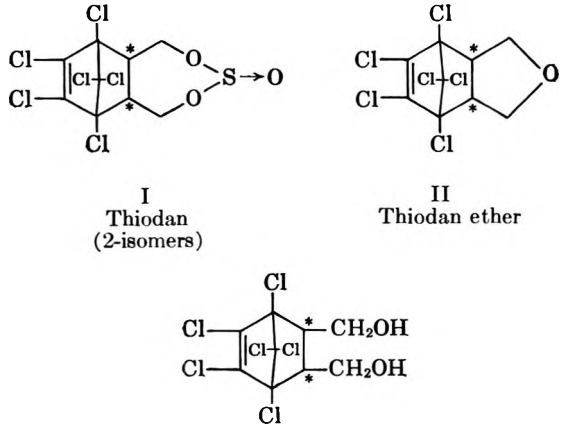
TABLE I

GAS CHROMATOGRAPHIC ANALYSES OF THIODAN SAMPLES

Sample	Activity, μc./mg.	Analyses, %[a] Age, weeks	Ether[b]	L.m.i.[c]	H.m.i.[d]	G(−M)[e]	Analyses, %[a] Age, weeks	Ether[b]	L.m.i.[c]	H.m.i.[d]	G(−M)[e]
1							257	3	67	26	
2A[f]		123[g]	2	39	42						
2B							203	2	61	37	
3							165	1	57	42	
4							134	1	66	33	
5							32	2	57	41	
6A	5.91	129	51	38	12	120	212	75	9	14	100
6B[h]	5.99						199[i]	40	0	0	
7	1.9	129	18	30	53	140					
8A	0.95	119	23	53	21	350	197	45	22	30	430
8B[j]	0.95	1	9	53	35		79	13	56	28	90

[a] Thiodan alcohol was usually present, 0 to 4%, except where noted. [b] Thiodan ether. [c] Lower melting Thiodan isomer. [d] Higher melting Thiodan isomer. [e] Molecules permanently altered per 100 e.v. See J. R. Catch, "Carbon-14 Compounds," Butterworths Inc., Washington, D. C., 1961, p. 69. [f] Samples 2A and 2B were portions of the same commercial preparation. 2A was kept in a tightly sealed drum. [g] Thiodan alcohol, 17%. [h] 6B is a sample of 6A which was recrystallized from hexane shortly after preparation. [i] Thiodan alcohol, 60%. [j] 8B is a column chromatographed sample of 8A. The age of 8B is taken from the time of the chromatogram.

SCHEME I



I
Thiodan
(2-isomers)

II
Thiodan ether

III
Thiodan alcohol

Gas chromatography was known to be suitable for the separation of the two Thiodan isomers[4] and a modification of this method can be employed to distinguish Thiodan alcohol (III) (1,4,5,6,7,7-hexachlorobicyclo[2,2,1]hept-5-ene-2,3-dimethanol) from the two Thiodan isomers (see Scheme I, asterisks show positions of C^{14}). Table I gives the data obtained by g.l.c. analysis on two different occasions of a number of nonradioactive technical samples, and radioactive samples of Thiodan. Nonradioactive samples contained scarcely any Thiodan ether, even after prolonged storage. The radioactive samples accumulated Thiodan ether[5] with increasing age. When access to moisture was permitted, either type of sample decomposed to Thiodan alcohol.

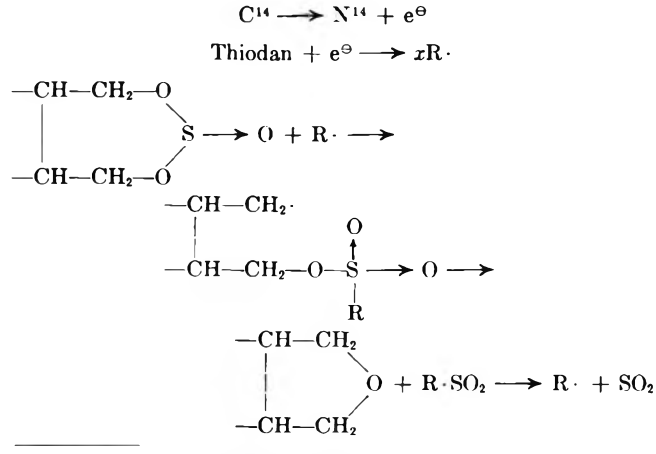
Infrared spectral analysis indicated that the ratio of higher melting to lower melting Thiodan isomers in the radioactive samples had increased from the ratio that was present shortly after preparation. Absorption bands which we usually used to determine the Thiodan isomer ratio are the bands at 1245 and 1266 cm.$^{-1}$, but these could not be used because Thiodan ether absorbs at 1250 cm.$^{-1}$. However, the Thiodan isomer ratio was determined by using the absorptions at 840 and 862 cm.$^{-1}$.

Crystallization of the 0.95-μc./mg. sample of radio-Thiodan from hexane gave mostly higher melting Thiodan isomer in the first crop and largely lower melting Thiodan isomer in the succeeding crops; but, all of the fractions contained Thiodan ether, and it was not possible to remove this contaminant by subsequent recrystallizations.

Column chromatography on Florisil[6] had been used previously to separate the two Thiodan isomers. With hexane and ethyl ether as the solvents, the lower melting isomer is eluted first from the column. The same adsorbent and solvent system was used to separate the higher melting radiotagged Thiodan isomer from Thiodan ether. Although a gas chromatogram showed only a single peak for the purified material, the infrared spectrum showed a weak band at 810 cm.$^{-1}$. Since none of the other infrared bands characteristic for Thiodan ether were apparent, this extraneous band was attributed to a small amount of an unidentified impurity.

Thiodan ether could not be removed by similar column chromatography from a fraction containing largely lower melting radio labeled Thiodan isomer, although some concentration of the Thiodan ether in the earlier fractions was observed.

The radiolysis probably occurs in the manner shown in the equations. β-Rays from the radioactive C^{14} generate free radials which attack the sulfur atoms and



(4) G. Zweig and T. E. Archer, *J. Agr. Food Chem.*, **8**, 190 (1960).

(5) The radioactive Thiodan ether would be 4,5,6,7,8,8-hexachloro-1,3,3a,4,7,7a-hexahydro-4,7-methanoisobenzofurane-3a,7a-C^{14} or Thiodan ether-3a,7a-C^{14}.

(6) Floridin Company, Tallahasse, Fla.

cause one of the C–O bonds to break. The resultant radical is in a favorable position to form Thiodan ether with expulsion of another radical which decomposes to sulfur dioxide and the original radical.

A similar mechanism could result if the radical attacked an oxygen atom.

Except upon the rare occasions when two radicals combine, other collisions of a radical with a Thiodan molecule can result in a chlorine radical, a hydrogen radical, or a radical in which the odd electron is attached to a carbon in the Thiodan molecule. The radicals should, therefore, have high efficiency in the production of Thiodan ether, for other types of radical decompositions would not readily occur, although radical transfers may be frequent, and radical rearrangements can occur.

The $G(-M)$ values were calculated for each sample, when this was possible, and are shown in Table I. Although most of the values are not far apart, the values for sample 8A are considerably larger than the others. This result may be due to the fact that β-rays and volatile free radicals can escape less easily from a large compact mass of matter than from smaller pieces. Samples 6A, 7, and 8A were solid lumps of 2.3, 14, and 31 g., respectively; samples 6B and 8B were loose crystals, 0.6 and 0.13 g., respectively.

Experimental

Recrystallization of Radio-Thiodan.—A 30-g. sample of radio-Thiodan, 0.95 μc./mg., 119 weeks after preparation, consisted of 23% Thiodan ether, 53% lower melting Thiodan isomer, 21% higher melting Thiodan isomer, and 3% Thiodan alcohol. The sample was recrystallized from 150 ml. of hexane. Infrared spectra showed that the first fraction was mostly higher melting Thiodan isomer with some Thiodan ether present and the three subsequent fractions were largely lower melting Thiodan isomer with diminishing amounts of Thiodan ether. Recrystallization of the third fraction from hexane gave as the first crop 1.7 g. with 11% Thiodan ether, 86% lower melting Thiodan isomer, and 3% higher melting Thiodan isomer as shown by gas phase chromatography.

Column Chromatography of Radio-Thiodan.—A 140-g. portion of Florisil[6] activated for 2 hr. at 300° was packed in a chromatographic column, 75 × 2.5 cm. After 500 ml. of hexane had been allowed to pass through the column, 2.0 g. of a fraction of radio-Thiodan from the preceding fractional crystallizations was applied in ethyl ether solution. The chromatogram was developed with hexane containing increasing per cents of ethyl ether.

The second radioactive fraction from the column chromatogram of the higher melting Thiodan isomer showed one peak in the gas phase chromatogram; but the infrared spectrum showed an extraneous weak band at 810 cm.$^{-1}$.

Similar column chromatography of samples of lower melting radio-Thiodan isomer gave, at best, a greater concentration of Thiodan ether in the earlier fractions than in the later ones.

Infrared Spectra.—Infrared spectra were determined with a Baird Model 4–55 apparatus. Samples for qualitative examination were best determined in a potassium bromide pellet, but frequently a film on a sodium chloride flat was used. Quantitative determinations were run in carbon disulfide solution in a 0.5-mm. cell.

The following characteristic bands were used: higher melting Thiodan isomer, 1245 and 840; lower melting Thiodan isomer, 1266 and 862; Thiodan ether, 649 (other bands at 1212, 1053, and 810); Thiodan alcohol, 3280 cm.$^{-1}$. Other bands were used to confirm the presence of the various compounds.

Gas Chromatography.—F & M Model 202 instrument was used with 10 ft. of 0.2-in. o.d. stainless steel tubing packed with 60–80-mesh Chromasorb W containing 20% Dow 11 silicone. The column temperature was 250° with a helium flow of 100 ml. per minute. Samples were injected in chloroform solution. Elution times were as follows: Thiodan ether, 9; lower melting Thiodan isomer, 21; higher melting Thiodan isomer, 32 min. Thiodan alcohol gave two or three unresolved peaks at *ca.* 15.5, 18–20, and 26 min. Peak areas were corrected for thermal response by multiplying with the following factors: Thiodan ether, 1.48; lower melting Thiodan isomer, 1.72; higher melting Thiodan isomer, 1.77.

Acknowledgment.—The authors wish to thank Mr. Arthur Weed and Mr. John Zarembo for doing the gas phase chromatographic work and Mr. Herman Adelman for the determination and interpretation of the infrared spectra. The mechanism for the formation of Thiodan ether evolved as a result of discussions with Professor R. H. Herber of Rutgers University.

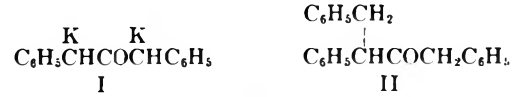
Formation and Benzylation of the Dianion of *sym*-Diphenylurea by Potassium Amide in Liquid Ammonia. Results with Related Compounds

DAVID R. BRYANT,[1a] STEWART D. WORK,[1b] AND CHARLES R. HAUSER

Department of Chemistry, Duke University, Durham, North Carolina

Received June 24, 1963

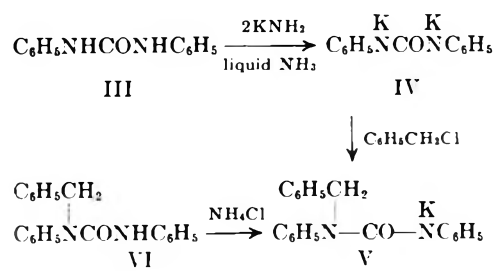
Dibenzyl ketone previously has been converted by two molecular equivalents of potassium amide in liquid ammonia to its dipotassio salt I, which was alkylated in this medium with a molecular equivalent of benzyl chloride to form the monobenzyl derivative (II) in 82% yield.[2] The monopotassio salt of dibenzyl ketone not only underwent benzylation much more slowly under similar conditions, but the dibenzyl derivative as well as II was obtained.[2]



I II

In the present investigation *sym*-diphenylurea (III), which may be regarded as a dinitrogen analog of dibenzyl ketone, likewise was converted to its dipotassio salt IV, which was benzylated to give the monobenzyl derivative (VI) in 75% yield (Scheme I). Benzylation

SCHEME I



of the monopotassio salt of III under similar conditions afforded VI in only 2% yield.

Structure VI was supported by analysis and by its infrared spectrum which exhibited a band at 2.96 μ, in-

(1) (a) National Science Foundation Predoctoral Fellow, 1958–1961; (b) National Science Foundation Cooperative Graduate Fellow, 1959–1962.

(2) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **81**, 1154 (1959).

dicating the presence of an N–H group.[3] This band would be absent in the possible dibenzylation product.

Structure VI was confirmed by an independent synthesis from phenyl isocyanate and benzylaniline (eq. 1).[4]

$$C_6H_5N{=}C{=}O \xrightarrow{C_6H_5NHCH_2C_6H_5} \text{VI} \qquad (1)$$

It may be concluded that dipotassio salt IV is not only much more nucleophilic than the monopotassio salt of *sym*-diphenylurea, but also much more nucleophilic than monopotassio salt V, since further alkylation of V was not observed under the conditions employed. The greater nucleophilicity of dipotassio salts such as IV and I may be ascribed to a reinforcing effect of each of the negative charges of the dianion on the other in the 1,3-resonance system.[5]

Attempted Benzylation of Other Urea Compounds.—As in the experiment with *sym*-diphenylurea (III), urea, phenylurea, benzoylurea, and acetylurea were each added to two molecular equivalents of potassium amide in liquid ammonia, followed by one equivalent of benzyl chloride. However, in contrast to III, none of these compounds afforded an isolable amount of the benzyl derivative. In the experiment with urea a purple color appeared and stilbene was obtained, but in the other experiments no purple color was observed and no stilbene was isolated. In the experiments with phenylurea, benzoylurea, and acetylurea the starting compounds were recovered. Results are summarized in Table I.

TABLE I

ATTEMPTED BENZYLATION OF CERTAIN UREA COMPOUNDS THROUGH DIANIONS IN LIQUID AMMONIA

Urea compound	Purple color	Stilbene yield, %	Starting compounds recovered: Urea compound, %	Starting compounds recovered: Halide, %
NH_2CONH_2	Yes	40	*a*	30
$C_6H_5NHCONH_2$	No	None	73	50
$C_6H_5CONHCONH_2$	No	None	97	73
$CH_3CONHCONH_2$	No	None	45	*a*

[a] No attempt was made to recover compound.

These results may be rationalized on the basis that the conversions of phenyl-, benzoyl-, and acetylureas to their dianions were essentially complete, whereas the conversion of urea to its dianion was not, and that amide ion in the latter equilibrium effected self-condensation of benzyl chloride to form stilbene (Scheme II).

SCHEME II

$$\bar{N}H_2 + H_2NCO\bar{N}H \underset{\text{liquid } NH_3}{\rightleftharpoons} NH_3 + H\bar{N}CO\bar{N}H$$

$$\downarrow C_6H_5CH_2Cl$$

$$C_6H_5\bar{C}HCl \xrightarrow{C_6H_5CH_2Cl} C_6H_5CH_2CHClC_6H_5 \xrightarrow{-HCl} C_6H_5CH{=}CHC_6H_5$$

It has been shown previously[6] that amide ion in liquid ammonia readily converts benzyl chloride to stilbene and that this reaction is accompanied by the appearance of a purple color like that observed in the experiment with urea (see Table I). However, the possibility that the dianion of urea effects this reaction is not excluded, since this dianion is more strongly basic than those of the other urea compounds listed in Table I. Incidentally, the isolation of dipotassio urea, prepared from urea and potassium amide in liquid ammonia, has been reported, but few details were given.[7]

The failure of the dianion of phenylurea to undergo benzylation (see Table I) may be ascribed to the extreme insolubility of its dipotassio salt in liquid ammonia, since the nucleophilicity of this dianion should be greater than that of diphenylurea which readily undergoes benzylation under similar conditions. However, the failure of the dianions of benzoyl- and acetylureas to undergo benzylation might be due either to insolubility or to lack of sufficient nucleophilicity. The benzylations of the dianion of phenylurea and even the dianions of the acylureas might be accomplished in another solvent.

Experimental[8]

Benzylation of *sym*-Diphenylurea (III) through Dipotassio Salt IV.—To a stirred suspension of 0.1 mole of potassium amide in 500 ml. of commercial anhydrous liquid ammonia[9] was added 10.61 g. (0.05 mole) of finely powdered *sym*-diphenylurea (III) from an erlenmeyer flask through Gooch tubing fitted with a standard taper joint. After stirring for 0.25 hr., the resulting white suspension was assumed to contain 0.05 mole of dipotassio salt IV. Benzyl chloride (6.33 g., 0.05 mole) in 25 ml. of anhydrous ether was added during 5 min. to the stirred suspension of IV; no change in the appearance of the reaction mixture was observed. After stirring for 1 hr., 5.35 g. (0.1 mole) of powdered ammonium chloride was added, and the ammonia evaporated as an equal volume of ether was added. Water (150 ml.) was added to the ethereal suspension to dissolve inorganic salts. The remaining precipitate was collected to give 1.79 g. (17%) of recovered *sym*-diphenylurea (III), m.p. 238–240°.

The aqueous and ethereal layers of the filtrate were shaken and separated. The ethereal phase was washed with 50 ml. of saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The solvent was removed to leave 14.8 g. of a clear, lightly colored oil, which crystallized on addition of 50 ml. of *n*-hexane. The mixture was filtered to give 10.73 g. (71%) of N-benzyl-N,N′-diphenylurea (VI), m.p. 83–85°, and 0.67 g. (4%) of a second crop, m.p. 79–81°. Recrystallization from absolute ethanol–hexane raised the melting point to 84–85.5°, lit.[10] m.p. 85°.

Anal. Calcd. for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.27. Found: C, 79.79; H, 5.99; N, 9.11.

The infrared spectrum of VI exhibited a band at 2.96 μ, indicating the presence of an N–H group.[3]

Independent synthesis of VI[4] was accomplished by addition, during 5 min., of 5.95 g. (0.05 mole) of phenyl isocyanate to a stirred solution of 9.16 g. (0.05 mole) of N-benzylaniline in 25 ml. of anhydrous ether. Most of the ether was removed on the steam bath and 2 drops of 3 *N* hydrochloric acid were added. After heating for 0.5 hr., the viscous oil was dissolved in 75 ml. of 95% ethanol and cooled overnight. The resulting precipitate was collected to give 10.3 g. (68%) of N-benzyl-N,N′-diphenylurea (VI), m.p. 83–85° and 84–86°, after one recrystallization from 95% ethanol. This compound was shown to be identical with VI prepared by the benzylation of dipotassio salt IV by comparison of infrared spectra and by the mixture melting point method.

(3) See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, New York, N. Y., 1958, p. 206.

(4) A. Mailhe, *Bull. soc. chim. France*, [4] 25, 321 (1919).

(5) The resonance forms shown may not make the most important contributions to the structures of the dianons, but they are the most convenient to use for the present purpose.

(6) C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Am. Chem. Soc.*, **78**, 1653 (1956).

(7) J. S. Blair, *ibid.*, **48**, 96 (1926); E. C. Franklin and O. F. Stafford, *Am. Chem. J.*, **28**, 83 (1902).

(8) Melting points were taken on a Mel-Temp capillary melting point apparatus. Infrared spectra were determined with a Perkin-Elmer Infracord by the potassium bromide pellet method. Elemental analysis was by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(9) See C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958).

(10) R. Stolle, *J. prakt. Chem.*, **117**, 185 (1927).

Benzylation of III through Its Monopotassio Salt.—To a stirred suspension of 0.05 mole of potassium amide in 500 ml. of liquid ammonia was added 10.61 g. (0.05 mole) of finely powdered III, followed, after 0.25 hr., by 6.33 g. (0.05 mole) of benzyl chloride in 25 ml. of anhydrous ether. After stirring for 1 hr., the reaction mixture was worked up essentially as described previously to give 0.25 g. (2%) of N-benzyl-N,N'-diphenylurea (VI), m.p. 84–85°, and 9.65 g. (91%) of recovered III, m.p. 243–243.5°.

Attempted Benzylation of Certain Urea Compounds.—In Table I are summarized the results obtained on adding other urea compounds to two molecular equivalents of potassium amide in liquid ammonia, followed by one molecular equivalent of benzyl chloride. These experiments were performed essentially as described previously for that with the dipotassio salt of *sym*-diphenylurea (IV).

The urea compounds remained as precipitates after the water was added to the ethereal suspension of the reaction products, and were collected by suction filtration. Additional quantities of the urea compounds were precipitated and recovered by evaporation of the ethereal layers of the filtrates. The remaining oils were fractionally distilled *in vacuo* to give recovered benzyl chloride.

The urea compounds were identified by their melting points and by mixture melting points with authentic samples. The benzyl chloride was identified by comparison of its boiling point and refractive index with known values.

In the experiment with urea a purple color was observed during the addition of the benzyl chloride and no precipitate remained after the addition of water. The layers of the reaction mixture were shaken and separated. The ethereal layer was washed with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and the solvent removed. The oily residue was triturated with cold methanol, and the mixture filtered. The solvent was removed from the filtrate, and the residue was distilled *in vacuo* to give benzyl chloride. The remaining pot residue was recrystallized from methanol to give stilbene, which was identified by melting point and mixture melting point with an authentic sample.

The Preparation of (2,2-Dicarbethoxypropyl)-ethoxydimethylsilane

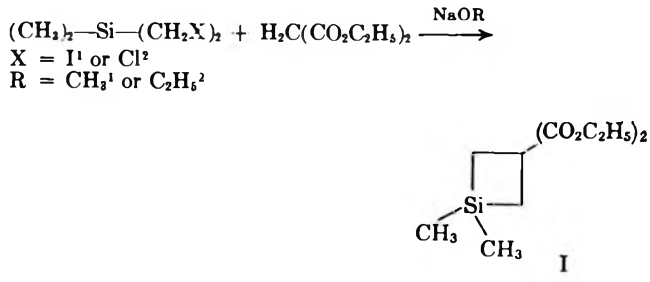
HENRY GILMAN AND WILLIAM H. ATWELL

Department of Chemistry,
Iowa State University, Ames, Iowa

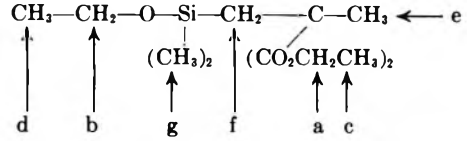
Received June 21, 1963

In connection with a program concerned with the preparation, properties, and reactions of small-ring organosilicon compounds, it became desirable to repeat the preparation of a compound previously designated as 3,3-dicarbethoxy-1,1-dimethyl-1-silacyclobutane (I). The preparation of this compound has been reported by several workers.[1,2] The general method utilized was a ring closure reaction of bis(halomethyl)dimethylsilane and diethyl malonate effected with sodium alkoxide. In our work we employed the published procedure reporting the highest yield of this material.[2]

In our preparation a compound was obtained the properties of which were in excellent agreement with those previously reported.[1,2] The infrared spectrum of this material was shown to be superimposable with that of a known sample.[3] However, an examination of the n.m.r. spectrum of this material showed that it was not the previously reported silacyclobutane I, but rather a ring opened product, namely, (2,2-dicarbethoxypropyl)ethoxydimethylsilane (II). The formation of II can be explained in terms of a cleavage of I by sodium ethoxide.

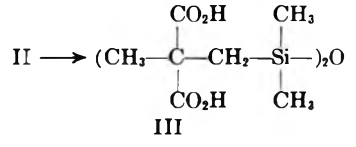


The n.m.r. spectrum of II contained a pair of quartets centered at 5.92 (J = 7.2 c.p.s.) and 6.42 τ (J = 7.2 c.p.s.) assigned to the protons a and b, respectively. The c and d protons appeared as a pair of triplets[4]



centered at 8.78 (J = 7.2 c.p.s.) and 8.89 τ (J = 7.2 c.p.s.), respectively. The remainder of the spectrum consisted of singlets centered at 8.62, 8.81, and 9.92 τ assigned to the e, f, and g protons, respectively. The relative areas of all peaks were in agreement with the proposed structure.

It was previously reported[1] that the basic hydrolysis of I proceeded with ring opening to yield *sym*-bis(2,2-dicarboxypropyl)tetramethyldisiloxane (III). Although the reactivity of other known silacyclobutanes[5–7] would predict such behavior for I, the above observation also can be explained in terms of our proposal. Thus, we have found that hydrolysis of II under similar conditions yields III. On the basis of



the physical, chemical, and spectral evidence presented in this report it appears that the compound previously designated as 3,3-dicarbethoxy-1-silacyclobutane (I) is (2,2-dicarbethoxypropyl)ethoxydimethylsilane (II).

(1) R. West, *J. Am. Chem. Soc.*, **77**, 2339 (1955).

(2) Incidental to the preparation of 4,4-dimethylsilacyclohexanone, R. A. Benkeser and W. E. Bennett [*ibid.*, **80**, 5414 (1958)] isolated a compound identical with that reported by Dr. West (ref. 1). Their identification was based on a comparison of physical constants with those reported in ref. 1.

(3) We wish to thank Dr. R. A. Benkeser for providing us with an infrared spectrum of this material. Dr. R. West informed us that unfortunately, due to a change in academic location, neither an authentic sample nor an infrared spectrum of his original material was available for comparison purposes.

(4) The pair of triplets overlapped giving rise to four peaks of unequal intensity.

(5) L. H. Sommer and G. A. Baum, *J. Am. Chem. Soc.*, **76**, 5002 (1954).

(6) L. H. Sommer, U. R. Bennett, P. G. Campbell, and D. R. Weyenberg, *ibid.*, **79**, 3295 (1957).

(7) W. H. Knoth, Jr., and R. V. Lindsey, Jr., *J. Org. Chem.*, **23**, 1392 (1958).

Experimental

Preparation of (2,2-Dicarbethoxypropyl)ethoxydimethylsilane (II).—Sodium, 7.3 g. (0.318 g.-atom), was treated with 100 ml. of absolute ethanol. To the cooled mixture was added 152.9 g. (0.954 mole) of diethyl malonate (200% excess). The mixture was then heated at reflux temperature as 25 g. (0.159 mole) of bis(chloromethyl)dimethylsilane[8] in 40 ml. of absolute ethanol was added slowly. Subsequent to refluxing for 24 hr., 100 ml. of ethanol was removed by distillation and replaced with 200 ml. of water. The mixture was extracted several times with ether and dried over sodium sulfate. Following the removal of solvent and excess diethyl malonate by distillation, there was obtained 28.5 g. (92.5%, based on the g.-atom of sodium employed) of product, b.p. 79–81° (0.25 mm.), $n^{20}D$ 1.4345, d^{20}_{20} 1.0101 [lit.[1] b.p. 141–143° (15 mm.), $n^{25}D$ 1.4318, d^{25}_{4} 0.997].

Anal. Calcd. for $C_{13}H_{26}O_5Si$: C, 53.80; H, 8.96; MD, 76.19. Found: C, 53.90, 54.09; H, 8.93, 8.72; MD, 74.96.

The infrared spectrum of II as a capillary cell contained the pertinent absorption bands shown in Table I.

TABLE I

THE INFRARED SPECTRUM OF II

Band position, μ	Intensity[a]	Characteristic[b,c]
3.35, 3.44	m, w	Aliphatic C–H
5.78	s	CO_2R
7.8	m	
8.0	m	$Si–CH_3$
8.2	s	CO_2R
8.50, 8.62	m, m	Possibly Si–alkyl
9.12, 9.27, 10.58	s, m, m	$Si–O–C_2H_5$
11.94, 12.67	s, m	$Si–CH_3$

[a] Letters indicate the relative intensities of absorption bands: s, strong; m, medium; w, weak. [b] L. J. Bellamy "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1954. [c] A. L. Smith, *Spectrochim. Acta*, 16, 87 (1960).

The reaction residue consisted of 3.5 g. of red oil. Distillation of this residue under reduced pressure gave small amounts of materials which were not investigated completely.[9]

Hydrolysis of II.—A mixture of 4.0 g. (0.1 mole) of sodium hydroxide, 5.0 g. (0.0172 mole) of II, and 50 ml. of ethanol was refluxed for 5 hr. The precipitated potassium salt was removed by filtration and the filtrate discarded. The crude potassium salt was dissolved in 10 ml. of warm water and made just acidic with concentrated hydrochloric acid. The acidified solution was extracted with four 30-ml. portions of ether and dried over sodium sulfate. Evaporation of the solvent gave a white solid which was taken up in ethyl acetate. Addition of petroleum ether (b.p. 60–70°) gave 1.76 g. (62%) of *sym*-bis(2,2-dicarboxypropyl)tetramethyldisiloxane (III), m.p. 133–135° dec. (lit.[2] m.p. 131–133° dec.).

The infrared spectrum of III as a potassium bromide pellet contained the pertinent absorption bands shown in Table II.

TABLE II

THE INFRARED SPECTRUM OF III

Band position, μ	Intensity[a]	Characteristic[b]
2.75 to 4.15	broad	CO_2H
5.76	s, s	CO_2H
7.8	m	
8.0	m	$Si–CH_3$
8.40	m	Possibly Si–alkyl
9.65	s	Si–O–Si
11.91, 12.35, 12.55	s, s, m	$Si–CH_3$

[a] See footnote *a* in Table I. [b] See footnotes *b* and *c* in Table I.

(8) We wish to express our thanks to Dr. R. N. Meals for providing us with this material.

(9) Earlier workers (see ref. 2) have reported the isolation of a material believed to be *sym*-tetramethyldi(2,2-dicarbethoxy)propyldisiloxane, b.p. 155–161° (0.05 mm.), $n^{24}D$ 1.4468. We isolated a small amount (*ca.* 0.5 g.) of material which on the basis of its physical constants [b.p. 140–142° (0.005 mm.), $n^{20}D$ 1.4500] and infrared spectrum (band at 9.55 μ indicative of the Si–O–Si linkage) may be this symmetrical siloxane.

Acknowledgment.—This research was supported by the United States Air Force under Contract AF 33(616)-6463 monitored by the Materials Laboratory, Directorate of Laboratories, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio. The authors are grateful to Dr. R. King for determination of the n.m.r. spectrum and to Dr. G. Morris for aid in its interpretation.

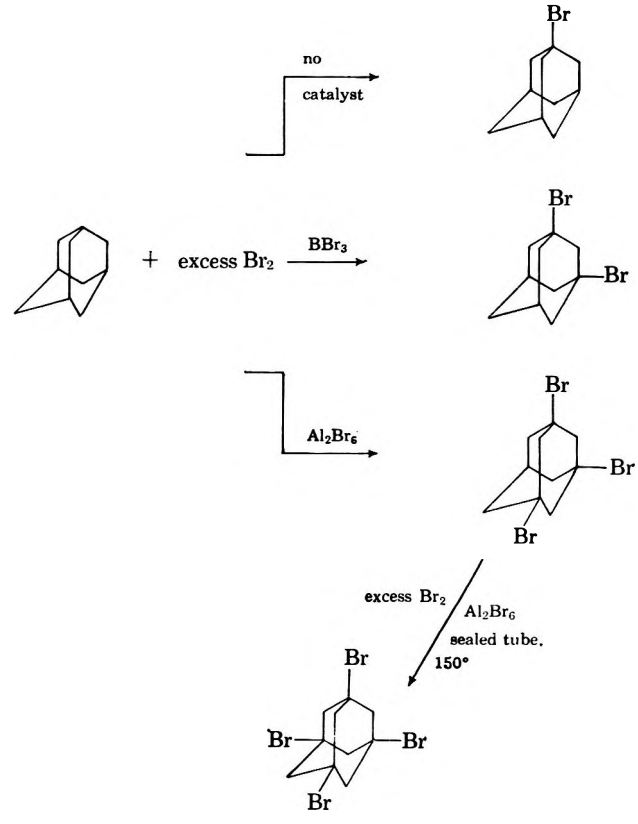
Dibromination of Adamantane[1]

G. L. BAUGHMAN

Fabrics and Finishes Department, Experimental Station Laboratory, E. I. du Pont de Nemours and Company, Wilmington, Delaware

Received July 10, 1963

It has been reported that highly selective substitution on the adamantane ring system can be effected by bromination.[2,3] Thus, by the use of proper catalysts and conditions, one, two, three, or four bromine atoms can be inserted on the bridgehead sites.



Attempts in this laboratory to prepare the dibromo-substituted adamantane derivative using boron bromide as catalyst resulted in every case in the isolation of monobrominated adamantane in yields of 60 to 80%.

It was postulated that trace amounts of aluminum bromide may be necessary as cocatalyst since boron bromide can be made easily by a metathetical reaction

(1) The semitrivial name "adamantane" has been used to designate the tricyclo[3.3.1.1^{3,7}]decane ring system.

(2) H. Stetter, M. Schwarz, and A. Hirschhorn, *Ber.*, **92**, 1629 (1959).

(3) H. Stetter and C. Wulff, *ibid.*, **93**, 1366 (1960).

of boron fluoride with aluminum bromide.[4,5] To investigate this hypothesis, a qualitative experiment was performed in which a trace of aluminum bromide was added to the boron bromide–bromine reaction mixture. The isolated product was identified as dibromoadamantane by melting point, depression of mixture melting point with authentic monobromoadamantane, and bromine analysis. Significant differences in retention times in vapor phase chromatograms, and in the chemical shifts and their relative intensities observed in proton magnetic resonance spectra for authentic monobromoadamantane and the product from the previous experiment also indicated nonidentity.

Repetition of this experiment resulted in a mixture of products with slightly high bromine content for disubstitution. This suggested, as might be predicted from earlier work,[3] that the degree of substitution might be quite sensitive to aluminum bromide concentration. Experiments with various boron bromide–aluminum bromide ratios indicated that at a molar ratio of BBr_3–Al_2Br_6 of 1000:1, dibromoadamantane was the major reaction product. At a ratio of 9:1, tribromination was the predominant course of reaction; while at a catalyst ratio significantly less than 1000:1, monobromide was the only product isolated. Aluminum bromide at this critical concentration (10^{-4} moles of Al_2Br_6 per mole of adamantane) in the absence of boron bromide did not effect dibromination.

Application of this information to a larger scale experiment (one mole of adamantane) resulted in the synthesis of dibromoadamantane in a 74% yield. Hydrolysis to give the diol added confirmatory evidence.

Although the mechanism for cocatalysis by aluminum bromide is not in hand, it would appear that both boron bromide and aluminum bromide are necessary, and that there exists a critical concentration of aluminum bromide required to selectively effect dibromination.

Experimental

Monobromination.—Procedures as described by Stetter[3] in all cases resulted in monobromination. Bromine content of the products in some cases was low even for monobromide, suggesting contamination with unreacted adamantane.

When bromine was dried with concentrated sulfuric acid and the boron bromide freshly distilled, crude monobromoadamantane was isolated in an 80% yield. An aliquot for analysis was purified by recrystallization from *n*-hexane at −78°, m.p. (sealed tube) 117°, lit.[2] m.p. 118° for 1-bromoadamantane.

Anal. Calcd. for $C_{10}H_{15}Br$: Br, 37.16. Found: Br, 37.34.

With bromine distilled from phosphorus pentoxide and boron bromide distilled from mercury, monobromoadamantane was isolated in a 65% yield after recrystallization from *n*-hexane at −78°, m.p. (sealed tube) 118°.

Anal. Calcd. for $C_{10}H_{15}Br$: Br, 37.16. Found: Br, 37.73.

Dibromination.—To a stirred mixture of 50 ml. (1 mole) of bromine and 2.5 ml. (0.025 mole) boron bromide there was added a few milligrams of aluminum bromide. The only precautions to operate under anhydrous conditions was to maintain a blanket of nitrogen over the reaction mixture during addition of reactants to a four-necked flask fitted with stirrer, reflux condenser, and gas inlet. Adamantane,[7] 13.6 g. (0.1 mole), was added portionwise from a small flask attached to the fourth neck by means of Gooch crucible tubing. After refluxing for 90 min., hydrogen bromide evolution was no longer evident. Excess bromine was decomposed and product isolation accomplished as described previously. The residue, after removal of carbon tetrachloride, was recrystallized from methanol and from *n*-hexane at room temperature, m.p. (sealed tube) 112–113°, lit.[3] m.p. 112° for 1,3-dibromoadamantane. A mixture of this material with authentic 1-bromoadamantane melted 88–100°.

Anal. Calcd. for $C_{10}H_{14}Br_2$: Br, 54.36. Found: Br, 54.65.

Vapor phase chromatographic analysis on a 1-m. column of 20% Dow Corning high vacuum grease on 40–60 Chromosorb W at 178°, preheater at 287°, and carrier gas flow of 60 cc. per min. gave a single peak with retention time of 6.7 min.[8] A proton magnetic resonance spectrum of three bands at 7.17, 7.70, and 8.28 τ with relative intensities of 1:5:1, respectively, was recorded in carbon tetrachloride with tetramethylsilane as internal standard.[9]

Additional dibromoadamantane, isolated from the hexane and methanol mother liquors, was found to be of 98–99% purity by v.p.c. The combined weights of all fractions was 17.9 g., a 61% yield of dibromoadamantane.

Repetition of the preceding experiment, using three times the quantities in the same proportions resulted in the isolation of two fractions: m.p. 113°, 54.98% Br; m.p. 96–105°, 55.41% Br. V.p.c. indicated the lower melting fraction to be a mixture of several components, some with retention times greater than that for dibromoadamantane.

Effects of Catalyst Ratio.—In a nitrogen atmosphere, 5.3 g. (0.01 mole as Al_2Br_6) of aluminum bromide was dissolved in bromine in a 10-ml. volumetric flask, resulting in a solution approximately 1 *M* in Al_2Br_6. Aliquots were diluted stepwise with bromine, giving aluminum bromide solutions of decreasing concentrations. A series of experiments was performed in which 6.8 g. (0.05 mole) adamantane was added portionwise in 30 min. to 25 ml. (0.5 mole) of bromine and a combination of boron bromide and of aluminum bromide–bromine solution. Boron bromide, 1.1 ml. (0.0113 mole), and 1.3 ml. of 1 *M* Al_2Br_6 in Br_2 was used in the first experiment, resulting in a molar ratio of BBr_3–Al_2Br_6 of approximately 9:1. For catalyst ratios of BBr_3–Al_2Br_6 of 10^3 and 10^5, 1.2 ml. (0.013 mole) of boron bromide and 1.3 ml. of 10^{-2} *M* and 10^{-4} *M* Al_2Br_6–Br_2 solutions, respectively, were used. The mixtures were refluxed for 90 min., allowed to cool to room temperature in 30 min., and poured into ice. Carbon tetrachloride, 75 ml., was added, excess bromine decomposed with sodium bisulfite, and the aqueous layer extracted twice with 25-ml. portions of carbon tetrachloride. The combined carbon tetrachloride layers were washed with 40 ml. of water, 40 ml. of 5% aqueous sodium carbonate, and dried over anhydrous calcium sulfate. The desiccant was removed by filtration and the solvent distilled at reduced pressure. The product from the experiment with a catalyst ratio of 9:1 was purified by sublimation at 5–7 mm., 110–125° bath temperature. Successive recrystallizations from methanol and *n*-hexane were used for the other two experiments (see Table I).

TABLE I

BROMINATED ADAMANTANE AS A FUNCTION OF CATALYST RATIO

BBr_3–Al_2Br_6	M.p. (sealed tube), °C.	% Br[a]
9:1	74–109[b]	62.88
10	114–116	54.50
10^5	119–120	38.11

[a] Calcd. for $C_{10}H_{15}Br$: Br, 37.16. Calcd. for $C_{10}H_{14}Br_2$: Br, 54.36. Calcd. for $C_{10}H_{13}Br_3$: Br, 64.29. [b] Vapor phase chromatographic analysis indicated a mixture of components, 80% of which had retention times greater than dibromoadamantane.

Repetition of the second experiment, using 1.3 ml. of 10^{-2} *M* Al_2Br_6–Br_2 solution but omitting the boron bromide completely,

(4) E. L. Gamble, "Inorganic Syntheses," Vol. III, L. F. Audrieth, Ed., McGraw-Hill Book Co. Inc., New York, N. Y., 1950, p. 27.

(5) Although there is a considerable difference in normal boiling points for BBr_3 and Al_2Br_6, 91.7° *vs.* 256.3°, aluminum bromide has a finite vapor pressure even as a solid (1 mm. at 81.3°[6]). It does not seem unlikely that some samples of boron bromide could be contaminated with traces of aluminum bromide by codistillation.

(6) D. R. Stull, *Ind. Eng. Chem.*, **39**, 540 (1947).

(7) Prepared by aluminum chloride isomerization of tetrahydrodicyclopentadiene; *cf.* F. von R. Schleyer and M. M. Donaldson, *J. Am. Chem. Soc.*, **82**, 4645 (1960).

(8) Adamantane and monobromoadamantane were eluted under the same conditions at 1.0 and 2.7 min., respectively.

(9) 1-Bromoadamantane shows three bands at 7.66, 8.05 and 8.24 τ with relative intensities of 3:1:3, respectively [H. F. Reinhardt, this laboratory, private communication].

resulted in the isolation of a monobromide product, m.p. 117–119° (sealed tube).

Anal. Calcd. for $C_{10}H_{15}Br$: Br, 37.16. Found: Br, 36.85.

Bromination of adamantane on a 1-mole scale, using the proportions described previously and a catalyst ratio of BBr_3–Al_2Br_6 of 10[3], resulted in the isolation of dibromoadamantane in a yield of 74%. The course of the reaction was established as dibromination on the basis of melting point, bromine analysis, and characteristic slight solubility in *n*-hexane at room temperature.

Silver ion-promoted hydrolysis of a portion of this material by Stetter's procedures[3] resulted in the synthesis of 1,3-dihydroxyadamantane, m.p. (sealed tube) 315°, lit.[3] m.p. 315°.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.14; H, 9.28.

Acknowledgment.—Grateful acknowledgments are made to Professor G. Stork and Professor J. H. Richards for helpful discussions, to Mrs. A. B. Richmond for vapor phase chromatographic analyses, and Mr. C. B. Matthews for n.m.r. spectroscopic examination.

Three-Membered Rings. VI. A Possible Explanation for the "Solvent Effect" Noted in the Partial Asymmetric Synthesis of *trans*-1,2-Cyclopropanedicarboxylic Acid

LAYTON L. MCCOY

Department of Chemistry, University of Missouri at Kansas City, Kansas City, Missouri

Received July 29, 1963

Recently, Walborsky and several co-workers[1] reported an apparent "solvent effect" in which the solvent used in a reaction to form the 1,2-cyclopropanedicarboxylate system controlled which enantiomer of the *trans* isomer was observed. Subsequently, in a paper on a related topic, Walborsky and Pitt[2] suggested briefly that the "solvent effect" might arise through the solvent controlling "the cisoidal–transoidal rotamer equilibrium" of the optically active chloro ester starting material.

The statement in ref. 9 of the original communication[1] that only "minor to trace amounts of the *cis* acid" could be isolated suggested two possibilities: (1) the bulky menthyl ester group controlled the stereochemistry of ring closure so that the *trans* isomer was formed independent of any stereoselective solvent effect[3]; (2) the *cis* isomer was present in the crude ester, but was isomerized to the *trans* isomer during the saponification step. If the first possibility were correct, it might offer a means of controlling the stereochemical formation of cyclopropane diesters by varying the size of the ester group. Consequently, the following brief investigation was carried out.

(−)-Menthyl chloroacetate and methyl acrylate were allowed to react with sodium hydride and methyl alcohol at about 25° in benzene diluent. Addition of water and removal of benzene left a mixture of unchanged (−)-menthyl chloroacetate and products. Half of this crude mixture was saponified by potassium hydroxide in boiling ethylene glycol[4] and resulted in the isolation of *trans*-1,2-cyclopropanedicarboxylic acid in 35% over-all yield from the (−)-menthyl chloroacetate; no indication of *cis* isomer was observed The other half of the mixture was reduced with lithium aluminum hydride and the resulting complex was decomposed with acetic anhydride and acetic acid.[5] The mixture of acetates obtained was analyzed by gas phase chromatography with the results shown in Table I. A similar sequence (the saponification step was omitted) run in dimethylformamide followed by reduction, acetylation, and gas phase chromatographic analysis gave the results also shown in Table I.

TABLE I

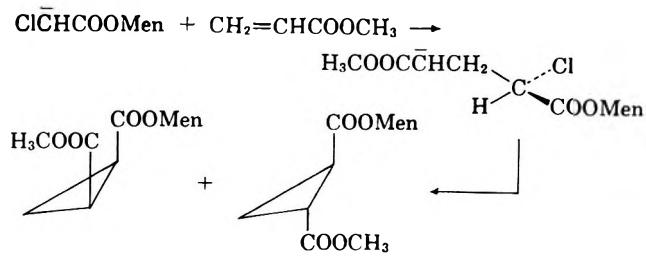
GAS PHASE CHROMATOGRAPHIC ANALYSIS OF THE REDUCTION–ACETYLATION PRODUCTS OBTAINED FROM CRUDE MENTHYL METHYL 1,2-CYCLOPROPANEDICARBOXYLATE

Compound	C_6H_6 solvent	$HCON(CH_3)_2$ solvent
Menthyl acetate	100[a]	92[a]
I[b] + II[b]	18[a]	24[a]
I[b]	18[c]	>92[c,d]
II[b]	82[c]	<8[c,d]

[a] These are over-all yields based on initial (−)-menthyl chloroacetate. [b] I is *trans*-1,2-bis(acetoxymethyl)cyclopropane; II is *cis*-1,2-bis(acetoxymethyl)cyclopropane. [c] These are the relative amounts of the two isomers. [d] The *cis* isomer peak appeared as an incompletely resolved small shoulder on the long retention time side of the *trans* peak.

The results clearly show that the crude 1,2-cyclopropanedicarboxylate esters have a "normal" isomer composition expected under solvent control of their formation.[3] The absence of *cis* isomer in the saponification product shows that the second possibility, isomerization from *cis* to *trans* during saponification, must occur.

This *cis* to *trans* isomerization permits a relatively simple interpretation of the previously observed "solvent effect" in partial asymmetric synthesis.[1] The initial addition of menthyl chloroacetate anion to methyl acrylate will establish an asymmetric center of the same enantiomeric form in all solvents, but the solvent will control the *cis* to *trans* ratio in the subsequent ring closure. Note that because the two ester groups are unlike, both the *trans* and *cis* isomers will be partially asymmetric and to the same extent because of their common origin. Saponification would be expected



to proceed stepwise, and for the *cis* isomer the initial product would be III. This methyl ester saponification should compete favorably with isomerization since it is known that saponification of methyl ethyl esters of these diacids produced in much the same way as described in this work does result in an excess of *cis*

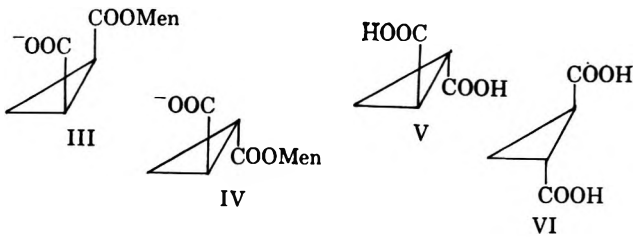
(1) Y. Inouye, S. Inamasu, M. Ohno, T. Sugita, and H. M. Walborsky, *J. Am. Chem. Soc.*, **83**, 2962 (1961).

(2) H. M. Walborsky and C. G. Pitt, *ibid.*, **84**, 4831 (1962).

(3) L. L. McCoy, *ibid.*, **84**, 2246 (1962).

(4) F. J. Impastato, L. Barash, H. M. Walborsky, *ibid.*, **81**, 1514 (1959).

(5) A. T. Blomquist and D. T. Longone, *ibid.*, **81**, 2012 (1959).



over *trans* diacid.[6] The menthyl group should hinder saponification of that ester, while the carboxylate anion should stabilize the adjacent position towards isomerization, at least relative to the ease of isomerization of the ester position. These two factors should lead to isomerization at the next step to produce IV. When the menthyl group eventually is saponified, the resulting *trans* diacid V will be the enantiomer of *trans* diacid VI, obtained directly by saponification of the *trans* diester.

Some isomerization of the *cis* diester undoubtedly will occur, but this should lead to *racemic* diacid. The rotations of the *trans* diacids obtained should be roughly proportional to the excess of one isomer over the other. For the present system, it is probably true that the *cis* to *trans* ratio in benzene will always be less than the *trans* to *cis* ratio in dimethylformamide. These two factors, isomerization of the diester and difference in the relative isomer ratios, should both operate so as to make the optical yield in benzene smaller than that in dimethylformamide. This is consistent with observation.[7]

In summary, it is suggested that partial asymmetric synthesis of the 1,2-cyclopropanedicarboxylate system is independent of the solvent, but that the solvent does control the *cis* to *trans* isomer ratio; and that the observed formation of enantiomeric *trans*-1,2-cyclopropanedicarboxylic acids can be accounted for by an asymmetric *cis* to *trans* isomerization during saponification.[7]

Experimental[8]

(−)-Menthyl chloroacetate was prepared in 87% yield, b.p. 125–126° (10 mm.).[9,10] *cis*-1,2-Bis(acetoxymethyl)cyclopropane, b.p. 115–120° (13–14 mm.), 46% yield, and *trans*-1,2-bis(acetoxymethyl)cyclopropane, b.p. 125–128° (17–18 mm.), m.p. 43–45° (petroleum ether, b.p. 30–60°), 67% yield, were prepared from the pure *cis* and *trans* dimethyl cyclopropanedicarboxylates essentially as described by Blomquist and Longone[5] for the *trans* isomer. Gas phase chromatographic analyses were made with a Beckman GC-2A chromatograph operating at 190° with a Beckman Column No. 70026.

Reaction in Benzene Diluent.—Methyl acrylate (10.4 g., 0.24 mole) and (−)-menthyl chloroacetate (28.0 g., 0.12 mole) were added to sodium hydride (2.88 g., 0.12 mole) in benzene (10 ml.). Methanol then was added dropwise very slowly until a convenient, steady rate of gas evolution was obtained. The reaction was maintained between 24–26° by a water bath. Gas evolution stopped after about 4 hr. and after an additional half hour of stirring, water was added, and the organic phase isolated and dried. Removal of the benzene at aspirator pressure left 39.1 g. of crude ester.

A.—Half of the crude ester was saponified with potassium hydroxide (13.4 g., 0.24 mole) in refluxing ethylene glycol (940 ml.).[4] After 72 hr., about 80% of the ethylene glycol was removed by distillation and water was added to the residue which was extracted continuously with ether until no more neutral material was removed. The aqueous solution then was acidified and extracted continuously with ether for 24 hr. Evaporation of the acidic ether extract left a mush which was diluted with a small amount of chloroform and filtered. The solid, 2.7 g., was identified as essentially pure *trans*-1,2-cyclopropanedicarboxylic acid, m.p. 174–176°, by its infrared spectrum; the yield was 35%. No indication for the presence of *cis* isomer was observed.

B.—The second half was reduced and acetylated essentially by the procedure of Blomquist and Longone,[5] but a slight modification of the work-up was used. After filtration of the metal acetate salts, the filtrate was washed with water, and the washes were extracted with ether. The combined ether extracts and organic filtrate were dried and distilled. The product fraction was taken over the range 105–135° (27 mm.) and amounted to 14.2 g.; there was negligible pot residue. This distillate was analyzed by gas phase chromatography; the chromatogram peaks were identified by comparison of retention times with those of known compounds. The analytical results are shown in Table I.

Reaction in Dimethylformamide.—Using dimethylformamide (50 ml.) in place of benzene, the reaction sequence was repeated. The crude ester amounted to 36.2 g. Reduction–acetylation of half of this gave 13.6 g. of product acetates which were analyzed by gas phase chromatography; the results are shown in Table I.

(6) L. L. McCoy, *J. Am. Chem. Soc.*, **80**, 6568 (1958).

(7) The most obvious way of refuting or establishing a direct "solvent effect" in partial asymmetric synthesis would be to isolate the *trans* diacetate (I) from the reduction–acetylation sequence for each solvent and compare their rotations. The small yield of the *trans* isomer in the benzene solvent and the close boiling points of the *cis* and *trans* isomers almost demands that separation be accomplished by preparative scale gas chromatographic equipment; unfortunately, the author does not have the necessary equipment.

(8) Melting points were taken on a Fisher-Johns hot stage and are corrected; boiling points are uncorrected.

(9) K. Sisido, O. Nakanisi, and H. Nozake, *J. Org. Chem.*, **26**, 4878 (1961).

(10) C. R. Hauser, B. E. Hudson, B. Abramovitch, and J. C. Shivers, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N.Y., 1955, p. 142.

Improved Procedures for Converting Higher α-Olefins to Methyl Ketones with Palladium Chloride

WILLIAM H. CLEMENT[1] AND CHARLES M. SELWITZ[2]

Petrochemicals Division,
Gulf Research and Development Company,
Pittsburgh, Pennsylvania

An attractive approach to the synthesis of methyl ketones from normal α-olefins has been described by J. Smidt, *et al.*[3] Their procedure employs an aqueous solution of palladium chloride to oxidize the olefin and utilizes the presence of cupric chloride and oxygen to maintain the palladium in a +2 state. The resulting reactions may be represented by the following equations.

$$PdCl_2 + R{-}CH{=}CH_2 + H_2O \longrightarrow R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}CH_3 + Pd + 2HCl \quad (1)$$

$$Pd + 2CuCl_2 \longrightarrow PdCl_2 + 2CuCl \quad (2)$$

$$2CuCl + 1/2O_2 + 2HCl \longrightarrow 2CuCl_2 + H_2O \quad (3)$$

Other investigators have utilized such reagents as *p*-benzoquinone or hydrogen peroxide to reoxidize the palladium.[4] The mechanism of the olefin oxidation step has been discussed in several publications.[5,6]

(1) Department of Chemistry, University of Cincinnati, Cincinnati, Ohio.

(2) To whom inquiries should be sent.

(3) J. Smidt, *et al.*, *Angew. Chem.*, **71**, 176 (1959).

(4) I. I. Moiseev, M. N. Vargaftik, and Ya. K. Syrkin, *Dokl. Akad. Nauk. SSSR*, **130**, 820 (1960).

(5) M. N. Vargaftik, I. I. Moiseev, and Ya. K. Syrkin, *ibid.*, **139**, 1396 (1961).

(6) J. Smidt, *et al.*, *Angew. Chem. Intern. Ed. Engl.*, **1**, 80 (1962).

Although experimental procedures have been disclosed for the treatment of lower olefins,[4,6-8] no convenient laboratory method is available in the literature for the handling of higher α-olefins. The higher molecular weight α-olefins (hexane-1 and larger) do not readily react with an entirely aqueous solution of palladium chloride as do the lower homologs. In addition to low yields, the product obtained is often highly contaminated with the more internal ketone isomers which are difficult to separate. We wish to describe two efficient procedures, as demonstrated with 1-dodecene, which afford excellent yields of higher molecular weight methyl ketones of high purity.

By employing an aqueous dimethylformamide (DMF) solvent and utilizing a regulated feed of olefin into the catalyst solution, it has been found possible to obtain product yields of greater than 80%.

The ketone which forms is 96%–99% methyl ketone, as determined by v.p.c. Typical results with 1-dodecene are summarized in Table I. The effect of water concentration is seen in the data shown in Table I. Best yields were obtained with solvent systems containing 12–17% water (by volume). When equal volumes of dimethylformamide and water were employed, the conversion dropped drastically (run 9). Undoubtedly, with additional variations in catalyst concentration, oxygen flow, temperature, and rate of feed, the results can be further improved.

TABLE I

CONVERSION OF 1-DODECENE TO 2-DODECANONE[a]

Run	Solvent—DMF, ml.	Solvent—water, ml.	1-Dodecene content of olefin, %	Yield,[b] %
1[c]		25	84	0
2	50	4	96	78
3	50	7	96	78
4	50	7	94	81
5	50	7	84	85
6	50	7	96	87
7	50	10	84	85
8	40	15	96	51
9	25	25	84	20

[a] Each experiment was carried out at 60–70° using 0.020 mole of $PdCl_2$, 0.020 mole of $CuCl_2 \cdot 2H_2O$, 0.20 mole of olefin, and an O_2 flow of 3.3 l./hr. In run 6 the olefin was added over a 3.5-hr. period; in all other cases the time of introduction was 2.5 hr. [b] Determined by v.p.c. [c] This experiment was stopped after 1.5 hr. as no reaction occurred.

The regulated feed of olefin is necessary to prevent build-up of unchanged olefin. When this occurs, the yield is lowered. A partial explanation for this observation lies in the fact that isomerization of the α-olefins is a competing reaction. More intensive research is required before a satisfactory explanation for the improvement obtained with dimethylformamide may be given. Conceivably, the dimethylformamide provides more intimate contact between the olefin and catalyst solution and also may exert a solvent effect which promotes reaction and selectivity. Certainly not all water-miscible solvents are equally applicable. For example, we examined dimethyl sulfoxide, acetone, acetic acid, tetrahydrofuran, dioxane, and acetonitrile and found each to be highly inferior to dimethylformamide. This technique can be used to oxidize olefinic compounds other than hydrocarbons to methyl ketones. The essentially unmodified optimum procedure was used to convert 10-undecenoic acid to 10-ketoundecanoic acid in 83% yield.

Where it is desirous to avoid the use of oxygen and/or copper salts, *p*-benzoquinone may be utilized to reoxidize palladium. In this case a slightly different experimental approach is required. The olefin, palladium chloride, quinone, and dimethylformamide are charged to the reaction flask, and then water is added portionwise at intervals. In this manner, 1-dodecene was converted in a 77% yield to 2-dodecanone.

The results of our investigation suggest that the above procedures may be extremely valuable in laboratory synthesis. Many organic compounds which possess a vinyl radical ($-CH=CH_2$) and which do not react to form pure ketones *via* the original Smidt[3] procedure may lend themselves to treatment through application of the modifications which we have described.

Experimental

All melting points and boiling points are uncorrected.

Materials.—Dimethylformamide (Eastman Kodak, White Label), $PdCl_2$ (60.00% Pd, J. Bishop and Co., Malvern, Pa.), $CuCl_2 \cdot 2H_2O$ (Baker and Adamson, Reagent Grade), and *p*-benzoquinone (Fisher Scientific, Purified) were used without further purification. Commercial samples of 1-dodecene (Gulf Oil Corp., Pittsburgh, Pa.) were analyzed by v.p.c. for C_{12} content and by infrared for *n*-1 olefin content.

Identification of 2-Dodecanone.—In an initial experiment, the reaction product was isolated by fractional distillation, b.p., 246–247° (lit. b.p. 246–247°).

Anal. Calcd. for $C_{12}H_{24}O$: C, 78.13; H, 13.13. Found: C, 78.13; H, 13.21.

The semicarbazide derivative melted at 122.5–123.5° (lit.[9] m.p. 122–123°), and the 2,4-dinitrophenylhydrazine derivative melted at 80° (lit.[9] m.p. 81°). The product had the same retention time (v.p.c.) as an authentic sample, and infrared examination further confirmed its structure.

Analytical Method.—Vapor phase chromatographic analyses were carried out on a 17-ft. column packed with tripentaerythritol octaisooctanoate on firebrick at 180° with a helium pressure of 20 p.s.i. (gage) and on a 2-ft. column packed with silicone rubber on firebrick with a helium flow of 125 ml./min. (temperature programmed). A sample of isolated and identified 2-dodecanone was used for tagging purposes and to establish retention times. To permit quantitative evaluation of 2-dodecanone formation, appropriate calibration curves were obtained with known blends of olefin and ketone. The 17-ft. column was capable of resolving a mixture of 2-, 3-, and 4-dodecanone.

2-Dodecanone Using Cupric Chloride and Oxygen (Table I).—The reactions were conducted in a cylindrical 250-ml. glass reactor which had a gas-dispersion inlet tube affixed to the bottom to permit efficient passage of oxygen through the reaction solution. A flowmeter was used to control the amount of oxygen. The reactor was equipped with a stirrer, condenser, and thermowell. A 6-mm. glass delivery tube was set into the flask so that the outlet was well below the surface of the initial solution and dropping funnel was connected to the top of the tube. The reactor was charged with the catalyst salts, DMF, and water, and the oxygen flow was adjusted. The stirred solution was heated at 60°, and the 1-dodecene was then fed dropwise through the delivery tube into the catalyst solution over a period of 2.5 hr. The temperature was maintained between 60° and 70° during the introduction of the olefin and for 0.5 hr. following complete addition. The mixture was cooled, and the upper phase which contained DMF, unchanged olefin, and products was analyzed by v.p.c. Reagent quantities and yields of 2-dodecanone are listed in Table I. To collect the ketone, the product

(7) Belgian Patent 592,633 (January 5, 1961).
(8) German Patent Application 1,080,994 (May 5, 1960).
(9) I. Heilbron, "Dictionary of Organic Compounds," Vol. III, Oxford University Press, New York, N. Y., 1953, p. 362.

phase was removed, washed several times with water, dried, and fractionally distilled.

10-Ketoundecanoic Acid.—Run 2 described before and in Table I was duplicated except that 27.5 g. (0.15 mole) of 10-undecenoic acid was added over a 2-hr. period in place of dodecene-1. The product was finally poured into excess, cold, dilute hydrochloric acid and the precipitated solid was isolated, dried, and taken up in benzene. After filtration and removal of the benzene the product was extracted with cold pentane to leave 18.0 grams of 10-ketoundecanoic acid, m.p. 52°, while the pentane contained 7.5 g. of cruder product. The keto acid was recrystallized from ethyl acetate, m.p. 57–59° (lit.[10] m.p. 58–60°).

Anal. Calcd. for $C_{11}H_{20}O_3$: neut. equiv., 280. Found: neut. equiv., 282.

2-Dodecanone Using *p*-Benzoquinone.—Palladium chloride (0.020 mole), *p*-benzoquinone (0.10 mole), 1-dodecene 0.10 mole), and 50 ml. of DMF were placed in a 250-ml. round-bottomed flask fitted with a stirrer, condenser, thermometer, and dropping funnel, and 1 ml. of water was added from the dropping funnel. The solution temperature rose to 70°. After 0.25 hr. an additional 1 ml. of water was added, and heat was applied to maintain a 70° temperature. A third milliliter of water was introduced at 0.75 hr. and a milliliter at 2.5 hr. The mixture was cooled and flooded with water after a total reaction time of 3 hr. and the product was extracted with pentane. The pentane solution was washed several times with water and then dried. Removal of the solvent left 17 g. of an oil which was analyzed by v.p.c. and found to contain 13.5 g. of 2-dodecanone (77%). Only trace amounts of other C_{12} ketone isomers were detected.

(10) J. Casey and F. S. Prout, *J. Am. Chem. Soc.*, **66**, 48 (1944).

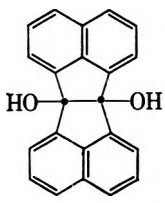
peri-Substituted Naphthalene Compounds. VI.[1,2] Acenaphth[1,2-*a*]acenaphthylene

ROBERT L. LETSINGER AND JO ANN GILPIN[3]

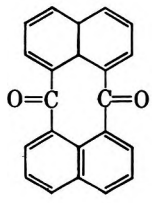
Department of Chemistry, Northwestern University, Evanston, Illinois

Received July 26, 1963

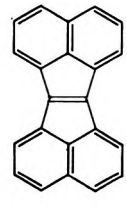
With the availability of 1,8-dilithionaphthalene,[1] a variety of *peri*-substituted naphthalene compounds have become accessible. The present paper reports the preparation of *cis*-6b,12b-dihydroxy-6b,12b-dihydroacenaphth[1,2-*a*]acenaphthylene (I) and conversion of this diol to diketone II and to hydrocarbon III.



I



II



III

Diol I was obtained in 14% yield on hydrolyzing the products from reaction of equimolar quantities of 1,8-dilithionaphthalene and acenaphthenequinone. It is a colorless, crystalline solid melting at 319–321°. The assigned structure is supported by the infrared spectrum (bands attributable to hydrogen bonded O–H at 3.00 and 3.12 μ), the mass spectrum (molecular ion at *m/e* 310), a Zerewitinoff determination (two active hydrogen atoms per molecule), and the elemental analysis. Of the two possible stereoisomeric forms, only that with *cis* fusion of the five-membered rings seems a plausible structure in view of the method of formation and the high degree of strain that would exist in the *trans* isomer. It was indeed found that diol I was produced by oxidation of acenaphth[1,2-*a*]acenaphthylene (III) with osmium tetroxide, a reagent well established to add *cis* to carbon–carbon double bonds. Furthermore, a sharp melting, crystalline ester was obtained from the reaction of I with benzeneboronic acid.

Oxidation of diol I with lead tetraacetate afforded 1,8-naphthalylnaphthalene (II) in 81% yield. A molecular model of this substance indicates that the carbonyl groups would not lie in the plane of either naphthalene ring. In agreement with the expectation that the geometry would lead to inhibition of resonance involving these groups, it was found that the carbonyl stretching frequency for II was 25 cm.$^{-1}$ greater than that for 1,8-dibenzoylnaphthalene and the extinction coefficient for the maximum occurring at 280 mμ was only 1120, as compared to 9680 for 1,8-dibenzoylnaphthalene. Also of interest is the fact that II dissolved in concentrated sulfuric acid to give a colorless solution, whereas naphthalene compounds which possess oxygen functions at the α-position in general give highly colored sulfuric acid solutions.[4] The ion formed from II seems best formulated as one in which hybridization of the carbonium ion is largely sp^3 and conjugation with the aromatic rings is minimal as a consequence of the molecular geometry.

On addition of I to hydrogen fluoride a green solution was obtained. Hydrolysis and chromatography of the resulting dark precipitate afforded in 29% yield a deep purple, sublimable hydrocarbon, $C_{22}H_{12}$. The same compound was obtained in 7% yield when a solution of diol I in sulfuric acid was hydrolyzed. The mass spectrum (molecular ion of mass 276) was consistent with an aromatic hydrocarbon structure, and the infrared spectrum was unusually simple, consisting of three strong bands (6.91, 12.16, and 13.06 μ), three medium intensity bands (6.80, 7.05, and 8.32 μ), and a few very weak bands. Evidence that no rearrangement of the carbon skeleton had occurred was provided by the fact that the purple hydrocarbon was reconverted to diol I by treatment with osmium tetroxide and hydrolysis of the resulting ester. These facts identify the hydrocarbon as acenaphth[1,2-*a*]acenaphthylene (III).

Formation of III from I involves elimination of *cis*-hydroxyl groups. A few other cases of production of olefinic substances from glycols under conditions for the pinacol rearrangement have been reported. For example, Bachmann and Chu[5] obtained 1,2-diarylacenaphthylenes as well as the expected pinacolones on treating 1,2-bis-*p*-chlorophenyl-1,2-acenaphthenediol and the corresponding fluorophenyl analog with iodine in acetic acid. In addition, Gomberg and Bachmann[6] reported that $\Delta^{9,9'}$-bixanthene was formed when 9,9'-bixanthydrol was warmed in an acetic acid–sulfuric acid solution. This result was questioned by Bergmann and Schuchardt,[7] who failed to obtain the bixanthene

(1) Paper V, R. L. Letsinger, J. A. Gilpin, and W. J. Vullo, *J. Org. Chem.*, **27**, 672 (1962).

(2) This work was supported in part by the National Science Foundation.

(3) Dow Chemical Co. Fellow, 1961–1962.

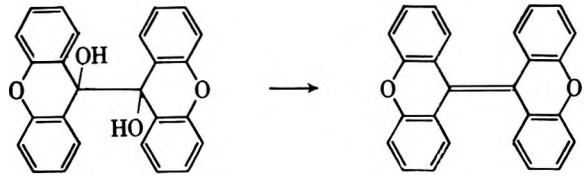
(4) A solution of 1,8-dibenzoylnaphthalene in sulfuric acid is red (λ_{max} 523 mμ).

(5) W. E. Bachmann and E. J. Chu, *J. Am. Chem. Soc.*, **58**, 1118 (1936).

(6) M. Gomberg and W. E. Bachmann, *ibid.*, **49**, 236 (1927).

(7) E. Bergmann and W. Schuchardt, *Ann.*, **487**, 240 (1931).

under these conditions; however, in confirmation of the observation of Gomberg and Bachmann, we obtained a low yield of $\Delta^{9,9'}$-bixanthene from the reaction of 9,9′-



bixanthydrol with sulfuric acid. Bachmann and Chu explained the appearance of 1,2-diarylacenaphthylenes in their reactions by assuming that small amounts of hydrogen iodide present in the mixture of iodine and acetic acid converted the diols to diiodides which then lost iodine. This explanation is not applicable for the elimination reactions leading to compound III and to $\Delta^{9,9'}$-bixanthene. It seems likely in these cases that the reactions involve loss of a positive oxygen fragment situated β to a carbonium ion.

Acenaphth[1,2-*a*]acenaphthylene yielded (95%) a colorless dibromide, probably the *cis*-6b,12b isomer, when treated with an equivalent amount of bromine in chloroform solution. The ease of the addition reaction indicates the low degree of "aromatic" character of the bond at the 6b,12b-position. On being heated to 210° the dibromide lost bromine, regenerating the purple hydrocarbon. Dehalogenation also was effected by warming the dibromide with aqueous sodium hydroxide.

Experimental

The carbon-hydrogen analyses were performed by Miss Hilda Beck and by the Micro-Tech Laboratories in Skokie, Illinois. Infrared spectra were obtained with a Baird double beam recording spectrophotometer with the samples in potassium bromide. The ultraviolet spectra were taken with a Beckman DK-2 spectrophotometer.

***cis*-6b,12b-Dihydroxy-6b,12b-dihydroacenaphth[1,2-*a*]acenaphthylene.**—To an ether solution of 1,8-dilithionaphthalene,[1] prepared from 4.0 g. of 1,8-dibromonaphthalene, was added in small portions 2.7 g. of acenaphthenequinone. After the red mixture had refluxed for 6 hr. it was hydrolyzed with saturated ammonium chloride solution. On concentrating the organic layer to a small volume and diluting with hexane, a yellow solid (3.5 g., m.p. 130–210°) precipitated. The crude diol (0.62 g., 14%, m.p. 290–300°) was obtained as an almost colorless residue by extracting the solid with several portions of warm carbon tetrachloride. For purification, the diol was chromatographed on silica gel, using benzene–ethyl ether mixtures as eluent, and the fractions melting above 300° were combined and recrystallized from acetone. Compound I thus prepared melted at 319–321°; λ_{max}^{EtOH} 224 mμ (log ε 4.78), 270 (3.67), 281 (3.79), 306 (4.07), 323 (4.08). The major bands in the infrared spectrum were found at 3.12, 9.10, 12.03, and 12.80 μ. There were no absorption bands in the carbonyl region.

Anal. Calcd. for $C_{22}H_{14}O_2$: C, 85.1; H, 4.55; active hydrogen, 2. Found: C, 84.3; H, 4.47; active hydrogen,[8] 2.03 g. atom per 310-g. sample (*i.e.*, per mole).

When the mixture from reaction of 1,8-dilithionaphthalene with acenaphthenequinone was carbonated on Dry Ice prior to hydrolysis, the yield of diol I was the same and only trace quantities of acidic products were isolated.

1,8-Naphthalylnaphthalene.—A mixture of 0.1012 g. (0.327 mmole) of diol I and 0.1483 g. (0.335 mmole) of lead tetraacetate in 10 ml. of dry benzene was allowed to react at room temperature for 2 hr. and then warmed on a steam bath for several minutes. The solution was washed with dilute hydrochloric acid, dilute sodium hydroxide, and water, respectively. Evaporation of the solvent afforded 0.0818 g. (81%) of ketone II, melting above 300°. After three recrystallizations from acetone–benzene the ketone melted at 333–334°; λ_{max}^{EtOH} 220 mμ (log ε 3.86), 280 (plateau, 3.05); $\lambda_{max}^{conc'd\ H_2SO_4}$ 220 mμ (log ε 4.07), 340 (3.78); major bands in infrared, 5.92, 7.77, 9.52, 11.90, and 12.82 μ.

Anal. Calcd. for $C_{22}H_{12}O_2$: C, 85.7; H, 3.92. Found: C, 85.7; H, 3.91.

Benzeneboronate Ester of *cis*-6b,12b-Dihydroxy-6b,12b-dihydroacenaphth[1,2-*a*]acenaphthylene.—On warming a benzene solution containing 0.1009 g. (0.325 mmole) of diol I and 0.0402 g. (0.330 mmole) of benzeneboronic acid, filtering the solution to remove small amounts of suspended matter, and concentrating the solution, crystals of the benzeneboronate ester of diol I were obtained, 0.0941 g. (73%), m.p. 326–333°. After three recrystallizations from benzene the compound melted at 347–348°. The sample burned with a strong green flame, indicative of boron, and the strongest band in the infrared spectrum occurred at 7.46 μ, characteristic of a boron–oxygen compound.

Anal. Calcd. for $C_{28}H_{17}O_2B$: C, 84.9; H, 4.33. Found: C, 85.0; H, 4.75.

As further evidence for the ester structure, a 23.9-mg. sample was stirred in an aqueous dioxane solution containing mannitol to hydrolyze it. On extraction with ether and evaporation of the ether, 8 mg. of diol I was recovered. As obtained in this way it was somewhat impure, m.p. 270–295°; however, the infrared spectrum was almost identical with that of the purified material and the sample did not give a green flame on burning. Titration of the aqueous layer required 4.6×10^{-5} mole of sodium hydroxide, 76% of the theoretical value for the boron in the sample.

Acenaphth[1,2-*a*]acenaphthylene.—A mixture of diol I (0.700 g.) and 15 ml. of anhydrous hydrogen fluoride in a copper vessel was allowed to stand 45 min. at 0° and then poured onto ice. On extracting with benzene, washing the benzene solution with water, drying, and evaporation, a dark solid was obtained. This material was then taken up in chloroform and chromatographed on alumina, using hexane–benzene mixtures as the eluent, to give 0.1983 g. (29%) of acenaphth[1,2-*a*]acenaphthylene, m.p. 284–285°, as purple crystals. The analytical sample, m.p. 285–286.5°, was obtained by recrystallization from a benzene–hexane mixture; λ_{max}^{EtOH} 224.5 mμ (log ε 4.72), 232 (4.61), 244.5 (4.36), 291 (4.09), 385 (4.19), 404 (4.17).

Anal. Calcd. for $C_{22}H_{12}$: C, 95.6; H, 4.38. Found: C, 94.3; H, 4.56.

Diol I was not changed by heating in refluxing acetic acid for 7 hr. or in phosphoric acid at 100° for 16 hr.

Hydroxylation of Acenaphth[1,2-*a*]acenaphthylene.—A solution containing 0.046 g. (0.18 mmole) of osmium tetroxide and 0.050 g. (0.18 mmole) of acenaphth[1,2-*a*]acenaphthylene in 15 ml. of ether was allowed to stand for 6 days, during which the purple color of the solution disappeared. Ether was then removed, water (4 ml.), ethanol (1.3 ml.), and sodium sulfite (0.6 g.) were added, and the mixture was refluxed for 4 hr. Extraction with ether and evaporation of the ether afforded 0.0326 g. (58%) of diol I, m.p. 295–300°. After two recrystallizations from an acetone–ether mixture the product melted at 313–318°. The product was identified by its infrared spectrum and a mixture melting point with the diol obtained from the reaction of 1,8-dilithionaphthalene.

6b,12b-Dibromo-6b,12b-dihydroacenaphth[1,2-*a*]acenaphthylene.—To a red solution of acenaphth[1,2-*a*]acenaphthylene (0.0452 g., 0.163 mmole) in chloroform was added dropwise an 0.85-ml. aliquot (0.16 mmole) of a 1.0% (by volume) solution of bromine in chloroform. Upon completion of the addition the solution was a pale yellow. The solution was shaken successively with a dilute sodium bisulfite solution and with water. On evaporation of the solvent 0.0677 g. (95%) of the dibromide derivative was obtained. On the melting point block a sample turned purple at 210–220° and melted at 248–255°. The analytical sample was recrystallized three times from benzene. Its behavior on heating was the same as that of the material isolated directly from the reaction mixture.

Anal. Calcd. for $C_{22}H_{12}Br_2$: C, 60.58; H, 2.8. Found: C, 60.51; H, 3.0.

The substance produced by heating the dibromide above 220° was acenaphth[1,2-*a*]acenaphthylene. This hydrocarbon (m.p. 255–257°, identified by the infrared spectrum) was likewise obtained (76% yield) when the dibromide was heated with excess aqueous, ethanolic sodium hydroxide on a steam bath.

(8) Method described in I. Gattermann and T. Wieland, "Die Praxis des organischen Chemikers," Walter De Gruyter and Co., Berlin, 1959, pp. 79–81.

Studies in the Norbornane Series. I. A Simple Stereospecific Synthesis of *exo*-2-Norbornyl Methyl Ketone

HANS STOCKMANN

Research and Development, American Viscose Division, FMC Corporation, Marcus Hook, Pennsylvania

Received August 26, 1963

The first sterically unequivocal synthesis of *exo*-2-norbornyl methyl ketone has been described by Berson.[1] The procedure consists of five steps and is too lengthy for preparations on a larger scale. This prompted us to investigate a simpler synthesis whose concept is based on the combination of two already known facts: (1) the free-radical addition of aldehydes to olefins yields ketones,[2,3] (2) the first step of the addition of free radicals or ions to the double bond of norbornene almost exclusively follows the "*exo*" course.[4]

Heating the commercially available norbornene with acetaldehyde at 80° for 40 hr. in presence of 0.02 mole of azobisisobutyronitrile[5] yielded 80% *exo*-norbornyl methyl ketone. The *exo* configuration of the ketone was proven by checking its refractive index and the melting point and mixture melting point of its semicarbazone and also by converting the ketone into *exo*-norborneol by reaction with perbenzoic acid. It had been shown previously[6] that the Baeyer–Villiger oxidation proceeds without change of configuration.

The steric uniformity of the ketone was demonstrated by the fact that the semicarbazone of the correct melting point was formed in 96% yield.

Experimental[7]

exo-**Norbornyl Methyl Ketone.**—Freshly distilled norbornene (47.0 g., 0.5 mole) was dissolved in 132 g. of freshly distilled acetaldehyde containing 0.01 mole of azobisisobutyronitrile. The mixture was heated in an autoclave at 80° for 40 hr. After removing most of the unchanged acetaldehyde at atmospheric pressure the remainder was distilled *in vacuo* to yield 56.7 g. of *exo*-norbornyl methyl ketone, b.p. 79–81° (15 mm.), lit.[1] b.p. 87° (19 mm.), and an unidentified high-boiling residue. The ketone which had $n^{24}D$ 1.4709, lit.[1] $n^{25}D$ 1.4710, formed a semicarbazone in 96% yield, m.p. 181.5–182.5°, lit.[1] m.p. 182–183°. The semicarbazone gave no melting point depression upon admixture with a semicarbazone, prepared from authentic *exo* ketone[1]; admixture with authentic *endo* semicarbazone,[1] m.p. 179–180°, resulted in a melting point depression of about 10°. Following the procedure already reported,[1] the *exo* ketone was converted into *exo*-norborneol, m.p. 126–127°; dinitrobenzoate, m.p. 104°.

Acknowledgment.—This author is indebted to Mr. R. W. Waite for performing some experiments and gratefully acknowledges a gift of norbornene from Enjay Chemical Company and Union Carbide Company.

(1) J. A. Berson and S. Suzuki, *J. Am. Chem. Soc.*, **81**, 4088 (1959).

(2) M. S. Kharasch, W. H. Urry, and B. M. Kuderna, *J. Org. Chem.*, **14**, 248 (1949).

(3) K. Ziegler, *Brennstoff-Chem.*, **30**, 181 (1949).

(4) See among others: (a) K. Alder and K. Backendorf, *Ann.*, **535**, 106 (1938); (b) G. Stork, E. E. Van Tamelen, L. J. Friedman and A. W. Burgstahler, *J. Am. Chem. Soc.*, **75**, 384 (1953); (c) L. Kaplan, H. Kwart, and P. von R. Schleyer, *ibid.*, **82**, 2341 (1960); (d) W. Reusch, *J. Org. Chem.*, **27**, 1882 (1962).

(5) It should be noted that *replacement of this initiator by other free-radical sources of peroxidic nature drastically reduces the amount of ketone formed in the present case.* Some reasons for this are given in ref. 2 and 3.

(6) R. B. Turner, *J. Am. Chem. Soc.*, **72**, 878 (1950); *cf.* also ref. 1

(7) Melting points were determined using the Kofler hot-stage apparatus.

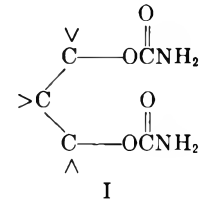
A 1,3,5-Dioxazine

BERNARD LOEV, KENNETH M. SNADER AND MINERVA F. KORMENDY

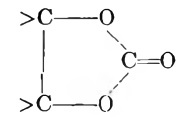
Research and Development Division, Smith Kline and French Laboratories, Inc., Philadelphia, Pennsylvania

Received August 5, 1963

In a recent publication, we described an improved method of synthesis of carbamates of alcohols, thiols, phenols, and oximes using a procedure that involves simply stirring a mixture of the alcohol, thiol or oxime, sodium cyanate, trifluoroacetic acid, and a solvent for a brief period.[1] When this reaction was applied to 1,3-glycols, the biscarbamate (I) was formed; when applied to 1,2-glycols, the cyclic carbonate (II) was the major product.

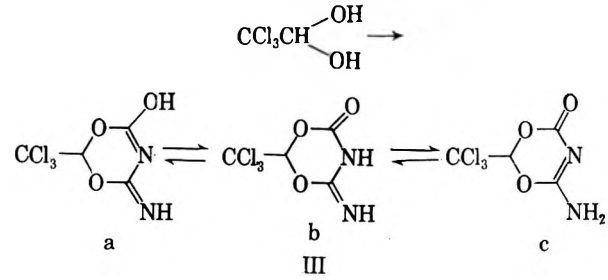


I



II

We now wish to report a novel product prepared by the reaction of a 1,1-glycol, chloral hydrate, under the same reaction conditions. This product, assigned the tautomeric substituted 1,3,5-dioxazine structures (III)



a b c

III

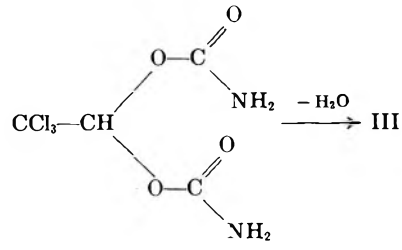
is a high-melting, water-insoluble, tasteless crystalline solid—in sharp contrast to the starting material, chloral hydrate, a low-melting, hygroscopic, bitter, amorphous solid. The compound is insoluble in aqueous acid, soluble in and decomposed by aqueous base, and insoluble in most of the ordinary organic solvents other than alcohols. It could not be catalytically reduced with platinum or palladium catalysts at 50 p.s.i.g.

The near-infrared absorption spectra[2] support the assigned structure and suggest that it is mainly in the form IIIb. The n.m.r.[2] shows only a single tertiary C–H; the compound does not absorb in the ultraviolet region (220 to 230 mμ).

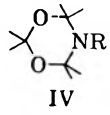
(1) B. Loev and M. F. Kormendy, *J. Org. Chem.*, **28**, 3421 (1963).

(2) We are indebted to Dr. W. Thompson and R. Warren for running these spectra for us. N.m.r. spectra were measured at 60 Mc. on a Varian Associates Model A-60 spectrophotometer, in perdeuteriomethanol solution. Chemical shifts are given with reference to tetramethylsilane. The near-infrared spectra were determined as a mineral oil mull on a Perkin-Elmer Model 137-G.

A possible mechanism for the reaction could be through dehydration of an intermediate biscarbamate.



The only other examples of 1,3,5-dioxazines that have been described previously are the dihydro derivatives (IV, R = H, CH_2COOH, CH_2COOEt, CH_2CONH_2, Cl, NO_2, NH_2).[3]



IV

Experimental

2-Trichloromethyl-4-keto-6-amino-4*H*-1,2,5-dioxazine.—To a solution of 16.6 g. (0.1 mole) of chloral hydrate in 250 ml. of tetrahydrofuran was added 26.0 g. (0.4 mole) of sodium cyanate. The mixture was chilled and 29.7 ml. (0.4 mole) of trifluoroacetic acid was added. The mixture was stirred for 2 hr. at room temperature and filtered to remove the sodium trifluoroacetate (more tetrahydrofuran may be added). The filtrate was evaporated at 25°, *in vacuo*, leaving an oil (35 g.). The infrared spectra of the oil showed no absorption at 4.4 μ (isocyanate). The oil solidified on standing, better on stirring with a little water; the solid was collected and dried in a desiccator. It was recrystallized twice from acetone–water or from tetrahydrofuran and petroleum ether (b.p. 60–70°), m.p. 240° dec.

Anal. Calcd. for $C_4H_3Cl_3N_2O_3$: C, 20.58; H, 1.30; Cl, 45.56; N, 12.00. Found: C, 20.88; H, 1.31; Cl, 45.58; N, 11.93.

The n.m.r. showed a single peak (—C–H) at 348 c.p.s. (5.81 p.p.m.). The near-infrared showed an absorption (—C—H) at 2.82 and a triplet at 5.55–5.78 μ from a tautomeric carbonyl. Attempts to determine the molecular weight by nonaqueous titration or cryoscopically gave inconsistent values ranging from 239 to 248 (theoretical, 233.45). The pK_a determined in 50% aqueous ethanol was 8.15.

When chloral was treated with sodium cyanate and trifluoroacetic acid under the same conditions described previously, *no reaction occurred*, and chloral was recovered.

(3) (a) T. Curtius and R. Jay, *Ber.*, **23**, 740 (1890); M. Bergmann, M. Jacobsohn, and H. Schotte, *Z. Physiol. Chem.*, **131**, 20 (1923). (b) NOTE ADDED IN PROOF.—After this work had been submitted, we learned of an article by F. W. Hoover, H. B. Stevenson, and H. S. Rothrock, *J. Org. Chem.*, **28**, 1825 (1963), in which is described the reaction of chloral with free isocyanic acid to give $CCl_3CH(OH)NCO$.

A New Conversion of Isonitriles to Isocyanates

HARRY W. JOHNSON, JR., AND PARKER H. DAUGHHETEE, JR.[1]

Department of Chemistry, University of California, Riverside, California

Received July 8, 1963

An apparently new oxidation of isonitriles with dimethyl sulfoxide in the presence of small amounts of halogen has been encountered in these laboratories.

(1) National Science Foundation Undergraduate Research Participant.

Previously isonitriles have been converted to isocyanates by the action of mercuric oxide,[2] ozone,[3] and similar reagents. The reaction of isonitrile dihalides with water to yield an amine, presumably *via* the isocyanate, was reported.[4]

In the studies of the effect of solvent on the reaction of silver cyanide with alkyl halides, isopropyl iodide and silver cyanide were heated in dimethyl sulfoxide for 24 hr. Examination of the infrared spectrum indicated the presence of an isocyanate (maximum, 2220 $cm.^{-1}$).[5] Further study of the reaction showed that isopropyl isonitrile (prepared by the dehydration of isopropylformamide with *p*-toluenesulfonyl chloride in quinoline[6]) was stable to dimethyl sulfoxide at the same temperatures and times, thus indicating that a direct oxidation of the isonitrile was not involved. Addition of 5 mole % of bromine to an equimolar mixture of isopropyl isonitrile and dimethyl sulfoxide in chloroform solvent at refluxing temperatures led to smooth formation of isopropyl isocyanate and dimethyl sulfide, both identified by comparison with authentic samples. The yield of isocyanate was approximately equal (±10%) to that of dimethyl sulfide. The chloroform and dimethyl sulfoxide used in this study were dried with calcium hydride to obviate the possible hydrolysis of isonitrile dihalide.[4] A preliminary infrared study of the reaction showed that the isonitrile maximum (2120 $cm.^{-1}$) decreased steadily with time. No peak at 1690 $cm.^{-1}$ (isonitrile dihalide) was observed, and the spectrum could be described by the superposition of the maxima of the isonitrile, isocyanate, dimethyl sulfoxide, and the chloroform. Addition of dimethyl sulfoxide to preformed isonitrile dibromide in chloroform (infrared maximum, 1690 $cm.^{-1}$) gave isocyanate in a rapid exothermic reaction at room temperature. Dimethyl sulfide was again identified as the other product.

On the basis of the information presently available, the most probable course of the reaction appears to be that shown in eq. 1 and 2. A chain reaction (presumably ionic) is implied by the necessity for the halogen coupled with the fact that only 5 mole % is required for the conversion. Equation 1 indicates a well known reaction of isonitriles.[4]

$$R{-}NC + X_2 \longrightarrow R{-}N{=}CX_2 \quad (1)$$

$$R{-}N{=}CX_2 + (CH_3)_2SO \longrightarrow RNCO + (CH_3)_2S + X_2 \quad (2)$$

What is written as eq. 2 is probably a multistep process, and the halogen may never be formed *per se*, but may be transferred from some intermediate adduct of dimethyl sulfoxide and isonitrile dihalide directly to another mole of isonitrile (eq. 3). Further study of the reaction is required to settle these points. It is, however, apparent that process 1 is not greatly faster than process 2, otherwise the build-up of the 1690 $cm.^{-1}$ isonitrile dihalide maximum would have been observed.

$$R{-}N{=}CX_2 \cdot (CH_3)_2SO + RNC \longrightarrow RNCO + (CH_3)_2S + RNCX_2 \quad (3)$$

(2) A. Gautier, *Ann. chim.* (Paris) [4] **17**, 229 (1869).

(3) H. Feuer, H. Rubinstein, and A. T. Nielsen, *J. Org. Chem.*, **23**, 1107 (1958).

(4) H. Guillemard, *Ann. chim.* (Paris), [8] **14**, 311 (1908); *Bull. Soc. Chem.*, (1904); J. J. Nef, *Ann.*, **270**, 257 (1892).

(5) H. Hoyer, *Ber.*, **89**, 2677 (1956).

(6) J. Casanova, Jr., R. E. Schuster, and N. D. Werner, *J. Chem. Soc.*, 4280 (1963). We thank Professor Casanova for a preprint of this paper.

Addition of iodine to a mixture of isopropyl isonitrile and dimethyl sulfoxide also led to isocyanate, but the reaction was slower and some tar was produced. The use of chlorine was also successful. Phenylisonitrile also gave phenyl isocyanate with bromine and dimethyl sulfoxide.

Kornblum has observed oxidations of benzyl halides with dimethyl sulfoxide to yield carbonyl compounds.[7] The reaction of isonitrile dihalides with dimethyl sulfoxide has some analogies in the reaction of acid chlorides and acid anhydrides with dimethyl sulfoxide.[8,9]

Preliminary results with W. H. Krutzsch show that pyridine N-oxide also reacts with isonitriles in the presence of halogen (but not in their absence) to yield isocyanates. These results will be reported later in detail.

Experimental

Isopropylformamide.—This compound was prepared in 85% yield by refluxing 85.6 ml. of isopropylamine with 80.5 ml. of ethyl formate for 4 hr.[10] The product distilled at 198–199°.

Isopropylisonitrile.—The isonitrile was prepared from the formamide by the method of Casanova.[6] To a well stirred solution of 41 g. of *p*-toluenesulfonyl chloride in 100 ml. of distilled quinoline was added 18.4 g. of isopropylformamide at 75°. The system was maintained at 70 mm. and the isopropylisonitrile distilled to a receiver cooled in liquid nitrogen as it formed. The yield was 4.2 g. (30%), b.p. 88–89° (735 mm.),[11] on redistillation.

Substitution of benzenesulfonyl chloride for the *p*-toluenesulfonyl chloride specified by Casanova gave substantially lower yields.

Isopropyl Isocyanate.—A solution of 0.38 g. of isopropyl isocyanide (5.5 mmoles) and 0.70 g. of dimethyl sulfoxide (10 mmoles), which had been dried over and distilled from calcium hydride in 5 ml. of chloroform which had been dried over calcium hydride, was prepared; 0.034 g. of bromine (0.21 mmole of dry bromine in 0.2 ml. of chloroform) was added. The solution was refluxed for 24 hr. Infrared spectra were recorded prior to the addition of the bromine and periodically throughout the rest of the reflux time. Following completion of the reflux period, approximately 0.5 ml. of isopropylamine was added to the cooled reaction mixture. The crystals which formed were removed by filtration and recrystallized from ethanol to yield diisopropylurea, m.p. 190–191°. An authentic sample of isopropyl isocyanate was prepared from isopropyl iodide and silver cyanate; reaction of the isocyanate with isopropylamine gave an authentic sample of diisopropylurea,[12] m.p. and m.m.p. 190–191° with the preceding sample. The infrared spectra of the two samples were identical.

The gases from the reaction mixture were passed through a liquid nitrogen trap, and the material which collected was subjected to vapor phase chromatography (4-ft. silicone column operated at room temperature). Chloroform and a maximum of retention time identical with that of dimethyl sulfide appeared; infrared spectra of the isolated dimethyl sulfide and an authentic sample were identical. The yield of dimethyl sulfide appeared to be essentially equivalent (±10%) to the yield of isocyanate as judged by the area of the dimethyl sulfide v.p.c. maximum compared with calibrated isocyanate infrared determinations. The yield of isocyanate was approximately 80% from infrared measurements.

To 10 ml. of chloroform was added 1 ml. of isopropylisonitrile. Bromine was added until its color persisted in the solvent. The solvent was evaporated. The viscous liquid (isopropylimidocarbonyl dibromide)[3] which formed was washed with chloroform by decantation; then 10 ml. of chloroform and 1 ml. of dimethyl sulfoxide were added. After completion of the vigorous exothermic reaction, infrared spectra indicated that the isonitrile absorption were missing and had been replaced by the isocyanate maximum (yield, 82%). V.p.c. of the reaction mixture on a silicone column gave a fraction whose retention time and infrared spectrum were identical with those of an authentic sample of isopropyl isocyanate. Dimethyl sulfide was identified by v.p.c. Diisopropylurea,[12] m.p. 190–191°, was formed upon addition of isopropylamine.

Acknowledgment.—The work reported herein was conducted under the Undergraduate Research Participation Program of the National Science Foundation; this support is gratefully acknowledged.

(7) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Carson, O. Levand, and W. M. Weaver, *J. Am. Chem. Soc.*, **79**, 6562 (1957); I. M. Hunsberger and J. M. Tien, *Chem. Ind.* (London), 88 (1959).

(8) L. Horner and P. Kaiser, *Ann.*, **626**, 19 (1959); H. W. Kircher, *Anal. Chem.*, **30**, 1540 (1958).

(9) F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, **77**, 572 (1955); T. Enkvist and C. Naupert, *Finska Kemistamfundets Medd.*, **69**, 98 (1961).

(10) J. Moffat, M. Newton, and G. Papenheimer, *J. Org. Chem.*, **27**, 4058 (1962).

(11) I. Ugi and R. Meyr, *Ber.*, **93**, 237 (1960).

(12) A. W. Hoffman, *ibid.*, **15**, 756 (1882).

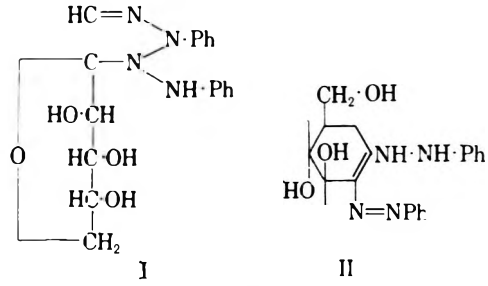
Analysis of the Structure of Dehydro-D-glucosazone by Nuclear Magnetic Resonance and by Comparison of Its Optical Isomers

L. MESTER AND E. MOCZAR

Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, Centre National de la Recherche Scientifique, Paris, France

Received January 28, 1963

Mester and Moczar[1] found structure II for dehydro-D-glucosazone rather than structure I previously proposed by Diels and co-workers.[2]



The gross structure (II) has now been confirmed by application of nuclear magnetic resonance spectroscopy. However, the n.m.r. evidence requires the D-*ribo* rather than the D-*arabino* configuration for II, a conclusion supported by chemical evidence reported herein. The n.m.r. spectrum of tri-*O*-acetyl-dehydro-D-glucosazone was determined at 60 Mc.p.s. in deuterated chloroform and the spectrum is shown in Fig. 1. The presence of three *O*-acetyl groups, five hydrogens attached to the sugar carbon chain, two hydrogens on nitrogen, and two phenyl groups was indicated by integration. The sharp doublet at 6.2 p.p.m. and well shifted chemically from other signals requires the presence of a hydrogen coupled with one only neighboring hydrogen. The spacing for this signal, 3 c.p.s., is found in the quartet of intensity one centered at 5.3 p.p.m. The position of the latter signal is characteristic of hydrogens on secondary carbons in carbohydrate structures which are

(1) L. Mester and E. Moczar, *Chem. Ind.* (London), 55 (1962).

(2) O. Diels, E. Cluss, H. J. Stephan, and R. König, *Ber.*, **71**, 1189 (1938).

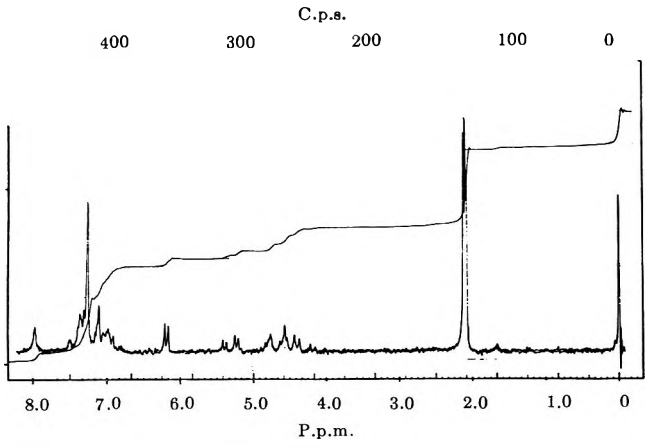
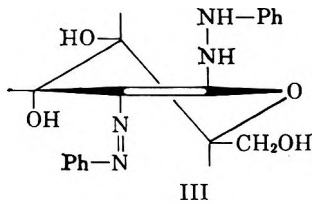


Fig. 1.—The nuclear magnetic resonance spectrum of tri-*O*-acetyldehydro-D-glucosazone.

bonded to an acetoxy group.[3,4] The latter signal can be assigned, therefore, to the 4-hydrogen and the broad spacing of 10 c.p.s. found in the quartet requires the hydrogen to be axially oriented and coupled with two hydrogens, one of which is axial in orientation and must be the 5-hydrogen. The other hydrogen must be quasi-equatorially oriented in view of the small coupling. This hydrogen must give rise to the doublet at 6.2 p.p.m. and must be located at the 3-position because of its chemical shift. Its position at 0.9 p.p.m. to lower field can be assigned to the decreased diamagnetic shielding of equatorial over axial hydrogens[5] together with paramagnetic deshielding arising from the neighboring double bond.

The multiplet from 4.60 to 5.32 p.p.m. corresponds to three hydrogen atoms and can be assigned to the hydrogen of C-5 and to the two hydrogens of C-6. Similar splitting in this region was observed in the case of the acetylated sugar osazones themselves[6] and are characteristic of a *C*-methylene group which holds an acetate function.[3-5] Signals at this position were not present in the spectrum of di-*O*-acetyl-dehydro-L-rhamnosazone. A doublet centered around 1.44 p.p.s., typical for a methyl group, was present.

The group of lines centered around 2.10 p.p.m. can be assigned to the three acetate methyl groups. Finally there are two peaks at 7.97 and at 12.50 p.p.m. which seem to correspond to the two N–H bonds. Therefore, structure III is assigned to dehydro-D-glucose phenylosazone. This is the same structure which we found for

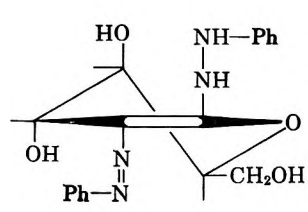


III

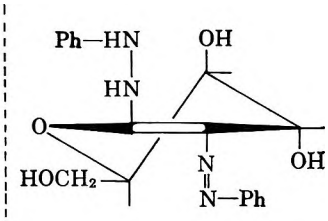
dehydro-D-glucosazone on the basis of chemical investigations,[1] except that the hydroxyl group of C-3 is *not* stabilized in the equatorial position corresponding to the original D-glucose configuration, but it is turned to the axial position (D-allose configuration). This transposition is certainly due to the encumbrance of this hydroxyl in the equatorial position with the *vicinal* azo group, and is brought about through the action of the alkaline medium during the dehydrogenation.

We found another proof of this transposition. In the D-series of hexoses four dehydroosazones (derived from D-glucose, D-galactose, D-allose, and D-gulose) may be expected, if *no* transposition occurs. If in the cases of D-glucose and D-galactose the C-3 hydroxyl undergoes a transposition to the axial position as expected, D-glucose should give the same dehydroosazone as D-allose, while D-galactose should give the same as D-gulose. Furthermore dehydro-D-glucosazone and dehydro-L-allosazone, on the one hand, and dehydro D-galactosazone and dehydro-L-gulosazone, on the other hand, must be optical antipodes (enantiomers)

The experimental data are in accord with this expectation. We found that dehydro-D-glucosazone [m.p. 202–203°, $[\alpha]^{24}D$ +346° (*c* 0.5, 1:1 pyridine–ethanol)] is identical with dehydro-D-allosazone [m.p. 203°, no depression with dehydro-D-glucosazone, identical infrared spectra, and optical rotatory power], while dehydro-D-galactosazone [m.p. 212°, $[\alpha]^{24}D$ +300° (*c* 1, 1:1 pyridine–ethanol] and dehydro-L-gulosazone [m.p. 212–213°, identical infrared spectra, but $[\alpha]^{24}D$ −298°] are enantiomers.



Dehydro-D-galactose phenylosazone $[\alpha]_D$ + 300°



Dehydro-L-gulose phenylosazone $[\alpha]_D$ − 298°

This is a direct proof of the transposition of the C-3 hydroxyl in dehydro-D-glucosazone to the axial position, as was found by n.m.r.

Experimental

Dehydro-D-glucosazone was prepared by air oxidation of D-glucose phenylosazone in pyridine–water solution containing potassium hydroxide, by the method of Diels and co-workers[2] m.p. 203–204°, $[\alpha]^{24}D$ −346° (*c* 0.5, 1:1 pyridine–ethanol).

Tri-*O*-acetyldehydro-D-glucosazone was obtained by acetylation of the former compound by a mixture of pyridine–acetic anhydride,[2] m.p. 173°. The n.m.r. spectrum was determined at 60 Mc. in deuterated chloroform with tetramethylsilane as an internal reference standard on a Varian Associates spectrometer, Palo Alto, California.

Dehydro-D-galactosazone was prepared by air oxidation of D-galactose phenylosazone in methanolic potassium hydroxide solution following the method of Diels and co-workers,[2] m.p. 212°, $[\alpha]^{24}D$ +300° (*c* 1, 1:1 pyridine–ethanol).

Dehydro-L-gulosazone was prepared from L-gulose phenylosazone in the same way, m.p. 212–214°, $[\alpha]^{24}D$ −298° (*c* 1, 1:1 pyridine–ethanol).

Anal. Calcd. for $C_{18}H_{20}O_4N_4$: C, 60.67; H, 5.62; N, 15.73. Found: C, 60.29; H, 5.52; N, 15.10.

Dehydro-D-allosazone was obtained by air oxidation of D-allose phenylosazone in methanolic potassium hydroxide solution in the same manner as the previous products, m.p. 203–204°, no depression with dehydro-D-glucosazone, identical infrared spectra, $[\alpha]^{24}D$ +346° (*c* 0.5, 1:1 pyridine–ethanol).

Dehydro-L-rhamnosazone was prepared from L-rhamnose phenylosazone by air oxidation in methanolic potassium hy-

(3) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **79**, 1005 (1957).

(4) M. L. Wolfrom, A. Thompson, and D. R. Lineback, *J. Org. Chem.*, **27**, 2563 (1962).

(5) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(6) L. Mester, E. Moczar, and J. Parello, unpublished results.

droxide solution. It was recrystallized from acetonitryl–acetone (1:2), m.p. 223°, $[\alpha]^{24}D$ −180° (*c* 0.5, 1:1 pyridine–ethanol).

Anal. Calcd. for $C_{15}H_{20}O_3N_4$: C, 63.51; H, 5.92; O, 14.11; N, 16.49. Found: C, 63.55; H, 5.88; O, 14.31; N, 16.71.

Di-*O*-acetyldehydro-L-rhamnosazone was obtained by acetylation of the former compound by a mixture of pyridine–acetic anhydride at 20°. It was recrystallized from ethanol, m.p. 180–181°.

Anal. Calcd. for $C_{22}H_{24}O_5N_4$: C, 62.25; H, 5.70; N, 13.20. Found: C, 62.64; H, 5.74; N, 13.29.

Acknowledgment.—We would like to express our appreciation to Professor M.-M. Janot (Paris) and Professor R. U. Lemieux (Alberta, Canada) for their suggestions, to Mr. J. Parello for the interpretation of the n.m.r. spectra, and to Mrs. M. Mester and Mrs. L. Allais for their assistance.

Addition of Acetaldehyde to Fluoroethylenes[1]

EUGENE R. BISSELL AND DOUGLAS B. FIELDS

Lawrence Radiation Laboratory, University of California, Livermore, California

Received April 30, 1963

Free-radical addition of aliphatic aldehydes to fluorinated olefins has been shown to yield ketones derived from addition of an acyl radical to the terminal carbon of the double bond.[2,3] It also has been shown that fluoroaldehydes add to fluoroolefins to give fluorooxetanes rather than carbonyl compounds.[4] In the present work it has been shown that under certain circumstances both types of products can be produced simultaneously.

Ultraviolet irradiation in the gas phase of mixtures of acetaldehyde and a fluorinated ethylene resulted in complex mixtures from which the ketone derived from addition of an acetyl radical to the CF_2 group of the olefin and the oxetane derived from cycloaddition of the aldehyde to the olefin were isolated by vapor–liquid partition chromatography (v.l.p.c.). Four olefins, tetrafluoroethylene, chlorotrifluoroethylene, bromotrifluoroethylene, and 1,1-dichloro-2,2-difluoroethylene, were studied. The major product in each case, as expected, was the ketone. The physical properties of the three new ketones isolated in this study are listed in Table I. 1,1-Dichloro-2,2-difluorobutanone-3, which has been described previously,[3] also is listed because some of the physical properties measured have not been reported. The yield of ketone is affected by reaction conditions (see Experimental) in approximately the way that would be expected assuming a free-radical mechanism as suggested by earlier workers.[2,3,5]

It is worth noting that, although both acetaldehyde and the olefin were present in substantial amount[6] in the final reaction mixture, increasing the time of irradiation actually decreased the yield. We attribute this to decomposition of the ketone under the influence of ultraviolet light.

The orientation of the addition was established by means of the n.m.r. spectra of the addition products. The data presented in Table II clearly excludes 2-halo-1,1,2-trifluorobutanone-3 as the structure of the ketone from either chlorotrifluoroethylene or bromotrifluoroethylene. The 2-halo structure would require CH chemical shifts more like that of 1,1,2,2-tetrafluorobutanone-3. The CF_2 shifts would be closer to that of the terminal CF_2 group in the tetrafluoro compound. The splittings of the CH, CF, and CF_2 groups would all be different from those observed, and the CH–CF and CH–CF_2 coupling constants would be smaller and greater, respectively, by about a factor of ten. Similar arguments exclude 1,1-difluoro-2,2-dichlorobutanone-3 as the structure of the ketone from 1,1-dichloro-2,2-difluoroethylene. These results support the conclusion of Muramatsu and Inukai[3] that the acyl radical attacks the CF_2 group.

In addition to the ketone, from tetrafluoroethylene and 1,1-dichloro-2,2-difluoroethylene, a second 1:1 adduct was isolated; and from chlorotrifluoroethylene, two more 1:1 adducts were obtained. Oxetane structures were assigned on the basis of infrared and n.m.r. spectra. In each case the infrared spectrum showed total absence of carbonyl absorption. Bands attributable to symmetric and asymmetric deformation of the methyl group were present. The proton n.m.r. spectra showed two resonances in the ratio of 3:1.

Only one oxetane is possible from tetrafluoroethylene, namely 2H-2-methyltetrafluorooxetane. Its F^{19} n.m.r. spectrum showed two approximately equal resonances both of which exhibited a typical weak-strong-strong-weak (AB) pattern (see Table III). The high-field pattern showed doublet fine structure indicating proximity to a single spin-one-half nucleus (the single proton). The pronounced shift of the other CF_2 resonance to lower field indicates that that CF_2 group is adjacent to an oxygen.[4]

Two oxetanes are possible from 1,1-dichloro-2,2-difluoroethylene. Only one was obtained, and it was assigned the structure 2H-3,3-dichloro-4,4-difluoro-2-methyloxetane on the basis of the very low-field position of the CF_2 resonance.

From chlorotrifluoroethylene four oxetanes (two *cis–trans* pairs) are possible; only two were isolated. The striking similarity in their infrared spectra suggested that they were a *cis–trans* pair. The low-field position of the CF_2 resonance in the n.m.r. spectra of both compounds supported this assignment and indicated that they were isomers of 2H-3-chloro-2-methyltrifluorooxetane. The n.m.r. spectrum of the lower boiling isomer was too complex for complete analysis, but the large CH–CF coupling constant and the apparent lack of coupling between the CH_3 and CF groups in the higher boiling isomer indicated that the latter was the *cis* (with respect to the CH_3 and Cl groups) isomer. Harris and Coffman[4] also assigned the *cis* configuration to the higher boiling isomer of the four fluorooxetanes for which they isolated *cis* and *trans* isomers.

The mass spectra of the four oxetanes were consistent with the assigned structures. The primary cracking

(1) This work was performed under the auspices of the U. S. Atomic Energy Commission.

(2) J. D. LaZerte and R. J. Koshar, *J. Am. Chem. Soc.*, **77**, 910 (1955).

(3) H. Muramatsu and K. Inukai, *J. Org. Chem.*, **27**, 1572 (1962).

(4) J. F. Harris and D. D. Coffman, *J. Am. Chem. Soc.*, **84**, 1553 (1962).

(5) M. S. Kharasch, W. H. Urry, and B. M. Kuderna, *J. Org. Chem.*, **14**, 248 (1949).

(6) Each was in the order of 20–30%.

TABLE I

PHYSICAL PROPERTIES OF SOME HALOGENATED 3-BUTANONES AND HALOGENATED OXETANES

Compound	Yield,[a] %	Conversion, %	Density, g./ml./°C.	A[b]	B[b]	N.b.p., °C.	ΔH, cal./mole	TR[c]
$CH_3COCF_2CHF_2$	7.2	4.8	1.318/19	7.88437	1700.4	66.6	7396	21.8
CH_3COCF_2CHFCl	10.0[d]	7.3	1.355/23	7.81710	1819.6	95.4	7876	21.4
CH_3COCF_2CHFBr	20.3	11.9	1.694/25	7.87013	1937.1	115.1	8385	21.6
$CH_3COCF_2CHCl_2$	5.5	4.7	1.412/22	7.79801	1967.4	126.9	8489	21.2
$CH_3\overline{CHCF_2CF_2O}$	2.8	1.8	1.279/19			44		
$CH_3\overline{CHCFClCF_2O}$[e]	1.3	0.9	1.344/22	8.00664	1741.9	66.6	7525	22.1
$CH_3\overline{CHCFClCF_2O}$[f]	1.1	0.8	1.344/26	7.77109	1716.9	77.9	7578	21.6
$CH_3\overline{CHCCl_2CF_2O}$	2.1	1.8	1.395/23	7.78871	1877.7	109.4	8107	21.2

[a] For the reaction conditions reported in the Experimental section, based on olefin consumed. [b] A and B are the constants for the vapor pressure equation $\log P_{(mm\ Hg)} = A - B/T$ (°K.) in the range 300 to 800 mm. The vapor pressure curves and constants derived therefrom were obtained as previously described: E. R. Bissell, *J. Org. Chem.*, 26, 5100 (1961). [c] Trouton ratio. [d] 17.2% with a 2:1 ratio of acetaldehyde to olefin. [e] *trans*. [f] *cis*.

TABLE II

NUCLEAR MAGNETIC RESONANCE SPECTRA OF FLUORINATED METHYL ETHYL KETONES[a]

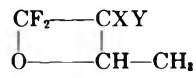
CH_2COCF_2CHXY

	X = F, Y = F	X = Cl, Y = F	X = Br, Y = F	X = Cl, Y = Cl
δ_{CH}	−0.70 T (T)	−1.45 D (Qa)	−2.00 D (Qa)	−1.23 T (S)
δ_{CH_2}	+2.95 S (T)	+2.65 T (D)	+2.43 S (T)	+2.45 S (T)
δ_{CF}		+79.63 D (T)	+82.20 D (T)	
δ_{CF_2}	+48.90 S (C)[b]	+44.13 } AB (C)	+41.28 } AB (Qa)	+35.73 D (Qi)
	+62.23 D (T)[c]	+40.63 }	+37.08 }	
$J_{CH,CF}$		47.5	45.2	
J_{CH,CF_2}	52.3,[c] 9.8[b]	8.9, 7.3[d]	10.2, 7.6[d]	10.2
$J_{CH_2,CF}$		~0.5	~0	
J_{CH_2,CF_2}		~2	1.9	1.7
J_{CF,CF_2}		14.3	17.4	
J_{CF_2,CF_2}[e]		276	282	

[a] Chemical shifts are given in p.p.m., coupling constants in c.p.s. measured at 40 Mc. Proton shifts are with respect to external water; and F^{19} shifts are with respect to external hexafluoroacetone. The symbols following the chemical shifts give the structure of the band with fine structures given in parentheses: S, singlet; D, doublet; T, triplet; Qa, quartet; Qi, quintet; AB, weak-strong-strong-weak four-line spectrum typical of a CA_2 grouping where the two A nuclei are chemically nonequivalent; C, complex and/or not completely resolved. The authors are indebted to James A. Happe for measurement of the n.m.r. spectra. [b] For the CF_2 adjacent to the carbonyl group. [c] For the terminal CF_2 group. [d] The two fluorines of the CF_2 group are chemically nonequivalent, hence have different coupling constants. [e] J_{CF_2,CF_2} is the coupling constant between the two nonequivalent fluorine atoms of the CF_2 group.

TABLE III

NUCLEAR MAGNETIC RESONANCE SPECTRA OF FLUORINATED METHYL OXETANES[a]



	X = F, Y = F	X = Cl, Y = F[b]	X = Cl, Y = F[c]	X = Cl, Y = Cl
δ_{CH}	+0.28 Qi	0.0 Qi	0.0 Qi	−0.15 Qi (D)
δ_{CH_2}	+3.68 D	+3.50 D	+3.45 D	+3.25 D
δ_{CF}			+42.75	
δ_{CF_2}	+4.58 } AB (C)[d]	−4.28 AB[e]	+1.95 } AB	−8.85 } AB
	+0.93 }		−8.45 }	−13.28 }
	+53.05 } AB (D)[f]			
	+41.55 }			
J_{CH,CH_2}	6.8		6.2	6.3
$J_{CH,CF}$			13.5	
J_{CH,CF_2}	9.3[f]		5.4, 0.9	6.6, 0.8
J_{CH_2,CF_2}			0.9, 0.2	
J_{CF,CF_2}			9.2, 4.0	
J_{CF_2,CF_2}	104[d]	96.0	96.1	90.5
	205[f]			

[a] See Table II for explanation of symbols. [b] *trans*. [c] *cis*. [d] For the CF_2 group adjacent to the oxygen. [e] Average shift measured to the center of the AB spectrum. [f] For the CF_2 group adjacent to the carbon bearing the methyl group.

TABLE IV

YIELD AND CONVERSION OF HALOBUTANONE-3 AND HALOOXETANE FROM CHLOROTRIFLUOROETHYLENE UNDER VARIOUS CONDITIONS

Expt.	Ratio[a]	Pressure[b]	Temp., °C.	$t_{1/2}$[c]	% yield[d] Ketone	% yield[d] Oxetane[e]	% conversion Ketone	% conversion Oxetane[e]
1	1:1	0.79	23	295	10.0	2.4	7.3	1.7
2	1:1	0.79	21	200	5.9	2.3	5.3	2.0
3	2:1	0.79	21	210	17.2	2.6	12.6	1.9
4	1:2	0.79	20	260	6.1	2.5	4.4	1.8
5	1:1	0.53	22	265	5.5	1.3	4.6	1.1
6	1:1	0.79	55	150	11.5	1.7	8.7	1.3

[a] Mole ratio of acetaldehyde to chlorotrifluoroethylene. [b] Initial total pressure in atmospheres. [c] Time in minutes for pressure to fall to approximately one-half its initial value. The reaction was terminated at about this point except in expt. 2, which was run for 395 min. [d] Based on chlorotrifluoroethylene consumed. [e] Total of *cis* + *trans*. The ratio of *cis* to *trans* was 0.9 to 1.0 except in expt. 2 and 3 where it was about 1.6.

mode was cleavage to acetaldehyde and the olefin from which the oxetane was synthesized.

Experimental[7]

Materials.—Tetrafluoroethylene was prepared by the thermal depolymerization of polytetrafluoroethylene at 550–600° and about 10^{-6} atm. Acetaldehyde, chlorotrifluoroethylene, bromotrifluoroethylene, and 1,1-dichloro-2,2-difluoroethylene were commercial products used without further purification.

Reactions of Acetaldehyde with Fluoroolefins.—The reactor consisted of a 5-l. flask into which was inserted through a standard taper joint a water-cooled quartz well. A 100-w., high-pressure, mercury-vapor lamp[8] was suspended in the well at the center of the flask. Gaseous reactants were introduced through a vacuum manifold having a total volume of about 60 ml. and attached to a side arm on the reactor. Pressures were measured by means of a Wallace and Tiernan Type FA 145 precision dial manometer.[9] One of the reactants was introduced from a supply cylinder until the desired pressure was obtained. The second component of the reaction mixture was then introduced from a second supply cylinder until the desired total pressure was reached. The mixture was irradiated until the pressure had fallen to approximately half its initial value. This did not represent complete consumption of either component, but the yields of both ketone and oxetane actually decreased if the irradiation time was extended much further. Sizable quantities of high boiling telomeric materials accumulated in the bottom of the reactor. They were generally allowed to accumulate until a series of reactions was started with a different olefin at which time the reactor was disassembled for cleaning. The volatile portion of the reaction mixture was pumped from the reactor through an acetone–solid carbon dioxide-cooled trap and a liquid nitrogen-cooled trap in series. The contents of the two traps were measured either by weight or by PVT measurements, analyzed by v.l.p.c., and the major components isolated by preparative scale chromatography. Yields and conversions for several typical sets of reaction conditions for chlorotrifluoroethylene are given in Table IV. Yields and conversions for the other olefins under the same conditions as expt. 1 are given in Table I.

Chromatography.—Analyses employed a 0.25 in. × 3 m. stainless steel column packed with 35 g. of di-*n*-decyl phthalate (20 wt. %) on 42–60-mesh GC-22 Firebrick. Each purified component was checked for purity on this column and also on similar columns in which the partitioning liquid was Zonyl E-91[10] or nonylphenoxy(polyethoxy)ethanol. For isolation of samples for measurement of physical properties and spectra, the crude materials from the acetone–solid carbon dioxide-cooled trap were chromatographed in 0.5- to 2-ml. portions on $^3/_4$-, $^1/_2$-, or $^3/_8$-in. columns packed with the same materials as used for the analytical columns. The individually collected components were rechromatographed as often as necessary to remove all impurities. Since the larger diameter columns are much less efficient than the smaller diameter ones, they were used only for the initial separations. Purification was continued for each compound reported in Table I until all three analytical columns showed less than 0.1% total impurities.

1,1,2,2-Tetrafluorobutanone-3.—Major infrared absorption bands were at 3.32 (vw, CH stretch), 5.70 (s, C=O stretch), 7.01 (w, CH_3 asym. def.), 7.18 (m), 7.30 (m, CH_3 sym. def.), 8.00 (s, C=O), 8.80 (vs, CF), 9.47 (s, CF), 9.91 (w), 10.70 (w), and 12.10 (s) μ. The 2,4-dinitrophenylhydrazone melted at 108.2–109.2°.

Anal. Calcd. for $C_{10}H_8F_4N_4O_4$: C, 37.05; H, 2.49; N, 17.28. Found: C, 37.11; H, 2.30; N, 17.98.

1-Chloro-1,2,2-trifluorobutanone-3.—Major infrared absorption bands were located at 3.35 (vw, CH stretch), 5.70 (s, C=O stretch), 7.03 (m, CH_3 asym. def.), 7.30 (m, CH_3 sym. def.), 8.10 (s, C=O), 8.80 (s, CF), 9.04 (s, CF), 9.24 (s, CF), 9.46 (s, CF), 9.95 (w), 10.70 (w), 11.81 (s), 12.24 (s), and 12.68 (s) μ. The 2,4-dinitrophenylhydrazone melted at 102.9–103.5°.

Anal. Calcd. for $C_{10}H_8ClF_3N_4O_4$: C, 35.26; H, 2.37; N, 16.45. Found: C, 35.05; H, 2.22; N, 16.96.

1-Bromo-1,2,2-trifluorobutanone-3.—The crude reaction mixture from the addition of acetaldehyde to bromotrifluoroethylene was distilled at atmospheric pressure until the temperature at the head of a small Vigreux column reached about 30°. The residue was then chromatographed as described before to obtain the ketone. Major infrared absorption bands were at 3.40 (vw, CH stretch), 5.72 (s, C=O stretch), 7.06 (w, CH_3 asym. def.), 7.38 (m, CH_3 sym. def.), 8.14 (m, C=O), 8.85 (s, CF), 9.15 (vs, CF), 9.20 (vs, CF), 9.51 (m, CF), 9.97 (w), 10.75 (vw), 12.30 (w), 12.85 (vw), and 13.60 (m) μ. The 2,4-dinitrophenylhydrazone melted at 104.8–105.4°.

Anal. Calcd. for $C_{10}H_8BrF_3N_4O_4$: C, 31.19; H, 2.09; N, 14.65. Found: C, 30.95; H, 1.97; N, 15.10.

1,1-Dichloro-2,2-difluorobutanone-3.—Major infrared bands were at 3.37 (vw, CH stretch), 5.73 (s, C=O stretch), 7.08 (w, CH_3 asym. def.), 7.37 (m, CH_3 sym. def.), 8.03 (w, C=O), 8.21 (s, CF), 9.10 (s, CF), 9.51 (m, CF), 9.99 (m), 12.15 (s), 12.95 (m), and 13.35 (w) μ. The 2,4-dinitrophenylhydrazone melted at 126.0–126.8°.

Anal. Calcd. for $C_{10}H_8Cl_2F_2N_4O_4$: C, 33.63; H, 2.26; N, 15.69. Found: C, 33.41; H, 2.08; N, 16.01.

2H-2-Methyltetrafluorooxetane.—Major infrared absorption bands were at 3.40 (vw, CH stretch), 6.90 (w, CH_3 asym. def.), 7.13 (w, CH_3 sym. def.), 7.50 (vw), 7.75 (m), 8.10 (m), 8.47 (s, CF), 8.90 (w), 9.50 (sh), 9.60 (m), 9.68 (m), 10.38 (s), and 11.65 (w) μ.

***cis*-2H-3-Chloro-3,4,4-trifluoro-2-methyloxetane.**—Major infrared absorption bands were at 3.40 (vw, CH stretch), 6.93 (vw, CH_3 asym. def.), 7.30 (m, CH_3 sym. def.), 7.65 (m), 7.83 (s), 8.35 (sh), 8.58 (s, CF), 8.95 (m, CF), 9.40 (s), 10.35 (m), 10.70 (m), 11.53 (w), 14.00 (vw), and about 14.8 (vw) μ.

Anal. Calcd. for $C_4H_4ClF_3O$: C, 29.93; H, 2.51. Found: C, 29.93; H, 2.74.

***trans*-2H-3-Chloro-3,4,4-trifluoro-2-methyloxetane.**—Major infrared absorption bands were at 3.38 (w, CH stretch), 6.95 (w, CH_3 asym. def.), 7.30 (m, CH_3 sym. def.), 7.65 (m), 7.80 (s), 8.40 (s, CF), 8.60 (sh) (CF), 8.90 (m, CF), 9.40 (s), 9.60 (s), 10.20 (s), 10.72 (m), 11.60 (w), 13.50 (w), and about 15 (w) μ.

(7) Melting and boiling points are corrected. Infrared absorption spectra were obtained in the vapor state on a Perkin-Elmer Model 137 Infracord spectrometer; wave lengths are in microns (μ). 2,4-Dinitrophenylhydrazones were prepared by the method of R. L. Shriner and R. C. Fuson ["The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171] and were recrystallized to constant melting point from 95% ethanol; their analysis was performed by Robert Lim and Elinor R. Smathers. The elemental analyses of the oxetanes were performed by J. W. Frazer and R. Crawford [*Mikrochim. Acta*, **3**, 561 (1963)].

(8) Engelhard Hanovia, Inc., 100 Chestnut St., Newark 5, N. J., type SOL #608A-36 operated from a Hanovia #7654-1 reactive transformer.

(9) Wallace and Tiernan, Inc., 25 Main St., Belleville 9, N. J.

(10) E. I. du Pont de Nemours and Co., Inc., Organic Chemicals Department, Dyes and Chemicals Division, Wilmington 98, Del.

2H-3,3-Dichloro-4,4-difluoro-2-methyloxetane.—The molecular weight was determined chromatographically by means of a gas density balance,[11] using nitrogen and chlorodifluoromethane as carrier gases and 1,1-dichloro-2,2-difluorobutanone-3 as an internal reference, as 185 ± 10 (calcd. 177). Major infrared absorption bands were at 3.40 (vw, CH stretch), 6.95 (vw, CH_3 asym. def.), 7.35 (m, CH_3 sym. def.), 7.87 (vs), 8.45 (s, CF), 8.72 (s, CF), 9.15 (s, CF), 9.60 (s), 9.83 (s), 11.40 (s), and about 14 (vw) μ.

Anal. Calcd. for $C_4H_4Cl_2F_2O$: C, 27.15; H, 2.28. Found: C, 27.27; H, 2.46.

(11) A. Liberti, L. Conti, and V. Crescenzi, *Nature*, **178**, 1067 (1956).

Some Isomers of Chloroiodotrifluoroethane[1]

EUGENE R. BISSELL

Lawrence Radiation Laboratory, University of California, Livermore, California

Received July 1, 1963

The synthesis of 1-chloro-2-iodo-1,1,2-trifluoroethane (I) by the addition of iodine monochloride to trifluoroethylene was first reported in 1956 by Park, Seffl, and Lacher.[2] The reaction was considered to be unidirectional, producing only I. Haszeldine and Steele[3] have offered some spectroscopic evidence that the concentration in the product of the isomer produced by reverse addition, 2-chloro-1-iodo-1,1,2-trifluoroethane (II) could not be more than 5%. However, in view of the recent discovery[4,5] that, contrary to earlier reports, both of the possible isomers from the addition of iodine monochloride to chlorotrifluoroethylene are in fact formed and, since several other addition reactions to trifluoroethylene have been shown to be bidirectional,[3,6] it was of interest to reinvestigate the trifluoroethylene–iodine monochloride system using more modern analytical techniques.

2-Chloro-1-iodo-1,1,2-trifluoroethane (II) has been prepared by addition of hydrogen iodide to chlorotrifluoroethylene.[3,7] Its ultraviolet absorption maximum was reported, but no experimental details were given for the synthesis, and the yield[3] was not stated. We were able to obtain only about 11% yields by this method. The remaining isomers of chloroiodotrifluoroethane have not been reported.

The present paper reports the results of a study of the addition of iodine monochloride to trifluoroethylene in both the presence and absence of a liquid phase and the results of a study of the effect of ultraviolet light and various metal chloride catalysts on the reaction and reaction products. One of these catalysts has lead to the synthesis of a third chloroiodotrifluoroethane isomer, 1-chloro-1-iodo-2,2,2-trifluoroethane (III).

The progress of the addition reactions was followed by observing changes in total pressure as a function of time, and the final product distribution was determined by means of vapor liquid phase chromatography (v.l.p.c.). Table I presents the results of a number of typical experiments in which a liquid phase was present. V.l.p.c. showed that along with the primary addition product (I) there was formed a small amount of a second material, which was shown by ultraviolet infrared, and n.m.r. spectra and by dehydrohalogenation to chlorotrifluoroethylene to be II. Raising the reaction temperature resulted in a decreased reaction rate but, unlike the effect of similar changes in the chlorotrifluoroethylene–iodine monochloride system,[4] did not materially effect the ratio of isomers produced. The failure of ferric chloride to catalyze the reaction or to alter the isomer ratio was also in marked contrast to its action in the chlorotrifluoroethylene system.[4] Aluminum chloride, on the other hand, did behave similarly in both systems. Stannic chloride appeared to be without effect.

The addition of iodine monochloride to trifluoroethylene was light catalyzed. Although the reaction was only slightly retarded in the dark if a liquid phase was present, it failed to occur at all in the dark if the reactants were completely in the vapor phase. Under these conditions reaction did occur in the light but at a much lower rate than when a liquid phase was present, and much larger amounts of II (26–36%) were formed.

In addition to its isolation as a by-product in the direct addition of iodine monochloride to trifluoroethylene, II was obtained from I by irradiation with ultraviolet light.[5] An equilibrium mixture containing 26–29% II was formed by irradiation of either I or II in the gas phase at room temperature.

Modification of the addition reaction by means of aluminum chloride resulted in the formation of two new compounds, III and 1-iodo-1,2,2,2-tetrafluoroethane (IV). Results for two typical small scale experiments are given in Table I (expt. 12 and 13), those for a larger scale experiment in the Experimental section. Compound III could be prepared more conveniently by treatment of I with aluminum chloride. Table II presents the results of several such experiments. The reaction was strongly exothermic, and yields decreased as the scale of the reaction was increased. However, if the temperature excursion was modified too much the reaction did not occur; for example, when I was added slowly under reflux to solid anhydrous aluminum chloride only 7–14% yields of III were obtained. The identities of III and IV were established by their ultraviolet, infrared, and n.m.r. spectra, by physical properties, and by their failure to dehydrohalogenate on treatment with bases. IV was identical with the product isolated from the addition of fluorine (from lead tetrafluoride) to 1,1-difluoro-2-iodoethylene.[8]

Reaction Mechanism.—The reaction conditions involving vapor phase and light catalysis are conditions generally associated with free-radical reactions, and the observed product distribution is in agreement with the observation of Haszeldine and Steel[3] that free-radical attack on trifluoroethylene is 60–80% on the CHF group and 20–40% on the CF_2 group. The fact that the isomer ratio is radically different when a liquid phase is present suggests a different mechanism under these conditions. That this mechanism is ionic, as originally proposed by Haszeldine and Steel,[3]

(1) This work was performed under the auspices of the U. S. Atomic Energy Commission.

(2) J. D. Park, R. J. Seffl, and J. R. Lacher, *J. Am. Chem. Soc.*, **78**, 59 (1956).

(3) R. N. Haszeldine and B. R. Steele, *J. Chem. Soc.*, 2800 (1957).

(4) M. Hauptschein, M. Braid, and A. H. Fainberg, *J. Am. Chem. Soc.*, **83**, 2495 (1961).

(5) E. R. Bissell and G. C. Shaw, *J. Org. Chem.*, **27**, 1482 (1962).

(6) A. T. Coscia, *ibid.*, **26**, 2995 (1961).

(7) R. N. Haszeldine and J. E. Osborne, *J. Chem. Soc.*, 61 (1956).

(8) E. R. Bissell and D. B. Fields, unpublished results.

TABLE I

ADDITION OF IODINE MONOCHLORIDE TO TRIFLUOROETHYLENE IN THE PRESENCE OF A LIQUID PHASE

Expt.	Temp., °C.	Catalyst	Mole %	$t_{1/2}$[a]	Product distribution[b] % I	% II	% III	% IV
1	20–22			2.8	91.5	1.6	Trace	
2	38–40			4.0	95.0	1.9	Trace	
3	50–52			7.7	90.8	2.4	1.0	
4	60–65			24	88.3	3.7		
5	70–72			50	92.8	2.5		
6	21–24	Ultraviolet[c]		1.9	90.0	3.7		
7	22–26	Dark		5.5	91.6	2.6		
8	48–52	Dark		12.5	88.3	3.2		
9	20–22	$FeCl_3$	5	2.7	90.9	3.1		0.2
10	35–40	$FeCl_3$	2	3.8	87.6	3.0		3.3
11	38–42	$FeCl_3$	4	7.5	91.9	2.0	1.7	
12	18–21	$AlCl_3$	9	4.0	78.9	3.9	2.6	4.2
13	27–29	$AlCl_3$	12	8.5	71.7		3.9	9.6

[a] Time in minutes for the pressure to fall to the arithmetic average of the initial and final pressures. [b] $CF_2ClCHFCl$ (2–9%) and smaller amounts of several other unidentified by-products also were formed. [c] Ultraviolet light was supplied by a Bausch and Lomb type 33-45-65 mercury arc. Unless otherwise specified the reactions were carried out in the presence of ordinary fluorescent room lights.

TABLE II

TREATMENT OF 1-CHLORO-2-IODO-1,1,2-TRIFLUOROETHANE WITH ALUMINUM CHLORIDE

Expt.	Temp., °C.	$AlCl_3$/I, g./g.	Time, hr.	% organic recovery	Product distribution % I	% II	% III	% IV
1	21–23	0.11	23	50	12.2	1.5	55.7	2.9
2	21–23	0.12	17	50	11.4	2.7	60.5	2.5
3	21–23	0.12	8	60	28.9	6.2	44.1	1.6
4	0	0.11	24	50	46.3	1.3	30.1	2.2

seems unlikely in view of the bidirectional nature of the addition of iodine monochloride to chlorotrifluoroethylene even in the presence of a liquid phase.[4,5] The mechanism of addition to the two olefins would be expected to be the same, and ionic addition reactions have thus far been found to occur in only one direction. An alternate possible mechanism is the initial formation of a complex between the π-electrons of the olefin and iodine monochloride which subsequently is attacked by a second molecule of iodine monochloride. Such a π-complex was postulated by White and Robertson[9] to account for their observation that the rate of addition of bromine, iodine, iodine monochloride, and iodine monobromide to hydrocarbon olefins was second order with respect to the halogen. The difference in isomer ratio between trifluoroethylene and chlorotrifluoroethylene then would be attributed to differences in the electronic and/or steric nature of the olefins.

The ultraviolet equilibration of I and II probably proceeds through reversal of the iodine monochloride addition followed by readdition under free-radical conditions.

Experimental[10]

Addition of Iodine Monochloride to Trifluoroethylene. A. In the Presence of a Liquid Phase.—Iodine monochloride (0.25 ml., 0.80 g., 0.0049 mole) and the catalyst, if any, were placed in a 35-ml. Florence flask which was attached to a vacuum manifold by means of a ground glass joint. The flask was immersed in liquid nitrogen and evacuated to a pressure of 10^{-6} atm. The reactor was then isolated from the manifold and warmed to the desired reaction temperature by means of an oil bath. Agitation was provided by a magnetically driven stirring bar. The reaction was initiated by opening a stopcock connecting the reactor to a 1100-ml. reservoir containing trifluoroethylene (initially at room temperature and approximately 0.92 atm.) and was followed by periodic observation of the total pressure. After the pressure had essentially become constant the reactor was disconnected from the reservoir, and its contents were vaporized through a 10-mm. i.d. by 20-cm. column packed with 1.6-mm. 5-Å. Molecular Sieve pellets.[11] Material passing the Molecular Sieve column was trapped at liquid nitrogen temperature and analyzed by v.l.p.c. Reactions also were carried out on an 0.1-mole scale in a Parr low pressure hydrogenation apparatus. A typical experiment yielded 14–15 g. of liquid halocarbons containing 87–90% I. Preparative scale chromatography yielded pure I, n.b.p. 84.9°, log P_{mm} = 7.56346 − 1676.7/T°K, ΔH 7282 cal./mole, Trouton ratio 20.3, $d_{22.5}$ 2.180 g./cc., ultraviolet λ_{max} 265 mμ (ϵ_{max} 295). The n.m.r. spectrum showed one CH resonance at −2.30, one CF resonance at −15.03, and one CF_2 resonance (AB_2 type) at +82.9 and +78.6 p.p.m.. The following coupling constants were determined: $J_{CH.CF}$ 43, $J_{CH.CF_2}$ 7.7 and 5.5, $J_{CF.CF_2}$ 23.2 and 22.2, and J_{CF_2} 159 c.p.s. Major infrared absorption bands were at 3.40 (vw), 7.52 (m), 8.22 (s), 8.77 (vs), 9.05 (s), 9.20 (s), 9.60 (s), 10.20 (vs), 12.30 (m), 13.05 (s), 13.45 (m), and 14.50 (w) μ.

B. In the Vapor Phase.—Iodine monochloride (25 μl., 81 mg., 0.0005 mole) was frozen by means of liquid nitrogen in a small side arm attached to a 5000-ml. round-bottomed flask which was then evacuated to a pressure of 10^{-6} atm. The flask was then isolated from the vacuum manifold, and the iodine monochloride was vaporized into it. An equimolar amount of trifluoroethylene was added from a reservoir of known volume. After 24 hr. at room temperature the reaction mixture was worked up as described previously.

(9) E. P. White and P. W. Robertson, *J. Chem. Soc.*, 1509 (1939).

(10) The vapor pressure equations and constants derived therefrom were obtained as previously described [E. R. Bissell, *J. Org. Chem.*, **26**, 5100 (1961)]. Infrared absorption bands were measured in the vapor phase on a Perkin-Elmer Model 137 Infracord spectrometer and are reported in microns. Ultraviolet absorption spectra were taken in methylcyclohexane solution on a Cary recording spectrophotometer. N.m.r. spectra were measured at 40 Mc. Proton chemical shifts are quoted with respect to external water; F^{19} shifts with respect to external hexafluoroacetone. The author is indebted to James A. Happe for these measurements. Chromatographic analyses employed 6 25-mm. o.d. by 4-m. copper columns packed with 20 wt. % nonylphenoxy(polyethoxy)ethanol on 42–60-mesh GC-22 firebrick and operated at 78–80°.

(11) Linde Air Products Co., 30 East 42nd St., New York 17, N. Y.

2-Chloro-1-iodo-1,1,2-trifluoroethane (II) by Ultraviolet Light-Catalyzed Isomerization of I.—Isomerization was carried out in a 5000-ml. Pyrex reactor. The light source was a 100-w. mercury-vapor lamp[12] centrally located in a water-cooled quartz well. The reactor was surrounded by an aluminum can which was wrapped with heating tapes for the experiments above room temperatures. Samples (2.0 ml.) were introduced into the evacuated reactor as liquids by means of a hypodermic syringe through a rubber septum which could be isolated from the flask by a stopcock through which the syringe needle could be inserted. The reaction mixture was removed after irradiation by pumping it through a 25-mm. i.d. by 75-cm. column filled with 1.6-mm. 5-Å. Molecular Sieve pellets.[11] Material passing through the column was condensed in a liquid nitrogen-cooled trap. Total recovery amounted to 85–90%. After irradiation for 1 hr. at room temperature the recovered halocarbons contained 86% I and 13% II, after 3 hr. 72% I and 26% II, after 3 hr. at 65–70° 76% I and 18% II. When the sample size was reduced to 1.0 ml. the recovered material contained 66% I and 26% II. Insertion of a Pyrex sleeve between the lamp and the quartz well completely prevented isomerization. Preparative scale chromatography was employed to obtain pure II which had the following physical properties: n.b.p. 85.4°, $\log P_{mm} = 7.66157 - 1714.2/T°_K$, ΔH 7448 cal./mole, Trouton ratio 20.8, d_{23} 2.185 g./cc., ultraviolet λ_{max} 270 mμ (ϵ_{max} 307). The n.m.r. spectrum showed one CH resonance at −1.20, one CF resonance at −21.5, and one CF_2 resonance (AB_2 type) at +63.4 and +61.3 p.p.m. The following coupling constants were measured: $J_{CH.CF}$ 48, $J_{CH.CF_2}$ 5.8 and 4.0, $J_{CF.CF_2}$ 21.7 and 20.9, and J_{CF_2} 191 c.p.s. Major infrared absorption bands were at 3.32 (w), 7.52 (m), 7.90 (w), 8.26 (s), 8.60 (sh), 8.80 (vs), 9.08 (s), 9.65 (vs), 10.50 (s), 11.70 (s), 12.00 (sh), 12.60 (m), and 13.55 (vs) μ.

1-Chloro-1-iodo-2,2,2-trifluoroethane (III) by Treatment of I with Aluminum Chloride.—I (1.0 ml., 2.18 g., 0.009 mole) and 0.25 g. (0.0019 mole) of anhydrous aluminum chloride were sealed in an evacuated Pyrex ampoule of about 10-ml. capacity. The ampoule was stored in the dark at the desired reaction temperature (see Table II) for 8 to 24 hr. The ampoule was then opened, and any volatile material in it was vaporized at room temperature and 10^{-6} atm. through a 10-mm. i.d. by 10-cm. bed of 5-Å. Molecular Sieve[11] and condensed in a liquid nitrogen-cooled trap. Pure III was obtained by preparative scale chromatography and had the following properties: n.b.p. 83.5°, $\log P_{mm} = 7.58749 - 1678.7/T°_K$, ΔH 7284 cal./mole, Trouton ratio 20.4, d_{23} 2.210 g./cc., ultraviolet λ_{max} 275.5 mμ (ϵ_{max} 418). The n.m.r. spectrum showed one CH resonance at −1.30 and one CF_3 resonance at −4.50 p.p.m. The coupling constant between the CH and CF_3 groups was 6.2 c.p.s. Major infrared absorption bands were at 3.32 (w), 7.20 (s), 7.92 (vs), 8.40 (s), 8.62 (s), 9.05 (vs), 11.50/11.60 (m), 12.40 (s), and 15.00 (m) μ.

Addition of Hydrogen Iodide to Chlorotrifluoroethylene.—Chlorotrifluoroethylene (0.011 mole) and hydrogen iodide (0.016 mole) were condensed by means of liquid nitrogen into a 25-ml. stainless steel pressure vessel. After 26 days at ambient temperature the contents of the bomb were vaporized through a small Molecular Sieve[11] bed into a liquid nitrogen-cooled trap. The most volatile portion of the material held by the trap was pumped off until the remaining liquid had a vapor pressure of about 300 mm. at 23°. This liquid weighed 0.31 g. and contained 94.9% II by v.l.p.c. analysis.

1-Iodo-1,2,2,2-tetrafluoroethane (IV).—Pure IV was isolated by preparative scale chromatography from the volatile impurities produced in the preparation of III by treatment of I with anhydrous aluminum chloride, n.b.p. 39.4°, $\log P_{mm} = 7.55172 - 1460.1/T°_K$, ΔH 6406 cal./mole, Trouton ratio 20.5, molecular weight (by PVT) 230 (theory 228), ultraviolet λ_{max} 262 mμ (ϵ_{max} 306). The n.m.r. spectrum showed one CH resonance at −5.35, one CF resonance at +90.9, and one CF_3 resonance at +0.88 p.p.m. The following coupling constants were measured: $J_{CH.CF}$ 46, $J_{CH.CF_3}$ 5.6, and J_{CF,CF_3} 16.7 c.p.s. Major infrared absorption bands were at 3.40 (w), 7.40 (m), 7.82 (vs), 8.10 (m), 8.85 (vs), 9.20 (vs), 10.15 (w), 11.55 (s), and 14.30 (s) μ.

(12) Engelhard Hanovia, Inc., 100 Chestnut St., Newark 5, N. J., type Sol #608A-36 operated from a Hanovia #7654-1 reactive transformer was used.

Rearrangement of Hydroperoxide Salts in the Oxidation of α-Trialkysilyl Organometallic Compounds[1]

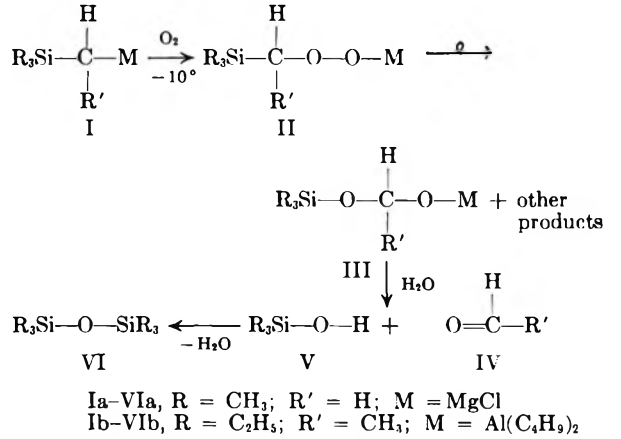
JOHN J. EISCH AND G. RONALD HUSK

Department of Chemistry, University of Michigan, Ann Arbor, Michigan

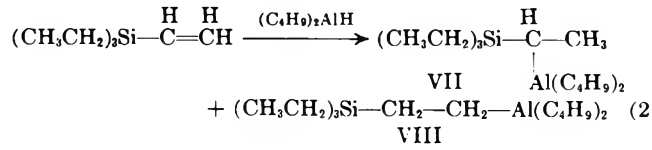
Received May 23, 1963

The ready oxidation of a wide variety of metal alkyls to form metal alkoxides by molecular oxygen has been shown to proceed *via* hydroperoxide salt intermediates, R–O–O–M.[2] However, despite the metalloid character of silicon, tetralkylsilanes, such as $(CH_3)_4Si$, are very resistant to the atmospheric oxidation of their carbon–silicon bonds.[3] Therefore, it was of interest to observe an extremely facile oxidation of carbon–silicon linkages when α-trialkylsilyl organometallic compounds (I) were subjected to air oxidation under very mild conditions. Thus, the air oxidation of trimethylsilylmethylmagnesium chloride (Ia) at −10° gave, upon hydrolysis, the expected alcohol, trimethylsilylmethanol, together with large amounts of trimethylsilanol (Va), hexamethyldisiloxane (VIa), formaldehyde (IVa), and higher siloxanes (Chart I). In a similar fashion, the

CHART I



addition products of triethylvinylsilane and diisobutylaluminum hydride (VII and VIII, eq. 2) underwent air oxidation to yield only minor amounts of the expected alcohols, 1-triethylsilylethanol and 2-triethylsilylethanol, respectively. Instead, triethylsilanol (Vb), hexaethyldisiloxane (VIb), and higher siloxanes were obtained as the principal oxidation products (Chart I). Since the relative proportion of adduct VII to adduct



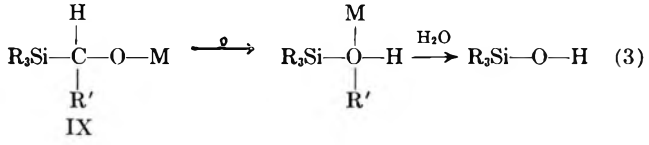
(1) Paper III in the series: Organosilicon Compounds with Functional Groups Proximate to Silicon. Previous papers: *J. Org. Chem.*, **28**, 487, 2870 (1963).

(2) *Cf.* (a) A. G. Davies, "Organic Peroxides," Butterworths Scientific Publications, London, England, 1961, pp. 120–126, 155–160; (b) H. Hock, H. Kropf, and F. Ernst, *Angew. Chem.*, **71**, 541 (1959).

(3) C. Eaborn, "Organosilicon Compounds," Academic Press Inc., New York, N. Y., 1960, pp. 123–124.

VIII formed according to eq. 2 has been shown to be 70:30,[4] the oxidation products arose principally from attack on the α-triethylsilyl isomer VII.

To rule out the possibility that carbon–silicon bond cleavage might have occurred in a reaction other than the oxidation process itself, the following control experiments were conducted. First, assurance that no cleavage had taken place during the preparation of the organometallic reagents themselves (Ia, VII, and VIII) was gained by the hydrolysis of aliquots. Only tetramethylsilane and tetraethylsilane were obtained from the respective organometallic systems. Secondly, the metal alkoxides (IX) expected to result upon the oxidation of I, VII, and VIII were prepared independently from the known alcohols and were shown not to undergo readily the rearrangement shown in eq. 3.[5] Thirdly,



(3)

IX

the alkoxide IX (R = CH_3, R′ = H, M = MgCl) was shown not to react significantly with molecular oxygen when subjected to the oxidation procedure.[6a]

In view of the foregoing observations, the prompt oxidation of carbon–silicon bonds in α-trialkylsilylorganometallic systems can arise reasonably from the formation[2] and rearrangement of the intermediate hydroperoxide salt (II → III, eq. 1).[6b] Although the production of higher molecular weight siloxanes indicates that the decomposition of II can pursue more than one course, the scheme portrayed in Chart I is consonant with the unexpected oxidation products observed with both organometallic compounds. This novel peroxide rearrangement in organosilicon chemistry[6c] finds its formal counterpart in the well known acid-catalyzed rearrangement of cumyl hydroperoxide to yield phenol and acetone.[7] Further support for the rearrangement pathway shown in eq. 1 is found in the fact that other oxidations which avoid the formation of II apparently proceed without carbon–silicon bond scission. For example, the oxidation of tris(trimethylsilylmethyl)borane (I, R = CH_3; R′ = H; M = BR_2') and of the hydroboration products from trimethylvinylsilane by means of hydrogen peroxide in alkaline solution takes place normally to yield the expected alcohols.[8]

Finally, as a consequence of the oxidative lability of carbon–silicon bonds in systems such as VII and VIII, air oxidation of the metal hydride adducts of vinylmetalloid systems and the isolation of the corresponding isomeric alcohols is not, in general, a reliable method for determining the mode of addition of metal hydrides to the alkenyl linkage.[4,9]

(4) The mixture of adducts resulting from the hydride addition has been hydrolyzed with deuterium oxide and the resulting isomeric mixture of monodeuterated tetraethylsilanes has been analyzed by n.m.r. spectroscopy (uncertainty = ±6%): J. J. Eisch and G. R. Husk, unpublished studies.

(5) *Cf.* A. G. Brook, *J. Am. Chem. Soc.*, **80**, 1886 (1958).

(6) (a) A referee has suggested that the observed silicon–carbon bond oxidation may arise from the thermal- or acid-catalyzed decomposition of the free hydroperoxide (II, M = H) obtained upon hydrolytic work-up. However, hydrolyzed samples of the oxidized organometallic solution (I) failed to give a positive test for the presence of peroxides in the potassium iodide–starch procedure. Therefore, significant amounts of II did not survive until the hydrolysis step. (b) Whether the hydroperoxide salt in Chart II decomposes via a polar or a free-radical pathway is undetermined. (c) *Cf.* E. Buncel and A. G. Davies, *J. Chem. Soc.*, 1550 (1958), for the reaction of trimethylchlorosilane with perbenzoic acid. The postulated trimethylsilyl perbenzoate is thought to rearrange to give the observed product, dimethylmethoxysilyl benzoate.

(7) B. Barnett, E. R. Bell, F. H. Dickey, F. F. Rust, and W. E. Vaughan; *Ind. Eng. Chem.*, **41**, 2612 (1949).

(8) D. Seyferth, *J. Am. Chem. Soc.*, **81**, 1844 (1959).

Experimental

Starting Materials and General Procedures.—The chloromethyltrimethylsilane was obtained from the Peninsular Chemical Co., Gainesville, Florida. The triethylvinylsilane was prepared according to a published procedure.[10] The diisobutylaluminum hydride was synthesized from triisobutylaluminum by the thermal elimination of isobutene[11] and the subsequent distillation of the resulting hydride, b.p. 96–106° (0.1 mm.).

All organometallic reactions were conducted under an atmosphere of dry, oxygen-free nitrogen. The glass apparatus employed was dried beforehand at 200° for several hours and then heated under vacuum after assembly. All reactions solvents were anhydrous, reagent-grade chemicals.

The composition of liquid products was determined by means of a Barber-Colman gas chromatography apparatus, Model 10, with an ionization detector system. The chromatography column consisted of 30% silicone oil on a firebrick support. Infrared spectra were recorded with a Perkin-Elmer infrared spectrophotometer, Model 21, on liquid film samples.

Synthesis of Oxidation Products. A. Known Compounds.—Trimethylsilylmethanol was obtained in two steps from chloromethyltrimethylsilane.[12] Refluxing chlorotrimethylsilane with water provided hexamethyldisiloxane.[13] On the other hand, treatment of chlorotrimethylsilane with ammonia in ether yielded hexamethyldisilazane, which gave upon mild acid hydrolysis trimethylsilanol.[14]

B. New Compounds. 1-Triethylsilylethanol.—Although previously reported in the literature,[15] this isomer was prepared in the pure state for the first time by a two-step procedure[4] starting from 1-(triethylsilyl)bromoethane.[16] The bromo compound was treated with silver acetate in hot benzene to produce 1-(triethylsilyl)ethyl acetate and the latter was reduced with lithium aluminum hydride to yield 1-triethylsilylethanol, b.p. 122° (80 mm.), $n^{25}D$ 1.4485.[4]

2-Triethylsilylethanol.—This previously unreported isomer was synthesized by the chloroplatinic acid-catalyzed addition of trichlorosilane to vinyl acetate to provide 2-trichlorosilylethyl acetate and the treatment of the latter compound with excess ethylmagnesium bromide.[4] The resulting 2-triethylsilylethanol boiled at 112° (11 mm.), $n^{25}D$ 1.4510.

Oxidation of Trialkylsilyl Organometallic Compounds. A. Trimethylsilylmethylmagnesium Chloride.—The Grignard reagent was prepared from chloromethyltrimethylsilane and magnesium turnings in anhydrous ethyl ether without any initiator. To ascertain whether any silicon–carbon bond cleavage had occurred during the preparation, a filtered solution of the Grignard reagent was allowed to stand under a nitrogen atmosphere for 20 hr. at room temperature. Usual hydrolytic work-up and vapor phase chromatographic analysis revealed the presence of tetramethylsilane and ether. The former constituted 99.3% of the silicon-containing products; only 0.7% of two unidentified components was detected.

The oxidation of 0.16 mole of the Grignard reagent in 100 ml. of ether solution was conducted in a three-necked, round-bottomed flask fitted with a gas inlet and stirrer, and situated in an ice–sodium chloride cooling bath (−10°). Dry oxygen was introduced at such a rate that no bubbling occurred at the mercury

(9) *Cf.* L. T. Zakharkin and L. A. Savena, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 253 (1962).

(10) R. Nagel and H. W. Post, *J. Org. Chem.*, **17**, 1379 (1952).

(11) K. Ziegler, H.-G. Gellert, H. Lehmkuhl, W. Pfohl, and K. Zosel, *Ann.*, **629**, 11 (1960).

(12) J. L. Speier, B. F. Daubert, and R. R. McGregor, *J. Am. Chem. Soc.*, **70**, 1117 (1948).

(13) R. O. Sauer, *ibid.*, **66**, 1707 (1944).

(14) M. F. Shostakovsky, D. A. Kochkin, I. A. Shikhaev, and V. M. Vlasov, *J. Gen. Chem. USSR*, 622 (1955).

(15) (a) C. Friedel and J. M. Crafts, *Ann.*, **138**, 19 (1866); (b) E. Niedzielski, *J. Am. Chem. Soc.*, **62**, 3519 (1940).

(16) E. Larson and L. Knopp, *Acta Chem. Scand.*, **1**, 268 (1947); *Trans. Chalmers Univ. Technol. Gothenberg*, **79**, 7 (1948); *Chem. Abstr.*, **43**, 2929 (1949).

exit bubbler surmounted on the condenser. After an hour oxygen was no longer absorbed by the system and a white precipitate was present in the reaction mixture. With a slow stream of oxygen passing through the system, the reaction mixture was allowed to come to room temperature over a 6-hr. period and maintained there for an additional 6 hr. Hydrolysis of an aliquot and the addition of the potassium iodide–acetic acid reagent gave a negative peroxide test. The suspension was then hydrolyzed with ammonium chloride solution and the separated ether extract was dried over anhydrous calcium sulfate. By means of vapor phase chromatographic analysis of the ether extract and comparison with the retention times and infrared spectra of authentic samples, the following product distribution (mole %) was determined: trimethylsilylmethanol (60), hexamethyldisiloxane (17), unknown A (15), unknown B (3.1), tetramethylsilane (2.7), and trimethylsilanol (2.3). The infrared spectra of unknowns A and B indicated them to be higher molecular weight hydroxyl siloxanes (bands at 1040–1060 and 3400 cm.$^{-1}$).

The acidified aqueous extract from the reaction mixture work-up was treated with a solution of 5,5-dimethyl-1,3-cyclohexanedione in alcohol. The colorless precipitate was collected and recrystallized from alcohol. The dimedone derivative melted at 189–190° and did not depress the melting point of an authentic sample of the dimedone derivative of formaldehyde (m.p. 189–190°).

B. **The Adduct of Triethylvinylsilane and Diisobutylaluminum Hydride.**—A three-necked, round-bottomed flask, equipped with a pressure-equalized addition funnel, stirrer, and gas-inlet tube and maintained under a nitrogen atmosphere, was charged with 20.0 g. (0.144 mole) of diisobutylaluminum hydride. After the hydride had been heated to 75°, the triethylvinylsilane (19.2 g., 0.134 mole) was added dropwise over a period of 30 min. The colorless mixture was stirred for an additional 3.25 hr. and then cooled to 0°. The mixture was hydrolyzed cautiously by the dropwise addition of water. After gas evolution had ceased, 6 *N* sulfuric acid was added to dissolve the aluminum hydroxide. The mixture was extracted with ether and the organic layer was washed with sodium bicarbonate solution and with water. The dried ether extract was freed of ether by fractional distillation to yield 18.4 g. (95%) of product. This was shown to be pure tetraethylsilane by v.p.c. and infrared spectral examination. No evidence for the presence of residual vinyl compound or of higher boiling dimers could be obtained.

In a run similar to the foregoing, the resulting organoaluminum adduct was diluted with 100 ml. of pure, dry hexane and cooled in an ice bath. Dry air (previously passed through two drying tubes filled with Linde Molecular Sieves and one tube charged with Ascarite) was passed over the surface of the stirred organoaluminum solution. The temperature was slowly raised to 55° over the total oxidation period of 8 hr. The cooled solution was then treated with ammonium chloride solution and the resulting suspension filtered from the aluminum hydroxide. The hydrocarbon layer was dried and then fractionally distilled to remove the hexane and isobutyl alcohol. The total yield of residue, based upon the calculated yield of alcohols, was 71%. Of this, 30% proved to be a 5.3:2.1:1.0 mixture of triethylsilanol (identified by elemental (Found: C, 54.27; H, 12.22.) and infrared spectral analyses), 1-triethylsilylethanol, and 2-triethylsilylethanol, and 70% was shown to be a mixture of hexaethyldisiloxane and higher molecular weight, carbonyl-containing hydroxyl siloxanes by infrared examination: prominent bands at 3400 and 1030–1100 cm.$^{-1}$ and modest bands at 1730–1750 cm.$^{-1}$.

Attempted Rearrangements. A. Trimethylsilylmethanol.—Assurance that the magnesium salt of trimethylsilylmethanol was not undergoing rearrangement or oxidation, leading to carbon–silicon bond cleavage, was obtained by treating the alcohol with ethylmagnesium chloride in ether. The resulting suspension was stirred for 20 hr. under nitrogen. Subsequent hydrolytic work-up gave only the unchanged alcohol.

Passage of oxygen gas through an ether suspension of trimethylsilylmethoxymagnesium chloride for 12 hr. gave upon work-up trimethylsilylmethanol containing only 0.6% of hexamethyldisiloxane.

B. **(Triethylsilyl)ethanol.**—Treatment of the two isomeric alcohols individually with triisobutylaluminum in hexane solution yielded the respective aluminum alkoxides. Subsequent hydrolytic work-up allowed the pure alcohols to be recovered unchanged.

Acknowledgment.—The foregoing research was supported by the Petroleum Research Fund of the American Chemical Society under Grant No. 723-A and the authors wish to express their appreciation to the Donors of this Fund.