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A Convenient General Method for the Preparation of Aldehydes

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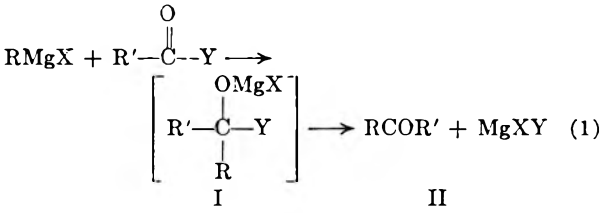
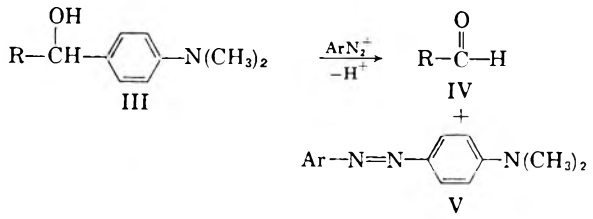
Ten aldehydes from both the aromatic and aliphatic series have been prepared by a two-step scheme. The crucial step in this scheme is the cleavage of an α-substituted *p*-dimethylaminobenzyl alcohol (III) by diazotized sulfanilic acid (Equation 2). The intermediate aminocarbinols are prepared from Grignard reagents and *p*-dimethylaminobenzaldehyde; the latter compound thus furnishes the formyl group in the final product.

The synthesis of aldehydes and ketones by reactions involving organometallic reagents is sharply limited because of attack of the reagent upon the product. Thus the scheme of Equation 1 involving a Grignard reagent succeeds only if the intermediate (I) is sufficiently stable so that the carbonyl product (II) is not produced in the presence of the Grignard reagent, or if the product is itself unreactive toward the reagent because of special structural features such as steric hindrance.[1]



The preparation of methyl ketones from a Grignard reagent and acetic anhydride at low temperatures[2] is a useful technique based on the former principle, as is the reaction of the Grignard reagent with amides and nitriles.[1] The difficulties inherent in Equation 1 can also be surmounted by the use of organocadmium and organozinc reagents[1,3] which do not attack ketones readily. This paper reports a general method for the preparation of aldehydes by a scheme analogous to Equation 1, in which the free carbinol corresponding to I (R′ = H;Y = *p*-dimethylaminophenyl) is prepared and cleaved in a separate step. The technique has proved to be a convenient one for preparing small to moderate quantities of aldehydes in good yield and high purity.

The success of the method rests upon the ease with which *p*-dimethylaminophenylcarbinols (III) are cleaved by electrophilic reagents such as diazonium salts (Equation 2).



This type of cleavage reaction was observed by Quilico and Freri[4] who showed that treatment of 4,4′-bis(dimethylamino)benzhydrol [III, R = *p*-$C_6H_4N(CH_3)_2$] with *p*-nitrobenzenediazonium sulfate produced the azobenzene (V, Ar = *p*-nitrophenyl). Ziegler and his collaborators identified benzaldehyde as a product of reaction of leuco-Malachite Green with *p*-nitrobenzenediazonium chloride[5] and also showed that a number of different *para* substituents could be displaced from aniline and phenol derivatives by diazonium salts.[6] Earlier investigators had shown that *p*-dimethyl-

(1) D. A. Shirley, *Org. Reactions*, **8**, 28 (1954).
(2) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).
(3) J. Cason, *Chem. Revs.*, **40**, 15 (1947).
(4) A. Quilico and M. Freri, *Gazz. chim. ital.*, **62**, 253 (1932).
(5) E. Ziegler and G. Snatzke, *Monatsh.*, **84**, 610 (1953).
(6) E. Ziegler, *Österr. Chemiker-Ztg.*, **53**, 31 (1952).

TABLE I

p-DIMETHYLAMINOPHENYLCARBINOLS (III)

p—$(CH_3)_2N$—C_6H_4—CHOH—R

R	Yield, %	M.P.	Analysis					
			Calcd.			Found		
			C	H	N	C	H	N
3-Methyl-1-butyl	55	50–51	75.97	10.47	6.33	75.88	10.37	6.39
2-Phenylethyl	74	69–71	79.96	8.29	5.48	79.81	8.04	5.62
Cyclohexyl	75	85–86	77.22	9.94	6.00	77.13	9.86	6.02
2-Chlorophenyl	50	94–95	68.84	6.17	5.36	68.86	6.12	5.34
2-Methoxyphenyl	58	79–80	74.68	7.44	5.44	74.81	7.27	5.35
3-Isopropylphenyl	60	53–54	80.25	8.61	5.20	80.31	8.40	5.24
2,5-Dimethylphenyl	60	73–74	79.96	8.29	5.48	80.05	8.29	5.48

aminobenzhydrol (III, R = C_6H_5) was cleaved in similar fashion by bromine,[7,8] nitrous acid,[8] and nitric acid.[8] In all this previous work attention was focused upon the non-carbonyl product, *i.e.*, the azobenzene derivative in the case of diazonium cleavage reactions. The carbonyl product was seldom isolated and characterized. Our attention was attracted to the synthetic possibilities of the reaction when it emerged in the form of a molecular rearrangement.[9]

Table I lists the amino carbinols (III) prepared from the appropriate Grignard reagent and *p*-dimethylaminobenzaldehyde. This inexpensive aldehyde thus serves as the source of the formyl group in the final product.

In Table II are listed the aldehydes prepared by cleavage of the amino carbinols (III) with diazotized sulfanilic acid at *p*H 5–6 and temperature 0–5°. Choice of this diazonium salt provides the necessary electrophilic reactivity and ensures that the by-product (methyl orange) can be easily eliminated because of its insolubility in ether. The conditions of the cleavage reaction are ideal for the manipulation of sensitive aldehydes. Ether extracts of the reaction mixtures contained nearly pure aldehydes as demonstrated by the distillation of colorless products with very little residue.

Smith and his students[10] have evaluated methods previously described for accomplishing the conversion of RMgX to RCHO. In favorable cases the yields of aldehyde-bisulfite addition compounds from the reaction of ethyl orthoformate or ethoxymethyleneaniline with the Grignard reagent were significantly higher than the yields reported here. However, our isolation of pure aldehyde probably constitutes a more realistic test of the synthetic applicability of the method. Furthermore, the scheme described here is a general one, working almost equally well for aliphatic aldehydes and

TABLE II

ALDEHYDES PREPARED BY EQUATION 2

Aldehyde	Yield, %	B.P./mm., found (reported)	2,4-DNP,[a] m.p., found (reported)
4-Methylpentanal	60	119–120/740 (121/747)[b]	99–100 (99)[b]
3-Phenylpropanal	64	71–72/1.5 (103/13)[c]	155–157 (149)[d]
Cyclohexanecarboxaldehyde	45, 69[e]	50–53/20 (55–57/20)[f]	175–176 (173–174)[f]
Benzaldehyde	80[g]	—	241–243 (237)[h]
2-Chlorobenzaldehyde	68	46–47/0.6 (132/60)[i]	208–209 (209)[j]
2-Methoxybenzaldehyde	75	79–80/1.5 (122/20)[k]	252–254 (249–250)[l]
3-Isopropylbenzaldehyde[m]	82	59–60/0.4	212–213[n]
2,5-Dimethylbenzaldehyde	72	58–59/1.0 (220/738)[o]	—
1-Naphthaldehyde	70	105/0.5 (150/13)[p]	256–257 (254–255)[q]
9-Phenanthraldehyde[r]	50	m.p. 100–101 (100–101)[s]	—

[a] 2,4-Dinitrophenylhydrazone. [b] H. Brunner and E. H. Farmer, *J. Chem. Soc.*, 1039 (1937). [c] E. Fischer and E. Hoffa, *Ber.*, **31**, 1992 (1898). [d] C. F. H. Allen and J. H. Richmond, *J. Org. Chem.*, 2, 224 (1936). [e] Isolated as bisulfite addition compound. [f] M. Mousseron, R. Jacquier, and R. Zagdoun, *Bull. Soc. Chim.*, 1042 (1952). [g] Isolated as 2,4-dinitrophenylhydrazone. [h] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *Systematic Identification of Organic Compounds*, 4th ed., New York, J. Wiley & Sons, 1956, p. 283. [i] R. R. Dreibach and S. A. Shrader, *Ind. Eng. Chem.*, **41**, 2879 (1949). [j] A. K. Macbeth and J. R. Rice, *J. Chem. Soc.*, 151 (1935). [k] F. B. Garner and S. Sugden, *J. Chem. Soc.*, 2882 (1927). [l] E. K. Harwill and R. M. Herbst, *J. Org. Chem.*, **9**, 21 (1944). [m] Calcd. for $C_{10}H_{12}O$: C, 81.08; H, 8.11. Found: C, 80.91; H, 8.22. [n] Calcd. for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.87; N, 17.08. Found: C, 58.54; H, 4.85; N, 17.18. [o] L. Gattermann, *Ann.*, **393**, 219 (1912). [p] G. M. Badger, *J. Chem. Soc.*, 535 (1941). [q] B. A. Gingrass and W. A. Waters, *J. Chem. Soc.*, 3508 (1954). [r] The amino carbinol precursor of this aldehyde, prepared in the same manner as those in Table I, was used without purification. The yield may be taken as minimal. [s] C. A. Dornfeld and G. H. Coleman, *Org. Syntheses*, Coll. Vol. III, 701 (1955).

(7) G. J. Esselen and L. Clarke, *J. Am. Chem. Soc.*, **36**, 308 (1914).

(8) E. P. Kohler and R. H. Patch, *J. Am. Chem. Soc.*, **38**, 1205 (1916).

(9) M. Stiles and A. J. Sisti, *J. Org. Chem.*, **24**, 268 (1959).

(10) L. I. Smith and M. Bayliss, *J. Org. Chem.*, **6**, 437 (1941); L. I. Smith and J. Nichols, *J. Org. Chem.*, **6**, 489 (1941).

being relatively insensitive to steric and electronic effects in the aldehyde moiety.

EXPERIMENTAL[11]

p-Dimethylaminophenylcarbinols (III). The new amino carbinols listed in Table I were prepared from the appropriate alkyl- or arylmagnesium bromide and *p*-dimethylaminobenzaldehyde, except for the cyclohexyl derivative, which was prepared from cyclohexylmagnesium chloride. The halides (except *m*-bromocumene) and the aldehyde were commercial products. The Grignard reagents were prepared by reaction of the halides, in 2–3 volumes of ether, with a slight excess of magnesium. *p*-Dimethylaminobenzaldehyde was added as a solution in benzene, and the reaction was stirred at room temperature for 2–10 hr. Hydrolysis was accomplished in aqueous ammonium chloride, the ether layer was dried over calcium sulfate, and the residue was recrystallized from benzene–petroleum ether (b.p. 30–60°) [except in the case of 1-(4-dimethylaminophenyl)-4-methyl-1-pentanol, which was crystallized from petroleum ether alone].

p-Dimethylaminobenzhydrol, m.p. 69–70° (reported[12] 69–70°) was prepared by the reduction of the ketone with sodium borohydride. *p*-Dimethylaminophenyl-1-naphthylcarbinol, m.p. 98–99° (reported[13] m.p. 97–98°) was prepared as described previously.[13]

Preparation of the aldehydes. Sulfanilic acid (60 g., 0.31 mole) was dissolved in a solution of 18.4 g. of sodium carbonate in 200 ml. of water, and diazotized at 0–5° by the addition of 64 ml. of concd. hydrochloric acid and a solution of 24.4 g. of sodium nitrite in 75 ml. of water in portions. When diazotization was complete and a slight excess of nitrous acid was present, the solution was buffered by the addition of 70 g. of sodium acetate in 200 ml. of water (*p*H *ca.* 6). A solution of 0.20 mole of the amino carbinol in 500 ml. of acetone was then added, followed by an additional 250 ml. of acetone. The mixture, which became red in a few minutes, was allowed to stir under a nitrogen atmosphere at 0–5° for 30 min. and then for an additional 30 min. after the removal of the ice bath. The mixture was diluted with water and extracted with ether. After removal of solvent from the dried solution, the aldehyde was distilled under an atmosphere of nitrogen.

Methyl m-bromobenzoate, b.p. 69–70°/0.2 mm. (reported[14] b.p. 122.5°/15 mm.), was prepared in 84% yield from commercial *m*-bromobenzoic acid by the method of Clinton and Laskowski.[15]

m-Bromophenyldimethylcarbinol. A solution of 150 g. (0.70 mole) of methyl *m*-bromobenzoate in 300 ml. of ether was added to 2.25 moles of methylmagnesium bromide in 1.5 l. of ether and the mixture was stirred overnight. Hydrolysis with aqueous ammonium chloride was followed by isolation in the usual manner. The product, 130 g. (85%), distilled at 79–80°/0.24 mm.

Anal. Calcd. for $C_9H_{11}BrO$: C, 50.25; H, 5.16. Found: C, 50.10; H, 5.03.

m-Bromocumene.[16] *m*-Bromophenyldimethylcarbinol (130 g., 0.60 mole) was hydrogenolyzed in three batches, each utilizing 3 g. of 5% palladium-on-charcoal catalyst in 200 ml. of glacial acetic acid and 1 ml. of 70% perchloric acid, under 40 lb. initial hydrogen pressure, at room temperature. Approximately 1 hr. was required for each reaction. After removal of the catalyst the combined acetic acid solutions were combined and about 75% of the acetic acid was removed under reduced pressure. The residue was diluted with water and steam distilled. Fractional distillation yielded 96 g. (80%) of colorless liquid, b.p. 208–210° (reported[17] b.p. 208–210°).

ANN ARBOR, MICH.

(11) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting and boiling points were not corrected for stem exposure.

(12) K. Albrecht, *Ber.*, **21**, 3292 (1888).

(13) F. Sachs and L. Sachs, *Ber.*, **38**, 511 (1905).

(14) A. M. Kellas, *Z. Physik. Chem.*, **24**, 245 (1897).

(15) R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).

(16) The synthesis of this compound was adapted from an unpublished procedure of Professor R. E. Ireland.

(17) E. C. Sterling and M. T. Bogert, *J. Org. Chem.*, **4**, 20 (1939).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Condensation of Alkyl Acetates with Benzophenone by Lithium Amide to Form β-Hydroxy Esters. Relative Ease of Self-condensation of Esters[1]

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The success of the aldol type of condensation of ethyl or isopropyl acetate with benzophenone by lithium amide in liquid ammonia to form the corresponding β-hydroxy ester was found to be dependent on minimizing the self-condensation of the alkyl acetate before adding the ketone to the reaction mixture. This was accomplished either by adding the ketone very soon after the ester or by employing excess reagent over the one equivalent required to form the intermediate lithio ester. This was not necessary with *t*-butyl acetate. When two equivalents of lithium amide were used, the monolithio derivative of the β-hydroxy ester first formed in the condensation was converted to the dilithio derivative of the β-hydroxy ester. This was demonstrated by adding benzyl chloride to the reaction mixture to form the α-benzyl derivative of the β-hydroxy ester. Consideration is given to the bearing of these results on the earlier general procedure for synthesizing β-hydroxy esters and to the relative ease of self-condensations of the alkyl acetates.

Recently[2] ethyl acetate was condensed with various ketones or aldehydes by means to two molecular equivalents of lithium amide in liquid ammonia to form the corresponding β-hydroxy esters. For example, this ester was condensed with benzophenone to give β-hydroxy ester I in

(1) Supported by the Office of Ordnance Research, U. S. Army.

(2) W. R. Dunnavant and C. R. Hauser, *J. Org. Chem.*, **25**, 503 (1960).

yields of 80–84%. Similarly, isopropyl and *t*-butyl acetates were condensed with this ketone to produce β-hydroxy esters II and III respectively.

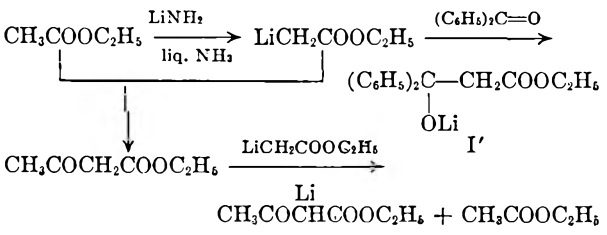
$$(C_6H_5)_2C(OH)-CH_2COOR$$

I. R = C_2H_5
II. R = $CH(CH_3)_2$
III. R = $C(CH_3)_3$

The general procedure involved the addition of the alkyl acetate to the reagent followed by the ketone after fifteen to twenty minutes. This time interval was allowed to permit the ionization of an α-hydrogen of the ester to form the lithio ester, which was presumably the reactive intermediate. The formation of such an intermediate might be expected to require only one equivalent of the reagent; indeed, this amount of reagent was satisfactory for the condensation of *t*-butyl acetate with benzophenone to form III. However, one equivalent of the reagent failed to effect the condensation of ethyl acetate with this ketone under similar conditions, and the ketone was largely recovered.

We have now found that ethyl acetate can be condensed with benzophenone by means of one equivalent of lithium amide provided the ketone is added immediately after the ester; this procedure produced a 69% yield of β-hydroxy ester I. On the other hand, when the ketone was added twenty minutes after the ester as in the earlier procedure, a 24% yield of acetoacetic ester was obtained, and 89% of the ketone was recovered. Evidently most of this β-keto ester was produced before the ketone was added, as about the same yield (28%) was realized on treating ethyl acetate alone with the reagent for twenty minutes. Some of the β-keto ester appeared to be formed within a few seconds when the reaction mixture turned from gray to black, as the material obtained on stopping the reaction after such an observation gave a positive enol test with ethanolic ferric chloride. These results show that ethyl acetate is first converted very rapidly to its lithio derivative by an equivalent of lithium amide in liquid ammonia but that, unless the ketone is added immediately, this intermediate condenses with unchanged ester to form acetoacetic ester. Both the β-hydroxy ester and β-keto ester are produced in the reaction mixture as their lithio derivatives (Scheme A).

Scheme A



Although ethyl acetate is first converted largely to its lithio derivative, the small amount of unchanged ester present in equilibrium is sufficient to lead to the formation of considerable acetoacetic ester because ethyl acetate is regenerated continually in the last step (see Scheme A).[3]

It should be mentioned that only a 22% yield of β-hydroxy ester I was obtained on repeating the experiment in which the ketone was added immediately after the ester. However, in this run the ethyl acetate–lithium amide mixture had turned from gray to black before all of the ketone had been added indicating that selfcondensation of the ester had begun (see above). Actually the so-called immediate addition of the ketone required a few seconds, and the time lapse might have been slightly greater in the second experiment. Also, because of the tendency of the lithium amide to cling to the walls of the reaction vessel above the liquid medium, the use of just one equivalent of the reagent might sometimes result in slightly less than an equivalent entering into the reaction. This should favor the selfcondensation of the ester.

Similarly, isopropyl acetate reacted rapidly and largely with one equivalent of lithium amide in liquid ammonia to form its lithio derivative, which condenses either with benzophenone or with unchanged ester depending on how soon the ketone is added after the ester. Thus, an 82% yield of β-hydroxy ester II was obtained when the ketone was added immediately after the ester, whereas only a 3% yield of the β-hydroxy ester was isolated when the ketone was added twenty minutes after the ester. In the latter experiment a 50% yield of isopropyl acetoacetate was produced. These two courses of reaction are analogous to those represented in Scheme A for ethyl acetate.

Thus, under appropriate conditions, ethyl and isopropyl acetates as well as *t*-butyl acetate can be condensed with benzophenone by means of one equivalent of lithium amide in liquid ammonia to form β-hydroxy esters, I, II, and III, respectively (Equation 1).

$$CH_3COOR \xrightarrow[\text{liq. } NH_3]{LiNH_2} LiCH_2COOR \xrightarrow[2.\ NH_4Cl]{1.\ (C_6H_5)_2C=O} \underset{\text{R = } C_2H_5,\ CH(CH_3)_2,\text{ or } C(CH_3)_3}{\text{I, II, or III}} \quad (1)$$

These results with one equivalent of lithium amide together with those with more than one equivalent of the reagent are summarized in Table I. The ionization-time column in this table indicates the period after adding the ester to the reagent before adding the ketone. The condensation time after adding the ketone was one hour, the reaction mixtures then being poured into ammonium chloride in liquid ammonia. This inverse neutrali-

(3) This last step may be effected by the lithium ethoxide formed as by-product in the condensation of lithio ethyl acetate with unchanged ester, but this would form ethanol which would then liberate ethyl acetate from the lithio ester.

zation procedure was employed to minimize possible cleavages of the β-hydroxy esters, although it has been shown not to be required in the preparation of β-hydroxy ester I (see note 5 in ref. 2).

TABLE I

YIELDS OF β-HYDROXY ESTERS FROM ALKYL ACETATES AND BENZOPHENONE BY LITHIUM AMIDE UNDER VARIOUS CONDITIONS

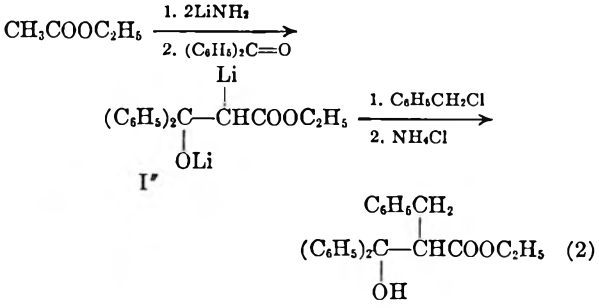
Exp. No.	Alkyl Acetate	Equiv. $LiNH_2$	Ioniz. Time, Min.[a]	β-Hydroxy Ester	Yield, %
1	Ethyl	1	15–20	I	0[b]
2	Ethyl	1	0[c]	I	69, 22[d]
3	Ethyl	1.1	0.5	I	67
4	Ethyl	1.25	0.5	I	78
5	Ethyl	2	3	I	82
6	Ethyl	2	15–20	I	80–84[e]
7	Ethyl	3	20	I	60
8	Ethyl	4	20	I	58
9	Isopropyl	1	15–20	II	3[f]
10	Isopropyl	1	0[c]	II	82
11	Isopropyl	2	15–20	II	80[e]
12	*t*-Butyl	1	15–20	III	71[e]
13	*t*-Butyl	1.25	3	III	71
14	*t*-Butyl	2	15–20	III	87[b]
15	*t*-Butyl	2.1	15–20	III	76

[a] The time allowed after adding the ester to the reagent before adding the ketone. [b] A 24% yield of acetoacetic ester was obtained; 89% of the ketone was recovered. [c] Although the ketone was added immediately after the ester, a few seconds probably elapsed. [d] In this experiment the ethyl acetate–lithium amide mixture turned black before all of the ketone was added. [e] Reported previously in ref. 2. [f] A 50%-yield of isopropyl acetoacetate was obtained, and 55% of the ketone was recovered.

It can be seen from Table I that the yields of I were more consistent with an excess of the reagent than with just one equivalent. Thus, even though the ketone was not added until thirty seconds after the ester, 1.1 and 1.25 equivalents of the reagent produced the β-hydroxy ester in yields of 67% and 78% respectively (experiments 3 and 4). The latter yield is about as high as that (80-84%) obtained with two equivalents of the reagent when the ketone was added three or twenty minutes after the ester (experiments 5 and 6).

The fact that two equivalents of lithium amide but not one produced β-hydroxy ester I when the ketone was added twenty minutes after the ester indicated that the extra equivalent of the reagent retarded the self-condensation of the ethyl acetate This was confirmed by treating ethyl acetate alone with two equivalents of the reagent for twenty minutes, after which no acetoacetic ester could be isolated. However, the selfcondensation of ethyl acetate was not stopped indefinitely by an extra equivalent of lithium amide, a 31% yield of acetoacetic ester being obtained with two equivalents of the reagent after two hours. A 40% yield of the β-keto ester was realized with one equivalent of the reagent after only one hour.[4]

Besides retarding the selfcondensation of ethyl acetate, the extra equivalent of lithium amide was found to convert the monolithio β-hydroxy ester I′ that is presumably first formed in the condensation of lithio ethyl acetate with benzophenone (see Scheme A) to the dilithio β-hydroxy ester I″. This was established by treating the reaction mixture with an equivalent of benzyl chloride, which produded the α-benzyl derivative IV in 61% yield (Equation 2).



IV was also obtained in 61% yield by treating β-hydroxy ester I with two equivalents of lithium amide followed by one equivalent of benzyl chloride.

That the benzylation product was the α-benzyl derivative and not the possible benzyl ether of β-hydroxy ester I[5] was supported by its infrared spectrum, which gave strong absorption at 2.8 μ indicating that the hydroxyl group had been retained. The structure of the benzylation product was established as IV by cleavage with sodium amide in liquid ammonia to form benzophenone and ethyl hydrocinnamate which was saponified and isolated as hydrocinnamic acid (Equation 3).[6]

$$\text{IV} \xrightarrow[\text{liq. } NH_3]{NaNH_2} (C_6H_5)_2C{=}O + C_6H_5CH_2CH_2COOC_2H_5 \quad (3)$$

Incidently, the type of alkylation of the dilithio β-hydroxy ester illustrated in Equation 2 may furnish a useful method for synthesizing not only IV which appears not to have been prepared previously, but also various other α-alkyl derivatives.

The condensation with two equivalents of lithium amide might appear to involve the intermediate formation of dilithio ethyl acetate, Va or Vb, which might add to the carbonyl group of benzophenone to form directly dilithio β-hydroxy ester

(4) The yields of acetoacetic ester reported here may not represent the maximum amount of the β-keto ester formed, as only 54% of the β-keto ester was recovered in a blank experiment with two equivalents of the reagent for one hour.

(5) Another preferential benzylation of a carbanion over an oxide anion has been observed with the dianion $(C_6H_5)_2\bar{C}—\bar{O}$; P. J. Hamrick and C. R. Hauser, *J. Am. Chem. Soc.*, 81, 493 (1959).

(6) Reactions with sodium amide will be further considered in a later paper by C. R. Hauser and W. R. Dunnavant.

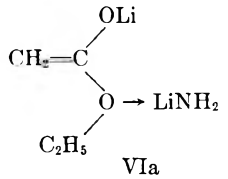
$Li_2CHCOOC_2H_5$ $LiCH{=}C{-}OLi$

OC_2H_5

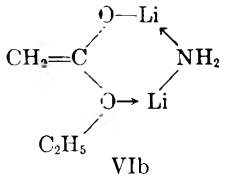
Va Vb

I″. However, lithium amide seems unlikely to be a sufficiently strong base to effect the secondary ionization that would be required to produce dilithio ethyl acetate. Indirect evidence against the formation of an appreciable amount of such a dilithio derivative is the previous observation[7] that treatment of ethyl acetate with two equivalents of lithium amide in liquid ammonia followed by two equivalents of benzyl chloride produced the monobenzyl derivative, ethyl 3-phenylpropionate (30%), but apparently none of the dibenzyl derivative of ethyl acetate. On repeating this experiment, we obtained, besides the monobenzylated ester, some stilbene (17%) which has previously been produced by the action of lithium amide in liquid ammonia on benzyl chloride.[8] The formation of this dimeric olefin may indicate the presence of some essentially free lithium amide, although other bases in the reaction mixture might have effected the reaction.

The reactive intermediate in the condensation of ethyl acetate with benzophenone by two equivalents of lithium amide seems more likely to be essentially monolithio ethyl acetate, possibly coordinated with the extra equivalent of the reagent as in VIa or VIb or in a dimer or trimer.



VIa

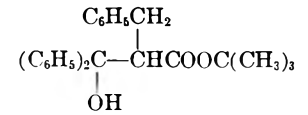


VIb

Some sort of coordination is indicated by the fact that an extra equivalent of lithium amide retards the selfcondensation of ethyl acetate (see above) whereas sodium amide, which should coordinate to a smaller degree, fails to exhibit such a retarding effect under similar conditions.[6] The retarding of the selfcondensation of ethyl acetate is presumably the result of more complete ionization of its α-hydrogen leaving relatively less unchanged ester to enter into condensation with the lithio ester as required by theory.[9] Apparently the two equivalents of lithium amide coordinate with the carbonyl as well as the alkoxide oxygen of ethyl acetate to make the ester an effectively stronger acid. This may lead to the formation of the coordinated monolithio derivative VIa or VIb, or perhaps to an anion of VIb resulting from the ionization of a hydrogen on nitrogen. The more complete ionization of the α-hydrogen of ethyl acetate cannot be ascribed solely to a mass action effect by amide ion, as this base is effectively weaker in lithium amide than in sodium amide towards diphenylmethane, which has no point for coordination of a metallic cation. Thus, whereas sodium amide in liquid ammonia converts this hydrocarbon to its anion which can be alkylated,[10] lithium amide produces an insufficient concentration of the carbanion for successful alkylation under similar conditions.[11]

Regardless of the structure of the intermediate lithio ethyl acetate, benzophenone must react preferentially with it rather than with excess lithium amide, as β-hydroxy ester I was obtained in approximately 60% yield when three equivalents or even four equivalents of the reagent were employed (see experiments 7 and 8, Table I). This result cannot be accounted for on the basis that benzophenone first adds reversibly an equivalent of lithium amide to form $(C_5H_5)_2C(OLi)NH_2$ and that the lithio ethyl acetate then condenses with the ketone present in equilibrium, as the addition of the amide is effectively irreversible in liquid ammonia. Thus, on first adding benzophenone to two equivalents of lithium amide followed by ethyl acetate, none of β-hydroxy ester I was obtained and the ketone was largely recovered on acidification.

In Table I, although the yields of β-hydroxy ester II from isopropyl acetate were about the same with one or two equivalents of the reagent under the appropriate conditions (experiments 10 and 11), those of β-hydroxy ester III from *t*-butyl acetate appeared to be slightly higher with two or 2.1 equivalents of the reagent (experiments 14 and 15) than with one or 1.25 equivalents (experiments 12 and 13). This might indicate that the maximum yield with *t*-butyl acetate requires the conversion of the product to its dilithio derivative. Some of this derivative was evidently produced on treating β-hydroxy ester III with two equivalents of the reagent, as subsequent addition of benzyl chloride gave VII (10%). The yield could probably be improved by longer reaction time (see Experimental).



VII

On the basis of the present results certain modifications may be made in the earlier procedure[2] for the synthesis of β-hydroxy esters from ethyl acetate and various ketones or aldehydes. The time interval after adding the ester to the reagent before adding the ketone may now be shortened, if de-

(7) C. R. Hauser and W. J. Chambers, *J. Org. Chem.*, **21** 1524 (1956).

(8) C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Am. Chem. Soc.*, **78**, 1653 1956).

(9) See C. R. Hauser and B. E. Hudson, *Org. Reactions*, Vol. I, 276 (1942).

(10) C. R. Hauser and P. J. Hamrick, Jr., *J. Am. Chem. Soc.*, **79**, 3142 (1957).

(11) Unpublished results of P. J. Hamrick and C. R. Hauser.

sired, from fifteen to twenty minutes to three minutes or less (see Table I). If this time interval is so shortened, the full extra equivalent of lithium amide is not required even in the condensation of ethyl acetate with benzophenone. However, this is not necessarily true for the condensations of this ester with other ketones, with certain of which the further driving force furnished by the conversion of the product to its dilithio derivative may be required for maximum yield.

While the general procedure employing two equivalents of the reagent has previously been shown[2] to produce good to excellent yields in the condensations of ethyl acetate with certain ketones having α-hydrogen, it has now been found not to be satisfactory with acetone, with which much tarry material was produced. However, a 44% yield of the corresponding β-hydroxy ester VIII was obtained with 1.25 equivalents of the reagent under special conditions (see Experimental).

$$(CH_3)_2C(OH)—CH_2COOC_2H_5$$

VIII

Relative rates of self-condensations of alkyl acetates. It has previously been observed in this laboratory[12] that ethyl acetate is selfcondensed by sodium triphenylmethide in ether somewhat faster than isopropyl acetate, and that these two esters are selfcondensed much more rapidly than *t*-butyl acetate (Scheme B).

Scheme B

$$CH_3COOR \xrightarrow[\text{ether}]{(C_6H_5)_3CNa} NaCH_2COOR + (C_6H_5)_3CH$$

$$CH_3COCH_2COOR \xrightarrow{NaCH_2COOR} CH_3COCHCOOR + CH_3COOR$$

(Na)

Relative rates, R = ethyl > isopropyl > *t*-butyl

Similar to the observation made above in connection with Scheme A, a small amount of unchanged alkyl acetate present in the equilibrium of the first step is sufficient for the production of good yields of the selfcondensation product, as the alkyl acetate is regenerated continually in the last step. That the equilibrium of the first step, acid-base reaction is far on the side of the ester anion is strikingly illustrated by the almost immediate discharge of the characteristic red color of the sodium triphenylmethide reagent by a molecular equivalent of the alkyl acetate.

In line with these relative rates of selfcondensations of alkyl acetates, treatment of ethyl and isopropyl acetates with equivalents of lithium amide in liquid ammonia for twenty minutes produced considerable ethyl and isopropyl acetoacetates, whereas similar treatment of *t*-butyl acetate gave no significant amount of its self-condensation product. Addition of benzophenone to the reaction mixtures after this time gave β-hydroxy esters I, II, and III in increasing yields of 0%, 3% and 71%, respectively (see Table I). However, the yield of the ethyl acetoacetate isolated was only about half of that of isopropyl acetoacetate (see notes b and f, Table I). This apparent discrepancy appears to have been due to some destruction of the former β-keto ester[4] or possibly to some attack of the lithium amide at the carbonyl group of ethyl acetate to form acetamide although an attempt to isolate this product was unsuccessful.

EXPERIMENTAL[13]

Condensations of alkyl acetates with benzophenone by lithium amide (Table I). The preparation of the lithium amide in liquid ammonia and the apparatus used were described previously.[2] After the blue color of the lithium metal had been discharged in the main body of the reaction mixture, the reaction flask was shaken manually to effect the conversion of particles of the metal on the walls above the liquid ammonia to lithium amide, which was obtained as a thick, white suspension.

In Table I are summarized the results obtained from the condensations of ethyl, isopropyl, and *t*-butyl acetates with benzophenone to form β-hydroxy esters I, II and III respectively. The β-keto esters resulting from selfcondensations of ethyl and isopropyl acetates are noted in this table. Some typical experiments are described in detail below.

A. Experiments with ethyl acetate. In Experiment 1, a solution of 35.2 g. (0.4 mole) of ethyl acetate in an equal volume of dry ether was added to a stirred suspension of 0.4 mole of lithium amide in 440 ml. of commercial, anhydrous liquid ammonia. The reaction flask was then shaken manually to effect contact of the ester with small amounts of lithium amide on the walls of the flask above the main body of the reaction mixture. After stirring for 20 min., 72.8 g. (0.4 mole) of benzophenone in sufficient ether to effect solution (140 ml.) was added. The reaction mixture was stirred for 1 hr. and was then inversely neutralized by pouring it with stirring into a solution of ammonium chloride in liquid ammonia. The ammonia was evaporated on the steam bath as 300 ml. of ether was added. The resulting ethereal suspension was shaken with 200 ml. of cold water and the aqueous layer was extracted with several 100-ml. portions of ether. The combined ethereal solution was dried over magnesium sulfate and then evaporated. The residue was dissolved in boiling petroleum ether (b.p. 60–90°) and the solution treated with charcoal and filtered. The solution was stirred with cooling in an ice bath to precipitate 65 g. (89%) of crystalline benzophenone, m.p. 46–47°. The solvent of the filtrate was removed, and the residue was distilled to yield 7.3 g. (24%) of ethyl acetoacetate, b.p. 73–74° at 14 mm; reported[14] b.p. 74° at 14 mm. The product gave an infrared spectrum identical with that of the authentic β-keto ester, and a positive enol test with ethanolic ferric chloride.

(12) Ph.D. thesis, B. Abramovitch, Duke University (1942) p. 33.

(13) The melting points were taken on a Fisher-Johns melting point apparatus. Infrared spectra were produced with a Perkin-Elmer Infracord using mineral oil mulls. The elemental analysis were by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(14) Heilbron, *Dictionary of Organic Compounds*, Vol. II, Oxford University Press, New York, N. Y., 1953, p. 486.

In Experiment 2, a solution of 17.6 g. (0.2 mole) of ethyl acetate in an equal volume of ether was added through the addition funnel as rapidly as possible to a stirred suspension of 0.2 mole of lithium amide in 400 ml. of anhydrous liquid ammonia. As frothing occurred, a reaction vessel having a volume twice that of the amide suspension was used. As the last of the ester passed through the stopcock, a solution of 36.4 g. (0.2 mole) of benzophenone in 70 ml. of ether was poured immediately into the addition funnel and allowed to run into the reaction flask as rapidly as possible, the addition funnel being rinsed with a little ether. The mixture was stirred for 1 hr. and was then inversely neutralized with ammonium chloride. The ammonia was replaced by ether. After adding water and thoroughly extracting the aqueous layer with ether, the combined ethereal solution was dried and solvent evaporated. The residue was crystallized from petroleum ether (b.p. 60–90°) to give 37.2 g. (69%) of ethyl β-hydroxy-β,β-diphenylpropionate (I), m.p. 86–87°; reported[15] m.p. 87°. The filtrate was reduced in volume and cooled with stirring in an ice bath to give 5.3 g. (14%) of crystalline benzophenone, m.p. 46–47°, after two crystallizations from petroleum ether (b.p. 60–90°).

Ethanol is a good crystallizing solvent for β-hydroxy ester I, but isolation of benzophenone is made difficult by its high solubility in this solvent.

B. Experiments with isopropyl acetate. In Experiment 9, a solution of 25 g. (0.24 mole) of isopropyl acetate in an equal volume of ether was added to a stirred suspension of 0.24 mole of lithium amide in 400 ml. of anhydrous liquid ammonia. After 15 min., a solution of 43.5 g. (0.24 mole) of benzophenone in 80 ml. of ether was added. After stirring for 1 hr., the reaction mixture was inversely neutralized with ammonium chloride. The ammonia was replaced by ether and water was added. After several ether extractions of the aqueous layer, the combined ethereal solution was dried over magnesium sulfate and then evaporated. The residue was crystallized from 95% ethanol to yield 2.2 g. (3%) of isopropyl β-hydroxy-β,β-diphenylpropionate (II), as colorless, rod-shaped crystals, m.p. 101–102°.

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.02; H, 7.09. Found: C, 75.93; H, 7.03.

Reducing the volume of the filtrate and cooling gave 37.5 g. (86%) of benzophenone, m.p. 46–47°, after recrystallization from petroleum ether (b.p. 60–90°). The filtrate, following removal of the ketone, was distilled to yield 8.8 g. (50%) of isopropyl acetoacetate, b.p. 78–80° at 10 mm., reported b.p. 79–80° at 11 mm.[16] The β-keto ester gave a positive enol test with ethanolic ferric chloride and reacted with aqueous cupric acetate to give a green crystalline salt, m.p. 177–178°, after two crystallizations from aqueous methanol; reported[17] m.p. 179–180°.[17]

In Experiment 10, a solution of 25 g. (0.24 mole) of isopropyl acetate in an equal volume of ether was added to a stirred suspension of 0.24 mole of lithium amide in 400 ml. of liquid ammonia, followed immediately by 44 g. (0.24 mole) of benzophenone in 100 ml. of ether (see Exp. 2 with ethyl acetate). The resulting gray suspension was stirred for 1 hr. and was inversely neutralized with ammonium chloride. The ammonia was replaced by ether and water was added. After several extractions of the aqueous layer with ether, the combined ethereal solution was dried and evaporated. The residue was crystallized from petroleum ether (b.p. 60–90°) to give 56 g. (82%) of ester II as large colorless, rod-shaped crystals, m.p. 101–102°.

C. Experiments with t-butyl acetate. In Experiment 12, a solution of 20 g. (0.17 mole) of *t*-butyl acetate in an equal volume of ether was added to a stirred suspension of 0.17 mole of lithium amide in 400 ml. of liquid ammonia. After stirring for 15 min., 31 g. (0.17 mole) of benzophenone in 60 ml. of ether was added. The resulting mixture was stirred for 1 hr. and was inversely neutralized with ammonium chloride. The ammonia was evaporated to dryness and the solid residue was treated with water and filtered. The dried solid was recrystallized from 95% ethanol to give 36.6 g. (71%) of β-hydroxy ester III, m.p. 93–94°; reported[18] m.p. 92–93°.

Benzylation of dilithio derivative I' *to form* IV. *A. From ethyl acetate and benzophenone.* To a stirred suspension of 0.4 mole of lithium amide in 400 ml. of anhydrous liquid ammonia was added 17.6 g. (0.2 mole) of ethyl acetate in an equal volume of ether. After stirring for 15 min., 36.4 g. (0.2 mole) of benzophenone in 50 ml. of ether was added to form a dark blue, then dark gray suspension. The mixture was stirred for another 15 min., and 25 g. (0.2 mole) of benzyl chloride in 25 ml. of ether was added. An insoluble gray mass formed in the ammonia. Stirring was continued for 1 hr. and the reaction mixture was then inversely neutralized with ammonium chloride. The ammonia was evaporated and the solid residue was stirred with cold water. The resulting mixture was filtered. The solid cake was crystallized from ethanol to yield 42.2 g. (61%) of ethyl α-benzyl-β-hydroxy-β,β-diphenylpropionate (IV), m.p. 109–109.5° after two crystallizations from ethanol. The infrared spectrum showed ester carbonyl absorption at 5.8 μ and hydroxyl absorption at 2.8 μ.

Anal. Calcd. for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 79.99; H, 6.70. C, 80.06; H, 6.85.

B. From β-hydroxy ester I. To 0.07 mole of lithium amide in 400 ml. of anhydrous liquid ammonia was added 10 g. (0.037 mole) of β-hydroxy ester I in 25 ml. of ether. After stirring for 30 min., 4.66 g. (0.037 mole) of benzyl chloride in 10 ml. of ether was added and the mixture was stirred for 1 hr., followed by neutralization with ammonium chloride. The ammonia was evaporated and the residue was treated with water. The resulting mixture was filtered and the solid cake was crystallized from ethanol to yield 8.8 g. (61%) of β-hydroxy ester IV, m.p. 109–110°. Reducing the volume of the filtrate gave 2.8 g. (28%) recovery of β-hydroxy ester I, m.p. 86–87°. The samples of IV prepared by the two methods gave identical infrared spectra and no mixed melting point depression.

Cleavage of β-hydroxy ester IV. To a stirred suspension of 0.017 mole of sodium amide in 200 ml. of anhydrous liquid ammonia was added 5.0 g. (0.014 mole) of β-hydroxy ester IV in ether solution. The resulting solution was stirred for 4 hr. and then was neutralized with ammonium chloride. The ammonia was replaced by ether and water was added. After thoroughly extracting the aqueous layer by ether, the combined ethereal solution was dried over magnesium sulfate and evaporated. The residue was treated with petroleum ether (b.p. 60–90°) and stirred in an ice bath to yield 2.1 g. (84%) of crystalline benzophenone, m.p. 47–48°. The sample gave no mixed melting point depression with, and an infrared spectrum identical with that of an authentic sample of benzophenone.

The petroleum ether filtrate was concentrated and the residue was refluxed with aqueous sodium hydroxide for 4 hr. The cooled alkaline solution was extracted with ether and was then acidified to produce a cloudy solution. The acidified solution was extracted with ether and the ether was evaporated to yield a residual oil. The oil upon crystallization from petroleum ether (b.p. 60–90°) gave 1.62 g. (78%) of crystalline hydrocinnamic acid, m.p. 47–48°; lit.[19] m.p. 48.5°. The admixture melting point with an authentic sample was 47–48°. The infrared spectrum was identical in every respect with that of the authentic sample.

(15) H. Rupe and E. Busolt, *Ber.*, **40**, 4537 (1907).

(16) J. C. Shivers, M. L. Dillon, and C. R. Hauser, *J. Am. Chem. Soc.*, **69**, 119 (1947).

(17) C. Moureu and R. Delange, *Compt. rend.*, **134**, 46 (1902).

(18) K. Sisido, H. Nozaki, and O. Kurihara, *J. Am. Chem. Soc.*, **74**, 6254 (1952).

(19) C. Willgerodt and F. H. Merk, *J. prakt. Chem.*, [2], **80**, 196 (1909).

Benzylation of β-hydroxy ester III *to give* VII. To a stirred suspension of 0.1 mole of lithium amide in 300 ml. of anhydrous liquid ammonia was added 15 g. (0.5 mole) of β-hydroxy ester III in 25 ml. of anhydrous ether. After stirring the resulting suspension for 20 min., 6.33 g. (0.5 mole) of benzyl chloride in 15 ml. of ether was added slowly. A gray precipitate formed immediately. The mixture was stirred for 1 hr. and was then inversely neutralized with ammonium chloride. The ammonia was evaporated and replaced by ether. Water was added and the aqueous layer was thoroughly extracted by ether. The combined ether solution was dried over magnesium sulfate and evaporated to a colorless oily residue having the odor of benzyl chloride. Treatment of the residue with 95% ethanol permitted crystallization of 3 g. (10%) of *t*-butyl α-benzyl-β-hydroxy-β,β-diphenylpropionate (VII) in the form of needle-like crystals, m.p. 104–105°. The infrared spectrum showed carbonyl absorption at 5.8 μ, and hydroxyl absorption at 2.75 μ.

Anal. Calcd. for $C_{26}H_{28}O_3$: C, 80.37; H, 7.26. Found: C, 80.29; H, 7.19.

The filtrate from above was reduced in volume and cooled to yield 8.6 g. (57%) of recovered starting ester III, m.p. 92–93° after a second crystallization from ethanol.

Treatment of ethyl acetate with excess lithium amide followed by benzyl chloride. To a stirred suspension of 1.0 mole of lithium amide in 600 ml. of liquid ammonia was added 44 g. (0.5 mole) of ethyl acetate in an equal volume of ether. The resulting gray suspension was stirred for 2 min. and 126.6 g. (1.0 mole) of benzyl chloride in 80 ml. of ether was added. After stirring for 1 hr. the ammonia was replaced by ether and the resulting mixture neutralized with cold, dilute hydrochloric acid. There was obtained 33 g. (26%) of recovered benzyl chloride b.p. 66–68° at 20 mm., and 18.2 g. (22%) of ethyl hydrocinnamate, b.p. 245–248° at 758 mm.; reported[20] b.p. 247° at 760 mm. The temperature of the distillate then rose rapidly to about 300°, at which temperature stilbene began to clog the column and apparatus. There was obtained 15.2 g. (17%) of crude stilbene, m.p. 119–120°. After recrystallization from ethanol (Norit), the product melted at 122–123°; reported[21] m.p. 124°.

Treatment of benzophenone with lithium amide followed by ethyl acetate. To a stirred suspension of 0.4 mole of lithium amide in 400 ml. of liquid ammonia was added 36.4 g. (0.2 mole) of benzophenone in 100 ml. of anhydrous ether. The gray suspension was stirred for 20 min., and 17.6 g. (0.2 mole) of ethyl acetate in an equal amount of ether was added. The resulting dark black solution was stirred for 1 hr. and was then neutralized with ammonium chloride. There was obtained 30.2 g. (84%) of recovered benzophenone, m.p. 47–48°, none of β-hydroxy ester I being isolated.

Condensation of lithioethyl acetate with acetone. To a stirred suspension of 0.62 mole of lithium amide in 400 ml. of anhydrous liquid ammonia was added 44 g. (0.5 mole) of ethyl acetate in an equal volume of ether. The resulting gray suspension was stirred for 2 min., and 21 g. (0.5 mole) of acetone (dried over magnesium sulfate) in a little anhydrous ether was added. The resulting black solution was stirred for 1 hr. and was then inversely neutralized with ammonium chloride. The ammonia was replaced by 300 ml. of ether, and 150 ml. of cold water was added. After thorough extraction of the aqueous layer with ether, the combined ethereal solution was dried and evaporated. The residue was distilled to give 16 g. (25%) of ethyl β-hydroxy-β-methylbutyrate (VIII), b.p. 175–176° at 738 mm.; reported[22] b.p. about 180°.

Anal. Calcd. for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.41; H, 9.65.

When the reaction was repeated allowing the condensation to proceed for 1 hr. instead of 10 min., a 25% yield of hydroxy ester VIII was obtained.

DURHAM, N. C.

(20) W. H. Perkin, *J. Chem. Soc.*, 69, 1025 (1896).

(21) T. W. J. Taylor and A. R. Murray, *J. Chem. Soc.*, 2079 (1938).

(22) A. Semljanizen and A. Saytzeff, *Ann.*, 197, 73 (1897)

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, UNION CARBIDE CHEMICALS CO.]

The Oxidation of Unsaturated Acetals and Acylals with Peracetic Acid

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A series of unsaturated dioxolanes, acetals, and acylals based on α,β-unsaturated aldehydes were prepared and oxidized with peracetic acid. The major products in most cases were the anticipated epoxides, but when noncyclic acetals were used, or when the reaction was catalyzed by sulfuric acid, the predominant products of oxidation were the corresponding unsaturated esters. The novel peracid oxidation of acetals to esters was found applicable to saturated acetals also.

The literature concerning epoxides of α,β-unsaturated aldehydes and their acetals and acylals is very sparse. The simplest member of the series, 2,3-epoxypropionaldehyde, has been referred to often in connection with the autoxidation of fats but was synthesized and statisfactorily characterized only recently.[1] Kögl prepared 2,3-epoxybutyraldehyde by lead tetraacetate cleavage of 2,3-6,7-diepoxyoctane-4,5-diol,[2] and the epoxides of 2-ethyl-2-hexenal and crotonaldehyde were prepared by sodium hypochlorite oxidation of the unsaturated aldehydes.[3] The diethyl and ethylene glycol acetals of 2,3-epoxypropionaldehyde were prepared by dehydrochlorination of the chlorohydrins,[4] and three other acetals (the diethyl and ethylene glycol acetals of 2,3-epoxypropionaldehyde and the ethylene glycol acetal of 2,3-epoxy-3-phenylpropionaldehyde) were prepared by perbenzoic acid

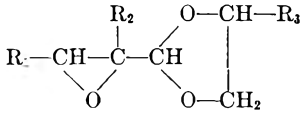
(1) G. B. Payne, *J. Am. Chem. Soc.*, 80, 6461 (1958); 81, 4901 (1959).

(2) F. Kögl and H. Veldstra, *Ann.*, 552, 1 (1942).

(3) C. Shaer, *Helv. Chim. Acta*, 41, 614 (1958).

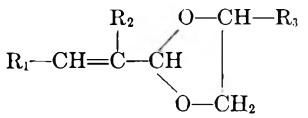
(4) K. Taufel and P. Sadler, *Z. Untersuch. Lebensm.*, 65, 540 (1933); *Chem. Abstr.*, 27, 4702 (1933).

oxidation of the olefins.[5] The diethyl acetal of 2,3-epoxypropionaldehyde was also studied recently by Wright.[6] In the total synthesis of lysergic acid an intermediate of this type was also prepared.[7] Reaction of 2,3-dichloroaldehydes with sodium methoxide in methanol leads to the formation of the dimethyl acetals of 2,3-epoxyaldehydes.[8] Finally, an acylal, the diacetate of 2,3-epoxybutyraldehyde, and its hydrolysis to methylglyceraldehyde were reported recently.[9]



Epoxyalkyl dioxolanes

VI. $R_1 = C_6H_5$; $R_2 = H$; $R_3 = CH_3$



Unsaturated dioxolanes

VIa. $R_1 = C_6H_5$; $R_2 = H$; $R_3 = CH_3$

A series of epoxides of the cyclic acetals of α,β-unsaturated aldehydes were conveniently prepared in good yield by epoxidation of the unsaturated dioxolanes with peracetic acid in ethyl acetate solution.[10] Epoxides so prepared are listed in Table I; the unsaturated dioxolanes were prepared by standard methods by acid-catalyzed acetalization of the glycol and unsaturated aldehyde.

An unexpected reaction was observed when a noncyclic acetal (crotonaldehyde di-*n*-butyl acetal, VII) was oxidized with peracetic acid. A higher temperature of reaction for a comparable conversion (based on peracid consumption) was required than for epoxidation of the cyclic acetals, and the major product was the unsaturated ester, butyl crotonate, VIII, in 73% yield.

$$\underset{\text{VII}}{CH_3CH{=}CHCH(OC_4H_9)_2} \xrightarrow{CH_3CO_3H} \underset{\text{VIII}}{CH_3CH{=}CHCO_2C_4H_9}$$

This reaction was found to be catalyzed by sulfuric acid. In fact, in the oxidation of an unsaturated cyclic acetal (VIa) from which the epoxide (VI) was isolated (45% yield) in the non-acid-catalyzed oxidation, none of the epoxide could be isolated from the acid-catalyzed oxidation. Only a high-boiling liquid which was difficult to purify could be isolated from the latter. The infrared spectrum and analysis of this liquid could be interpreted on the basis of a propylene glycol monocinnamate. The fairly large residues formed in the preparation of most of the epoxy-acetals may be attributable to this competing reaction.

TABLE I

UNSATURATED DIOXOLANES AND EPOXIDES

Compound	Name	R_1	R_2	R_3
I	2-(1,2-Epoxypropyl)-1,3-dioxolane	CH_3	H	H
Ia	2-(1-Propenyl)-1,3-dioxolane	CH_3	H	H
II	2-(1,2-Epoxypropyl)-4-methyl-1,3-dioxolane	CH_3	H	CH_3
IIa	2-(1-Propenyl)-4-methyl-1,3-dioxolane	CH_3	H	CH_3
III	2-(1,2-Epoxy-1-methylethyl)-1,3-dioxolane	H	CH_3	H
IIIa	2-Isopropenyl-1,3-dioxolane	H	CH_3	H
IV	2-(1,2-Epoxy-1-ethylpentyl)-1,3-dioxolane	n-C_3H_7	C_2H_5	H
IVa	2-(1-Ethyl-1-pentenyl)-1,3-dioxolane	n-C_3H_7	C_2H_5	H
V	2-(1,2-Epoxy-1-ethylpentyl)-4-methyl-1,3-dioxolane	n-C_3H_7	C_2H_5	CH_3
Va	2-(1-Ethyl-1-pentenyl)-4-methyl-1,3-dioxolane	n-C_3H_7	C_2H_5	CH_3
VI	2-(1,2-Epoxy-2-phenylethyl)-4-methyl-1,3-dioxolane	C_6H_5	H	CH_3
VIa	2-(β-Styryl)-4-methyl-1,3-dioxolane	C_6H_5	H	CH_3

Three saturated acetals (the diethyl acetals of butyraldehyde, benzaldehyde, and β-phenyl-β-ethoxypropionaldehyde) were oxidized with peracetic acid in the presence of sulfuric acid. These oxidations proceeded readily to give the corresponding ethyl esters, in yields of 69, 90, and 61%

$$R{-}CH(OC_2H_5)_2 + CH_3CO_3H \xrightarrow{H+} R{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5 + C_2H_5OH + HOAc$$

IX. R = n-C_3H_7—
X. R = C_6H_5—
XI. R = C_6H_5—$CH(OC_2H_5)$—CH_2—

respectively. It was observed qualitatively that the oxidation proceeds most readily for those acetals in which an electron deficiency on the "aldehyde" carbon can be stabilized by an adjacent unsaturation.

In all the literature of peracids there is no indication of this reaction. The oxidation of acetals to the corresponding acids by air or oxygen is known,[11] but the free acid is the exclusive or major product. Very little free acid was observed in the present peracid oxidation, and concentrations of the (presumed) alcohol coproduct could not have been high enough for a mechanism involving intermediate formation of free unsaturated acid followed

(5) J. P. Fourneau and S. Chantalou, *Bull. Soc. Chim. France*, **12**, 845 (1945); *Chem. Abstr.*, **40**, 6465 (1946).

(6) J. B. Wright, *J. Am. Chem. Soc.*, **79**, 1694 (1957).

(7) E. C. Kornfeld, *et al.*, *J. Am. Chem. Soc.*, **78**, 3087 (1956).

(8) S. Searles, Jr., E. K. Ives, and H. M. Kash, *J. Org. Chem.*, **22**, 919 (1957).

(9) G. Zasaki, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **78**, 113 (1957); *Chem. Zentr.*, **1957**, 6713.

(10) B. Phillips, F. C. Frostick, Jr., and P. S. Starcher, *J. Am. Chem. Soc.*, **79**, 5982 (1957).

(11) J. C. Martin and J. P. Hawk, U. S. Patent **2,887,512**, May 19, 1959.

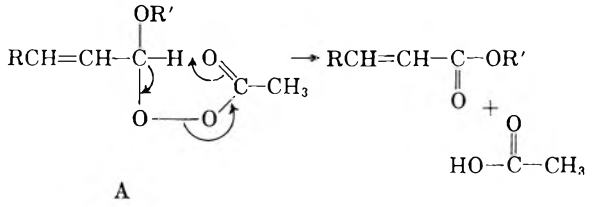
TABLE II

UNSATURATED DIOXOLANES

Compound	Yield, %	B.P., Mm.	n_D^{30}	Notes	Formula	Analysis: Calcd. C	Calcd. H	Calcd. Equiv. Wt.	Found C	Found H	Found Equiv. Wt.[a]
Ia	35	71/50	1.4380	b,c	$C_6H_{10}O_2$	—	—	114	—	—	117
IIa	55	71–73/40	1.4304	d	$C_7H_{12}O_2$	65.59	9.44	128	64.80	9.28	132
IIIa	—	31/10	1.4311 at 21°	e	$C_6H_{10}O_2$	—	—	—	—	—	—
IVa	71	86–88/10	1.4486		$C_{10}H_{18}O_2$	70.54	10.66	170	70.59	10.64	171
Va	41	92–95/10	1.4441	c	$C_{11}H_{20}O_2$	71.69	10.94	184	71.74	11.04	187
VIa	90	109/2	1.5428	d	$C_{12}H_{14}O_2$	75.76	7.42	190	76.33	7.62	189

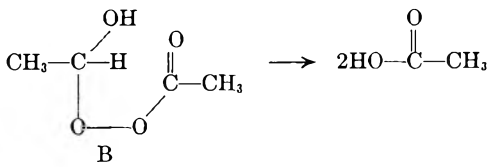
[a] See ref. 15. [b] Reported[6] b.p. 147°/760 mm. [c] No acid catalyst used. [d] 0.025% *p*-Methoxyphenol inhibitor added, and orthophosphoric acid catalyst used. [e] Prepared by H. A. Stansbury of this department.

by esterification. The ferrous ion induced decomposition of α-hydroperoxy ethers to esters is formally similar, although probably not mechanistically related, to the present oxidation.[12] It is possible that oxidation of the acetal to the ester proceeds through a hemiacetal peracetate (A), the formation of which would be catalyzed by strong acid



A

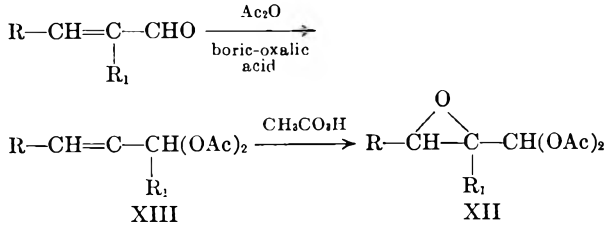
and which could decompose as indicated. A formal analogy is seen in the decomposition of acetaldehyde monoperacetate (B) to two molecules of acetic



B

acid.[10] However, other plausible mechanisms for oxidation of the unsaturated acetal to ester may be written, and it is not possible at present to define the most likely.

Two 1,1-diacetoxy-2-alkyl-2,3-epoxyalkanes (XII) were also prepared by peracetic acid epoxidation of the unsaturated acylals (XIII); the latter



XIII XII

were made by reaction of the unsaturated aldehydes with acetic anhydride, catalyzed by mixed boric-oxalic acid.[13] These were 1,1-diacetoxy-2-ethyl-2,3-epoxybutane (XII, R = CH_3, R_1 = C_2H_5) and 1,1-diacetoxy-2-ethyl-2,3-epoxyhexane (XII, R = *n*-C_3H_7, R_1 = C_2H_5).

(12) N. A. Milas, R. L. Peeler, Jr., and O. L. Mageli, *J. Am. Chem. Soc.*, **76**, 2322 (1954).

EXPERIMENTAL

Preparation of unsaturated dioxolanes. The following preparations of *2-(1-ethyl-1-pentenyl)-1,3-dioxolane* (IVa) illustrates the method which, with minor modifications, was used for the other dioxolanes listed in Table II.

The following mixture was refluxed for 13 hr. in a flask equipped with a condenser and Dean-Stark trap for continuous removal of water as formed: 378 g. (3.0 moles) of 2-ethyl-3-propylacrolein, 186 g. (3.0 moles) of ethylene glycol, 1000 ml. of benzene, and 1.9 g. of *p*-toluenesulfonic acid monohydrate. During this time 55 g. of water was removed. The reaction mixture was neutralized with 1.06 g. of sodium carbonate and fractionated to give 361 g. (71% yield) of 2-(1-ethyl-1-pentenyl)-1,3-dioxolane, b.p. 86–88°/10 mm., n_D^{30} 1.4486; lit.,[14] b.p. 98–101°/20 mm., n_D^{25} 1.4510.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66; equiv. wt., 170.24. Found: C, 70.59; H, 10.64; equiv. wt., 171.[15]

Epoxidation of unsaturated dioxolanes. The preparation of *2-(1,2-epoxypropyl)-4-methyl-1,3-dioxolane* (II) is illustrative of the method used for preparation of the epoxides listed in Table III.

To 128 g. (1.0 mole) of 2-(1-propenyl)-4-methyl-1,3-dioxolane (IIa) was added 349 g. of a solution of peracetic acid in ethyl acetate[10] (24.0%; *i.e.*, containing 84 g. or 1.1 moles peracetic acid) over a period of 4 hr. During this period the reaction mixture was stirred vigorously, and the temperature was maintained at 40°. After an additional 7 hr. at 40°, titration for peracetic acid[10] indicated that 93% of the theoretical peracetic acid has been consumed. The cooled reaction mixture was fed into ethylbenzene under reflux at 30–40 mm. pressure, and a mixture of acetic acid, ethylbenzene, and ethyl acetate was removed at the head of the column. Fractionation of the residue gave 67 g. (46% yield) of 2-(1,2-epoxypropyl)-4-methyl-1,3-dioxolane, b.p. 81–83°/15 mm., n_D^{30} 1.4291.

(13) This method of preparing acylals was developed and kindly furnished to us by L. W. McTeer, Development Department, Union Carbide Chemicals Company, U. S. Patent **2,866,813**, December 30, 1958.

(14) H. R. Nace and E. P. Goldberg, *J. Am. Chem. Soc.*, **75**, 3646 (1953).

(15) Double bond equivalent weights were determined by titration with bromine–sodium bromide reagent in methanol, a modification of the method outlined in S. Siggia, *Quantitative Organic Analysis via Functional Group*, 2nd ed., J. Wiley & Sons, N. Y., 1954, pp. 69–71.

TABLE III

EPOXYALKYL DIOXOLANES

Compound	Yield, %	B.P., Mm.	n_D^{30}	Formula	Analysis Calcd. C	Calcd. H	Found C	Found H
I	28	70–73/9[a]	1.4337	$C_6H_{10}O_3$	—	—	—	—
II	46	81–83/15	1.4291	$C_7H_{12}O_3$	58.31	8.39	57.83	8.32
III	64	78/20	1.4344	$C_6H_{10}O_3$	55.37	7.75	55.17	7.72
IV	67	90–93/5	1.4426	$C_{10}H_{18}O_3$	64.49	9.74	63.79	9.55
V	66	57–60/.4	1.4382	$C_{11}H_{20}O_3$	65.97	10.07	66.49	10.26
VI	45	111–112/1	1.5197	$C_{12}H_{14}O_3$	69.88	6.84	70.79	7.16

[a] Reported[5] b.p. 80°/18 mm.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.39; equiv. wt., 144. Found: C, 57.83; H, 8.32; equiv. wt.,[16] 149.

Oxidation of crotonaldehyde dibutyl acetal with peracetic acid. Crotonaldehyde dibutyl acetal was prepared by a known method[17] and exhibited the following properties b.p. 96–99°/10 mm., n_D^{31} 1.4247.

Peracetic acid in ethyl acetate (117 g. of a 22.9% solution; *i.e.*, containing 26.8 g. or 0.352 mole peracetic acid) was added over a period of 1 hr. to 64 g. (0.32 mole) crotonaldehyde dibutyl acetal. The temperature was maintained at 60°, and titration for peracetic acid at the end of this period indicated that the theoretical amount was consumed. The cooled reaction mixture was fed into ethylbenzene under reflux at 35 mm., and ethylbenzene, acetic acid, and ethyl acetate were removed at the head of the column. Fractionation of the residue gave 33 g. (73% yield) of butyl crotonate, b.p. 75–80°/20 mm. A redistilled sample exhibited the following properties: b.p. 75–78°/20 mm., n_D^{30} 1.4286.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.93; sapon. equiv. 142. Found: C, 68.26; H, 9.92; sapon. equiv. 139.5.

A portion of the butyl crotonate obtained above was saponified and acidified in the usual fashion, giving crystalline crotonic acid, m.p. and mixed m.p. with authentic *trans*-crotonic acid, 69–72°.

Oxidation of n-butyraldehyde diethyl acetal. The starting acetal[18] was prepared by reaction of the aldehyde with ethanol in the presence of calcium chloride and exhibited the following properties: b.p. 142°, n_D^{30} 1.3904.

To *n*-butyraldehyde diethyl acetal (10 g., 0.07 mole) containing 1 drop of concd. sulfuric acid was added 23 g. of a solution of peracetic acid (5.7 g., 0.075 mole) in ethyl acetate over a period of 30 min. The mixture was warmed to 40° and held there for 11 hr., at the end of which time titration for peracetic acid indicated a consumption of 99.3% of the theoretical. The cooled solution was washed with aqueous sodium carbonate, the layers were separated, and the organic layer was fractionated. There was obtained 4.0 g. of pure ethyl butyrate (b.p. 118–120°, n_D^{30} 1.3864), in addition to 6.0 g. of a mixed ethyl acetate and ethyl butyrate fraction (b.p. 80–118°) which, by gas chromatographic analysis, contained 1.6 g. of ethyl butyrate. Yield was thus 5.6 g. or 69%. The infrared spectrum of the isolated ethyl butyrate was identical with the standard (Sadtler) spectrum.

Oxidation of benzaldehyde diethyl acetal. The starting acetal[18] was prepared by reaction of benzaldehyde and ethyl orthoformate catalyzed by ammonium nitrate and exhibited the following properties: b.p. 75°/4 mm., n_D^{30} 1.4742.

Benzaldehyde diethyl acetal (54 g., 0.3 mole) containing 2 drops of concd. sulfuric acid was treated with 109 g. of a solution of peracetic acid (26.6 g., 0.35 mole) in ethyl acetate. The addition required 3 hr., during which time the temperature was maintained at 26–40° by ice-water cooling. After standing for 20 hr., the mixture was titrated for peracid, and it was found that the theoretical amount had been consumed. The solution was worked up as in the preceding experiment to give 41 g. (90% yield) of ethyl benzoate, b.p. 87–90°/10 mm., n_D^{30} 1.4993, the infrared spectrum of which was identical with that of an authentic specimen. From the distillation residue a small amount (*ca.* 0.5 g.) of benzoic acid (melting point and mixed melting point with an authentic sample, 117–119°) was isolated.

Oxidation of β-phenyl-β-ethoxypropionaldehyde diethyl acetal. The starting acetal was prepared by the method of Haworth and Lapworth[19] and exhibited the following properties: b.p. 127–130°/6 mm., n_D^{30} 1.4721.

β-Phenyl-β-ethoxypropionaldehyde diethyl acetal (37 g., 0.146 mole) was mixed with 67 g. of a solution of peracetic acid in ethyl acetate (a 22.5% solution; *i.e.*, containing 15 g. or 0.198 mole peracetic acid) and held at 40–60° for 7 hr. At this point 42% of the theoretical amount of peracid was consumed; upon adding 4 drops of concd. sulfuric acid the reaction became exothermic and warmed to 92°. After cooling, the solution was treated with 1 drop of cobalt naphthenate (to destroy peroxides) and 1.34 g. sodium acetate (to neutralize the sulfuric acid). Direct distillation of the reaction mixture gave 20 g. (61% yield) of ethyl β-phenyl-β-ethoxypropionate, b.p. 122–130°/10 mm., n_D^{30} 1.4866.

The ester (6.4 g.) was saponified with potassium hydroxide (3.6 g.) in ethanol-water in the usual fashion to give crystalline β-phenyl-β-ethoxypropionic acid (5.0 g.), m.p. 74–75° (ligroin).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27; equiv. wt., 194.2. Found: C, 68.47; H, 7.34; equiv. wt., 195.3.

The melting point reported in the literature for this acid

(16) Equivalent weight was determined by titration of epoxide group with pyridinium chloride–pyridine solution. See J. J. Jungnickel, E. D. Peters, A. Polgar, and F. T. Weiss in *Organic Analysis*, Vol. I, Interscience Publishers, Inc., N. Y., 1953, p. 136.

(17) R. H. Saunders, U. S. Patent 2,573,678, November 6, 1951.

(18) These acetals were prepared by H. E. Johnson of this department, to whom we are indebted for furnishing generous samples.

(19) Utilization of a literature method for preparing cinnamaldehyde diethyl acetal [R. D. Haworth and A. Lapworth, *J. Chem. Soc.*, **121**, 83 (1922)] gave, in our hands, β-phenyl-β-ethoxypropionaldehyde diethyl acetal as the only isolable product; the boiling point of this product was indistinguishable from the boiling point of cinnamaldehyde diethyl acetal (127–130°/6 mm.) prepared by another method [M. M. Kreevoy and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **77**, 5590 (1955)], the structure of which was confirmed by elemental analysis, infrared absorption spectrum, and oxidation by the method of this paper to ethyl cinnamate. The index of refraction of the unsaturated acetal was appreciably higher (1.5091 at 30°) than that of the β-ethoxy compound.

is 75°;[20] these authors also reported its conversion to cinnamic acid by boiling hydrochloric acid, a result which we duplicated. A sample of the acid (0.6 g.) was heated to boiling with 25 cc. 6.0*N* hydrochloric acid and gave, on cooling, crystalline cinnamic acid (0.45 g.), melting point and mixed melting point with authentic cinnamic acid, 130–132°.

Oxidation of 2-(β-styryl)-4-methyl-1,3-dioxolane (VIa) *with peracetic acid catalyzed by sulfuric acid.* To 76 g. (0.4 mole) of 2-(β-styryl)-4-methyl-1,3-dioxolane containing 0.76 g. of sulfuric acid was added with stirring 157 g. of a 24.3% solution of peracetic acid in ethyl acetate (*i.e.*, containing 38.0 g. or 0.5 mole peracetic acid) over a period of 1 hr. The reaction was exothermic from the outset, and the temperature was maintained at 25–33° by ice-water cooling. After an additional 4 hr. at 30°, titration for peracetic acid indicated the theoretical amount had been consumed. Sodium acetate, 1.25 g., was added to neutralize the sulfuric acid. Distillation through a glass helix-packed column gave, after recovery of solvent and acetic acid, 23 g. (28% yield) of impure propylene glycol monocinnamate, b.p. *ca.* 195°/1.25 mm., n_D^{30} 1.5483.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 71.92; H, 7.25.

1,1-Diacetoxy-2-ethyl-2-butene. To acetic anhydride (217 g., 2.15 moles) containing 0.34 g. of a mixed boric-oxalic acid catalyst[13] (1:1 molar ratio) was added 139 g. (1.42 moles) of 2-ethylcrotonaldehyde over a period of 35 min. The solution was stirred constantly, and slight cooling was required to maintain a temperature of 30°. After the mixture had stood for an additional 20 hr., the catalyst was neutralized with 0.93 g. of sodium acetate, and the reaction mixture was fractionated directly to give 212 g. (75% yield) of 1,1-diacetoxy-2-ethyl-2-butene, b.p. 88–90°/4 mm., n_D^{30} 1.4339.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.58; H, 8.21.

1,1-Diacetoxy-2,3-epoxy-2-ethylbutane. To 200 g. (1.0 mole) of 1,1-diacetoxy-2-ethyl-2-butene was added 396 g. of a solution containing 23.0% peracetic acid in ethyl acetate (91 g. or 1.2 moles peracetic acid). The addition and subsequent stirring (both at 60°) required 4 hr., at the end of which time the theoretical quantity of peracid was consumed. The cooled reaction mixture was fed to ethylbenzene under reflux in a still at 30 mm. pressure while acetic acid and unchanged peracetic acid was removed continuously at the still head as an ethylbenzene azeotrope. Fractionation of the residue gave 119 g. (55% yield) of 1,1-diacetoxy-2,3-epoxy-2-ethylbutane, b.p. 95–96°/3.0 mm., n_D^{30} 1.4289.

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.46; H, 7.42.

1,1-Diacetoxy-2-ethyl-2-hexene. This preparation based on 2-ethyl-3-propyl acrolein and acetic anhydride was similar to that for 1,1-diacetoxy-2-ethyl-2-butene. Yield of 1,1-diacetoxy-2-ethyl-2-hexene was 75%, b.p. 91–95°/2.0 mm., n_D^{30} 1.4366.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.48; H, 8.82.

1,1-Diacetoxy-2,3-epoxy-2-ethylhexane. The epoxidation of the above olefin was analogous to the preparation of 1,1-diacetoxy-2,3-epoxy-2-ethylbutane with the following results. Yield of 1,1-diacetoxy-2,3-epoxy-2-ethylhexane was 72%, b.p. 102–103°/1.25 mm.; n_D^{30} 1.4308.

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.17; H, 7.90.

SOUTH CHARLESTON, W. VA.

(20) W. Schreuth, W. Schoeller and R. Streunsee, *Ber.*, 44, 1432 (1911).

[CONTRIBUTION FROM THE SUMMIT RESEARCH LABORATORIES, CELANESE CORP. OF AMERICA]

Decomposition of Mixed Carboxylic-Carbonic Anhydrides[1a]

THOMAS B. WINDHOLZ[1b]

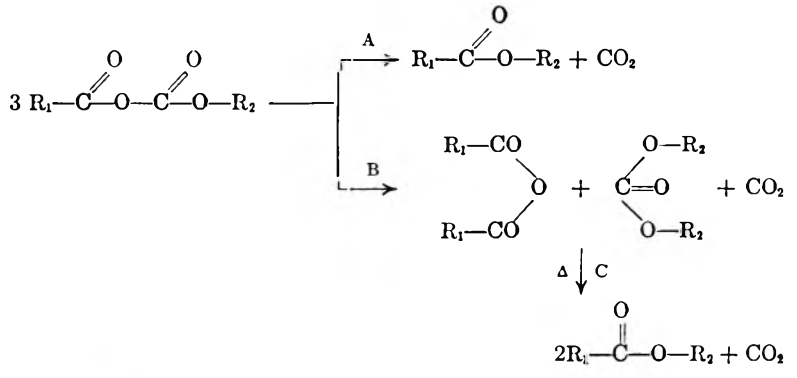
Received June 22, 1959

The decomposition of a number of mixed carboxylic-carbonic anhydrides has been investigated and the occuring reactions established. It was found that the structures of both the carboxylic (R_1) and carbonic (R_2) components have directing influences on the possible paths of decomposition. Polar and steric effects as well as proposed reaction mechanisms are discussed. A method of preferential ester formation from mixed anhydrides is demonstrated for ethyl benzoate.

The preparation and characterization of stable carboxylic-carbonic anhydrides was first reported by Tarbell and Leister.[2] Since then it has been established[3a,3b] that mixed carboxylic-carbonic anhydrides decompose according to Equations A and B

(1)(a) Part of this work has been presented before the Division of Organic Chemistry at the 136th Meeting of the American Chemical Society, Atlantic City, September 1959.

(1)(b) Present Address: Merck Sharp and Dohme Research Laboratories, Rahway, N. J.



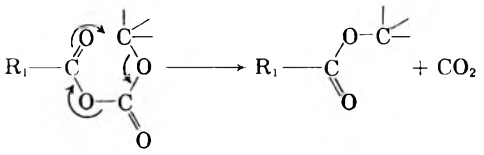
Decomposition may occur exclusively by either path A or B, or by both paths simultaneously with the formation of ester, symmetrical anhydride, carbonate, and carbon dioxide. In the present work it has been found that in some cases the ratio of products formed may vary with the temperature of decomposition. Certain mixed anhydrides which decompose equally by path A and B at 160°, yield more ester than symmetrical anhydride when the temperature of decomposition is raised to 200°. When the temperature is 250° however, ester is the only decomposition product. This fact suggests a secondary reaction (C) between symmetrical anhydrides and carbonates and it was possible to demonstrate this reaction experimentally by the preparation of certain esters in very good yields by this procedure at elevated temperatures. From these experiments it was concluded that at the decomposition temperatures reported in the table below, the isolated esters are formed only according to reaction path A, and the possibility of reaction C occurring under these conditions can be excluded.

The procedure for the preparation and quantitative decomposition of the mixed anhydrides is described in the experimental part and includes the volumetric determination of the amount of carbon dioxide formed. This amount was in good agreement with the ratio of ester to symmetrical anhydride that was obtained. Since the instability of some mixed anhydrides made it necessary to decompose them *in situ*, it was necessary to decompose all mixed anhydrides in this way without isolation and purification so that standard conditions would be maintained. To ascertain whether the possibility of impurities present in the crude carboxylic-carbonic anhydride may influence the direction of decomposition, a number of stable mixed anhydrides were prepared and purified according to Tarbell and Leister[2] and submitted to decomposition. These results were in good agreement with the values obtained with the crude mixed anhydrides. Decomposition temperatures for unstable mixed anhydrides were determined in the original tetrahydrofuran solution in order to obtain information on their relative stabilities. In the isolation and characterization of reaction products heating was avoided to prevent any secondary reactions.

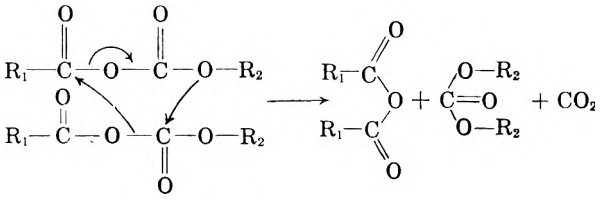
The results of the experiments with carboxylic-carbonic anhydrides are listed in Table I. Relative yields of esters and symmetrical anhydrides are considered sufficient to represent reaction paths A and B.

A number of mixed anhydrides derived from aliphatic acids decompose exclusively by path A (Experiments 1–5) while aromatic derivatives tend to decompose equally along paths A and B. The differences in reactivity are not fully understood, although steric factors are apparently significant. Directing influences of the alkyl radicals R_2 have been examined only for a few typical examples. These experiments indicate that the more electron releasing isopropyl group favors easier decomposition by path A. Phenyl as R_2 favors path B as shown by the high yields of symmetrical anhydride obtained in Experiments 10 and 15. This effect is counterbalanced only in the cases where the acyl radicals have been shown to cause ester formation exclusively (*cf.* Experiment 5).

An S_Ni-type reaction mechanism, involving a six membered cyclic transition state is suggested



to explain ester formation (path A) by intramolecular decarboxylation.[4] The disproportionation (path



B) can best be represented as in accordance with the disproportionation mechanism of phenyl chloroformates suggested by Wiberg and Shryne.[5]

A number of experiments were made to influence the direction of decomposition of benzoic-ethyl carbonic anhydride, which was considered to be a suitable model compound. It was noticed that heating the mixed anhydride in the presence of triethylamine hydrochloride lowered the decomposition temperature and favored ester formation. Triethylamine alone lowered the decomposition temperature but the ratio of the products formed, remained unchanged. Boron trifluoride etherate has proved to be most efficient in directing the decarboxylation of benzoic-ethyl carbonic anhydride. It lowered the decomposition temperature considerably and caused exclusively ethyl benzoate formation. Acid catalysis of this type substantiates the mechanism proposed for path A. This method of preparing esters from mixed anhydrides is being investigated further.

(2) D. S. Tarbell and N. A. Leister, *J. Org. Chem.*, **23**, 1149 (1958).

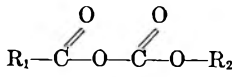
(3) (a) Preliminary communication: T. B. Windholz, *J. Org. Chem.*, **23**, 2044 (1958); (b) D. S. Tarbell and F. J. Longosz, *J. Org. Chem.*, **24**, 774 (1959).

(4) R. Boschan: *J. Am. Chem. Soc.* **81**, 3341 (1959) has postulated a four-membered cyclic transition state with acyl fission based largely on analogies with the preparation of nitrate esters from alkylchloroformates. The observation of Tarbell and Longosz, ref. 3b that ester formation proceeds with retention of configuration, supports our proposed mechanism.

(5) K. B. Wiberg and T. M. Shryne, *J. Am. Chem. Soc.*, **77**, 2774 (1955).

TABLE I

DECOMPOSITION OF CARBOXYLIC-CARBONIC ANHYDRIDES



Expt. No.	R_1	R_2	Decomp. Temp. in THF	Decomp. Temp. When isolated	% of CO_2 formed[a]	% Products formed: Ester (A)	% Products formed: Symmetrical Anhydride (B)
1	$CN-CH_2-$	$-C_2H_5$	25	...	97	95[b]	...
2	NO_2-C$_6$H$_4$-CH_2-	$-CH(CH_3)_2$	25	...	92	95[c]	...
3	NO_2-C$_6$H$_4$-CH_2-	$-C_2H_5$	25–40	...	94	90[d]	...
4	C$_6$H$_5$-CH_2-	$-C_2H_5$	35–60	...	92	90[b]	...
5	NO_2-C$_6$H$_4$-CH_2-	-C$_6$H$_5$	25–40	...	88	90[c]	...
6	$CH_3-CH_2-CH_2-$	$-C_2H_5$	...	120–130	85	75[e]	15
7	$(CH_3)_3C-$	$-C_2H_5$	...	120–130	70	50	30
8	C$_{13}$H$_9$-CH-	$-CH(CH_3)_2$	...	[f]	..	20[d]	60
9	C$_{13}$H$_9$-CH-	$-C_2H_5$	...	[c]	..	10[c]	70
10	C$_{13}$H$_9$-CH-	-C$_6$H$_5$	...		..	...	95[d,g]
11	NO_2-C$_6$H$_4$-	$-C_2H_5$	...	150–160	77	50[c]	50
12	C$_{10}$H$_7$-	$-C_2H_5$	...	150–160	72	50[e]	50
13	C$_6$H$_5$-	$-CH(CH_3)_2$	...	160–170	78	60[e]	40
14	C$_6$H$_5$-	$-C_2H_5$	...	175–185	72	50[c]	50
15	C$_6$H$_5$-	-C$_6$H$_5$	...	[f]	..	10	80[d,g]

[a] Theoretical yield calculated for path A. [b] Distilled from the reaction mixture, characterized by boiling point, analysis and comparison of infrared spectrum with an authentic sample. [c] See experimental part. [d] Isolated from the reaction mixture, identified by analysis and melting point. [e] Ratios of formed products were satisfactorily determined by preparing artificial mixtures of the expected products and comparing the infrared spectra. [f] Decomposed in a few hours at room temperature. [g] Diphenyl carbonate was isolated in nearly the same yield from the reaction mixture.

It should be mentioned that the decarboxylation of alkyl chloroformates is reported[6] to be catalyzed by pyridine and boron trifluoride.

EXPERIMENTAL

Melting points are uncorrected. Microanalyses are by Mr. Grant Gustin of our Analytical Department. Infrared spectra were taken on a Perkin Elmer Infracord, Model 137. Commercially available carboxylic acids, dry tetrahydrofuran, and dry triethylamine were used in all preparations. The chloroformates were obtained from the Food Machinery and Chemical Corporation and redistilled before use. All preparations and decompositions of mixed anhydrides were run in a closed system equipped for volumetric determination of the carbon dioxide formed.[7]

(6) S. Nakanishi, T. C. Myers, and E. V. Jensen, *J. Am. Chem. Soc.*, **77**, 5033 (1955).

I. *Preparation of esters. A. From a mixed anhydride. Glycol dibenzoate.* Benzoic-ethylene carbonic anhydride was prepared from benzoic acid and ethylene glycol bischloroformate, according to the general procedure described below. The product isolated by crystallization from petroleum ether (b.p. 45–60°) melted at 70–72° and had infrared bands at 1820, 1740 cm^{-1}.

Anal: Calcd. for $C_{18}H_{14}O_6$: C, 60.40; H, 3.90. Found: C, 60.27; H, 3.81.

The crystalline mixed anhydride was gradually heated and at 130°–150° approximately 72% of the theoretical carbon dioxide was eliminated. The infrared spectrum of the reaction products was identical with that of an artificial mixture of equimolecular amounts of glycol dibenzoate, benzoic anhydride, and ethylene carbonate. When heating was continued to 250°, additional carbon dioxide was eliminated, and the mixture showed an increase in glycol dibenzoate content. In another experiment 3.58 g. (0.01 mole) of the same mixed anhydride was heated directly to 275°. A loss in weight of 0.82 g. was recorded, in good agreement with the nearly quantitative carbon dioxide elimination. The solid residue, after one recrystallization from methanol, yielded 2.20 g. (82%) glycol dibenzoate, m.p. 73–74°, undepressed by an authentic sample prepared from ethylene glycol and benzoyl chloride.

B. From symmetrical anhydrides and neutral carbonates. Glycol dibenzoate. A mixture of 2.26 g. (0.01 mole) of benzoic anhydride and 0.88 g. (0.01 mole) of ethylene carbonate was heated and at 220–275°, 92% of the theoretical amount of carbon dioxide was formed. The cooled product was recrystallized from methanol yielding 2.17 g. (80%) glycol dibenzoate, m.p. 73–74°.

Phenyl benzoate. On heating equimolecular amounts of benzoic anhydride and diphenyl carbonate at 205°–245°, 90% of the ester melting at 70°, was obtained.

Attempted preparation of ethyl benzoate. No reaction took place between benzoic anhydride and diethyl carbonate at 200°. Attempts to promote the reaction by heating the reactants in the presence of ethyl benzoate, benzoic-ethyl carbonic anhydride or boron trifluoride etherate also failed to produce the expected ester.

II. Preparation and decomposition of mixed carboxylic-carbonic anhydrides. A. Preparation. A solution of 0.02 mole of carboxylic acid and 0.02 mole of triethylamine in 35 ml. tetrahydrofuran was cooled to −1° to −5°. To this stirred solution was added a solution of 0.02 mole of the chloroformate in 15 ml. of tetrahydrofuran maintaining the above temperature during addition and for an additional 30 min. The stirred mixture was allowed to warm to room temperature and held there for 30 min.

B. Decomposition. 1. Stable compounds. When the mixed anhydrides were stable, *i.e.* no carbon dioxide evolution occurred at this point, the precipitated triethylamine hydrochloride was filtered, washed, and dried, and isolated in nearly quantitative yield. The salt was also checked for water solubility and its solution acidified to indicate any unchanged carboxylic acid. The tetrahydrofuran filtrate was concentrated *in vacuo* to constant weight at room temperature. The stable products obtained from experiments 6, 7, 11, 12, 13, and 14 were heated without further purification, the carbon dioxide formed was determined and the decomposition products identified. The emphasis was on the identification of esters and anhydrides, since the more volatile carbonates were frequently evaporated during the concentration step. Crystalline products were isolated and characterized, avoiding any heating. Ratios of oily products were satisfactorily determined by preparing artificial mixtures of the expected materials and comparing the infrared spectra. To check the results, experiments 11, 12 and 14 were also run with pure mixed anhydrides prepared as described by Tarbell and Leister.[2] These had the same infrared spectra as the crude mixed anhydrides and on heating gave the same amounts of decomposition products. A few examples are given to illustrate typical procedures.

p-Nitrobenzoic–ethyl carbonic anhydride,[2] 2.40 g. (0.01 mole) was heated at 150–180° until evolution of carbon dioxide ceased; at this point 77% of the theoretical amount was collected. Treatment with petroleum ether (b.p. 45–60°) and ether yielded 0.80 g. of insoluble product having only anhydride absorption. The filtrate on concentration gave a fluffy yellow powder which on crystallization from ethanol gave 0.96 g. (49%) of ethyl nitrobenzoate, m.p. 56–57°. The 0.80 g. insoluble product was treated with cold ethylacetate and filtered yielding 0.71 g. (46%) of *p*-nitrobenzoic anhydride, m.p. 189°.

2. Unstable compounds. Whenever the mixed anhydrides were unstable as shown by carbon dioxide evolution in their preparation, the reaction mixtures were kept for 2 hr. at 0°, cooled to −5° and the triethylamine hydrochloride filtered. Even in these experiments the salt was obtained in nearly quantitative yield. The cold filtrate was divided into two parts. One half was allowed to warm up to room temperature and heated if necessary to complete the carbon dioxide elimination. The other half was concentrated *in vacuo* without heating. The decomposition products were characterized and their ratios found to be almost identical in both cases.

p-Nitrophenylacetic–isopropyl carbonic anhydride. The tetrahydrofuran filtrate decomposed at room temperature in 30 min. After concentration, the reaction product (2.12 g.) was a semisolid material which showed only traces of anhydride absorption in the infrared. Isopropyl *p*-nitrophenylacetate,[3] m.p. 33–34° was isolated by careful addition of water to an ethanol solution of the reaction product.

Diphenylacetic-ethyl carbonic anhydride. The tetrahydrofuran filtrate was refluxed for 20 min. No carbon dioxide was eliminated. The mixture was cooled, and concentrated to give a semicrystalline residue. On treatment with petroleum ether (b.p. 45–60°) ether, 3.15 g. of solid was obtained. After washing with cold ethanol, 2.70 g. (66.5%) of diphenylacetic anhydride, m.p. 96–97° remained. The petroleum ether–ether filtrate on concentration yielded 0.42 g. (9%) of ethyl diphenylacetate, m.p. 59°.

III. *Directed decarboxylation of benzoic–ethyl carbonic anhydride.* When the mixed anhydride was prepared in tetrachloroethane instead of tetrahydrofuran, the triethylamine hydrochloride did not precipitate. Carbon dioxide was eliminated on refluxing to 145° and was completed after 45 min. The solution was cooled, washed with water, and concentrated. It contained 75% ethyl benzoate and 25% benzoic anhydride as shown by infrared analysis. Refluxing pure mixed anhydride in tetrachloroethane in the absence of triethylamine salt produced no decomposition and the mixed anhydride was recovered unchanged after 1 hr. When pure benzoic–ethyl carbonic anhydride was heated in the presence of triethylamine, decarboxylation started at 120° and was terminated at 140°. Equal amounts of ester and symmetrical anhydride formed, as shown by infrared analysis.

Addition of 25% of the molar amount of boron trifluoride etherate to the mixed anhydride caused slow elimination of carbon dioxide accompanied by the evolution of heat. However further heating was needed to complete gas evolution. After 30 min. the brown mixture was dissolved in ether, washed with dilute hydrochloric acid, bicarbonate solution, water, then dried and concentrated. It consisted of 85% ethyl benzoate and 15% benzoic anhydride. Addition of one molar amount of boron trifluoride etherate to the mixed an-

(7) The apparatus was a modification of that described by W. M. Schubert, *J. Am. Chem. Soc.*, **71**, 2639 (1949).

(8) H. P. Ward and E. F. Jankins, *J. Org. Chem.*, **10**, 371 (1945).

hydride caused exothermic decarboxylation with elimination of the theoretical amount of carbon dioxide. The reaction mixture was worked up by hydrolizing the boron trifluoride complex that was formed. No more anhydride could be detected, the decarboxylation yielding ethyl benzoate exclusively, in excellent yield.

Acknowledgments. The author expresses his appreciation to Dr. J. B. Clements and Dr. A. B. Conciatori for reviewing this manuscript and to Mr. Harry Barnum for skilled technical assistance.

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[CONTRIBUTION FROM THE CARWIN CO.]

Ketones as Catalysts in the Reduction of Aromatic Nitrogen Compounds

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The use of aromatic ketones in catalytic amounts in the methanolic sodium hydroxide reduction of *o*-nitrotoluene has considerably improved the yields of the desired azoxytoluene; further reduction of the latter and of azoxybenzene to their hydrazo derivatives has been effected by the use of a catalytic amount of 9-fluorenone.

Aromatic hydrazo compounds are available *via* the reduction of azoxy or azo compounds,[1-10] which are intermediates in the properly controlled reduction of nitro compounds. The direct reduction of nitro compounds to the corresponding hydrazo derivatives can be accomplished with zinc dust and sodium hydroxide or electrolytically; both procedures have been used to give the simplest member, hydrazobenzene.[7,11]

The chemical reduction of *o*-nitrobromobenzene to dibromohydrazobenzene is accomplished with the halo groups remaining intact[12]; many electrolytic reduction procedures have been reported with yields varying from 50 to 95%.[10,13]

A magnesium–magnesium iodide system has also been employed as a reducing agent for the azobenzenes.[14]

The earliest method of reducing aromatic nitro compounds[4] to their azoxyderivatives by the use of methanolic sodium methoxide is limited in its application, mainly because the reduction of the nitro compounds does not proceed beyond the azoxy stage, and it is confined to substituted nitrobenzenes in which the substituents are not affected by the reagent. Thus, in the case of *o*-chloronitrobenzene, considerable displacement of the chloride with methoxide ion occurs, and in the case of nitrotoluenes, extensive intramolecular oxidation-reduction takes place.[15]

In order to extend the scope of this method to the reduction of azoxy and azo compounds to their hydrazo derivatives and to improve the yields of the former, a number of catalysts were investigated. In the reduction of *o*-nitrotoluene (Table I), the addition of 3–5% of a ketone as a catalyst to the reducing medium has considerably increased both the yield and the purity of azoxytoluene; also, 9-fluorenone is an effective catalyst in the reduction of azo and azoxy benzene and toluene (Table I) to their corresponding hydrazo derivatives.

Bamberger, *et al.*[16] proposed that the formation of azoxybenzene in the reduction of nitrobenzene results from condensation between the intermediates phenyl hydroxylamine and nitrosobenzene; this has been further confirmed by Ogata, *et al.*,[17] who also found that a rapid equilibrium takes place between phenyl hydroxylamines and nitrosobenzene. The poor yield of azoxytoluene encountered in the methanolic sodium hydroxide reduction of *o*-nitrotoluene could be attributed in

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(1) H. E. Bigelow and D. B. Robinson, *Org. Syntheses*, Coll. Vol. III, 103 (1955).

(2) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, 70, 3738 (1948).

(3) M. Busch and K. Schulz, *Ber.*, 62, 1458 (1929).

(4) H. S. Fry and J. L. Cameron, *J. Am. Chem. Soc.*, 49, 864 (1927); C. M. Suter and F. B. Dains, *J. Am. Chem. Soc.*, 50, 2733 (1928).

(5) H. E. Bigelow and A. Palmer, *Org. Syntheses*, Coll. Vol. II, 57 (1943).

(6) G. Bacharach and R. Weinstein, *Rec. trav. chim.*, 54, 932 (1935).

(7) P. Ruggli and M. Kinovker, *Helv. Chim. Acta*, 17, 396 (1934).

(8) L. Zechmeister and P. Rom, *Ann.*, 468, 128 (1929).

(9) C. Weygand, *Organic Preparations*, Interscience Publishers, New York, 1945, p. 249.

(10) S. Swann, Jr., *Technique of Organic Chemistry*, A. Weissberger, Ed., Vol. II, Interscience Publishers, New York, 1956, p. 486.

(11) L. Gattermann and H. Wieland, *Laboratory Methods of Organic Chemistry*, The Macmillan Company, New York, 1938, p. 184.

(12) H. R. Snyder, C. Weaver, and C. D. Marshall, *J. Am. Chem. Soc.*, 71, 289 (1949).

(13) S. Swann, Jr., *Trans. Electrochem. Soc.*, 69, 307 (1936); 77, 479 (1940).

(14) W. E. Bachmann, *J. Am. Chem. Soc.*, 53, 1524 (1931).

(15) *Chem. Zentr.*, 1908, I, 1345; O. Fischer and E. Hepp *Ber.*, 26, 2231 (1893).

(16) E. Bamberger and E. Renauld, *Ber.*, 30, 2278 (1897); E. Bamberger and A. Rising, *Ann.*, 316, 257 (1901); V. O. Lukashevich, *Compt. rend. acad. sci. U.R.S.S.*, 21, 376 (1938); *Chem. Abstr.*, 33, 3769 (1939).

(17) Y. Ogata, M. Tsuchida, and Y. Takagi, *J. Am. Chem. Soc.*, 79, 3397 (1957).

TABLE I

Compound	Catalyst, g.	Product	Yield, %
o-Nitrotoluene[a]	None	Azoxytoluene	62
o-Nitrotoluene[a]	9-Fluorenone, 5	Azoxytoluene	93
o-Nitrotoluene[a]	Benzanthrone, 5	Azoxytoluene	90
o-Nitrotoluene[a]	Anthrone, 5	Azoxytoluene	84
o-Nitrotoluene[a]	Benzophenone, 5	Azoxytoluene	78
o-Nitrotoluene[a]	Xanthone, 5	Azoxytoluene	76
Azoxybenzene[b]	None	Azoxybenzene	—
Azobenzene[b]	9-Fluorenone, 5	Hydrazobenzene	98
Azoxybenzene[b]	9-Fluorenone, 5	Hydrazobenzene	98
Azoxytoluene[b]	9-Fluorenone, 5	Hydrazotoluene	83

[a] In this experiment, 137 g. (1 mole) of *o*-nitrotoluene was reduced with 80 g. of sodium hydroxide and 80 g. of methanol. [b] In this experiment, 140 g. of azo or azoxy compound was reduced with 108 g. of sodium hydroxide and 192 g. of methanol.

large part to an extensive oxidation of the methyl group in *o*-nitrotoluene.[15] The addition of a catalytic amount of a ketone, therefore, appears to decrease the extent of this side reaction by increasing both the rate of the formation of nitrosotoluene and its subsequent reduction to *o*-tolylhydroxylamine; the latter, in turn, condenses with the nitroso compound to give azoxytoluene. Similarly 9-fluorenone acts as a catalyst in the reduction of azo and azoxy compounds to their hydrazo derivatives with methanolic sodium hydroxide, a reagent quite ineffective for this reduction without the catalyst. In both of these cases, 9-fluorenone has presumably acted as an intermediary in the reaction; its role as a catalyst, therefore, must involve its initial reduction to fluorenol by the reducing medium, resulting in the formation of the rapid oxidation-reduction system[18,19] fluorenone-fluorenol, equation (a), which is essential in effecting further reduction of the azo and azoxy compounds to their hydrazo derivatives. In fact, fluorenol was an equally effective catalyst in these reductions, and when fluorenone was refluxed in methanolic sodium hydroxide, it was converted quantitatively to fluorenol. The various steps in the reductions could be formulated by the following reaction sequence:

(a) Fluorenone + CH_3ONa ⟶ Fluorenol + HCOONa

Fluorenone ⇌ Fluorenol

(b) Fluorenol + $ArNO_2$ ⟶ Fluorenone + ArNO + H_2O

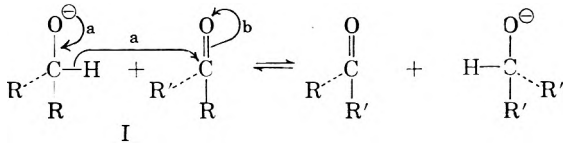
(c) Fluorenol + ArNO ⇌ Fluorenone + ArNHOH

(d) ArNHOH + ArNO ⟶ ArN(O)=NAr + H_2O

(e) Fluorenol + ArN(O)=NAr ⟶ ArN=NAr + Fluorenone + H_2O

(f) ArN=NAr + Fluorenol ⇌ ArNHNHAr + Fluorenone

The mechanism for the base-catalyzed carbinol-carbonyl equilibrium was formulated by Woodward, *et al.*,[20] in close analogy to Hammett's mechanism for the Cannizzaro reaction,[21] involving the direct transfer of hydrogen with its two bonded electrons from the carbinol carbon to the carbonyl carbon. Further, Doering and Aschner[22] have demonstrated that the mechanism of the equilibrium proceeds through a carbon to carbon transfer of hydrogen with its electrons, and was unaffected by substances which often inhibit free-radical chain reactions. The role of the alkoxide is probably to facilitate hydride transfer (I, Process a)



I

and to increase the acceptor capacity of the carbonyl carbon (I, Process b). In fact, in the absence of alkoxide ion, such an equilibrium is too slow to be detectable.

Doering and Aschner[23] have used the rapid oxidation-reduction system fluorenol—fluorenone in the stereochemical equilibration of optically active secondary alcohols and the epimerization of fenchol.

To illustrate the mechanism of the fluorenol-catalyzed reduction of an aromatic nitro compound, nitrobenzene to azoxybenzene, two schemes could be written: (A) where the nitrogen, the least electronegative atom, is shown to be the

(18) R. H. Baker and H. Adkins, *J. Am. Chem. Soc.*, 62, 3305 (1940); H. Adkins, *J. Chem. Ed.*, 19, 218 (1942).

(19) We have found that this system could be used also as catalyst in effecting the reduction of 2-dimethylaminomethyl-4-methylphenol with methanolic sodium hydroxide to 2,4-dimethylphenol at 90°, while in the absence of such catalyst temperatures as high as 220° are required; thus, R. B. Woodward and W. E. Doering, *J. Am. Chem. Soc.*, 67, 860 (1945), reduced 7-hydroxy-8-piperidinomethylisoquinoline to 7-hydroxy-8-methylisoquinoline with methanolic sodium methoxide at 220° for ten hours, and similar conditions were used by Conforth, Conforth, and Robinson, *J. Chem. Soc.*, 682 (1942), in the reduction of piperidinomethylphenols.

(20) R. B. Woodward, N. Wendler, and F. Butschy, *J. Am. Chem. Soc.*, 67, 1426 (1945).

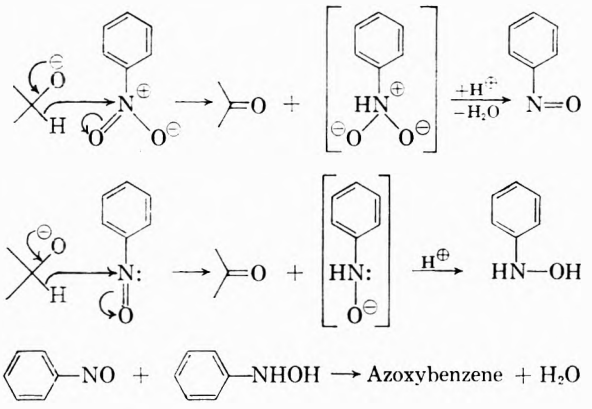
(21) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 350–353.

(22) W. von E. Doering and T. C. Aschner, *J. Am. Chem. Soc.*, 75, 393 (1953).

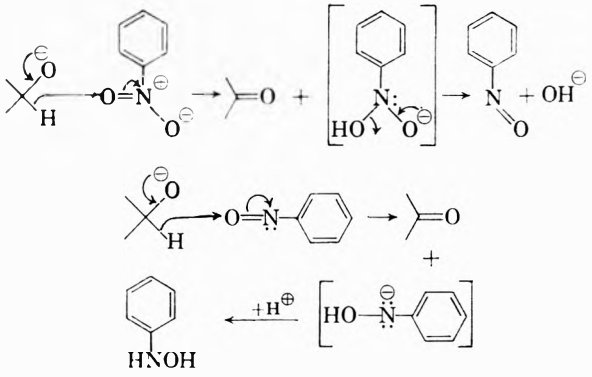
(23) W. von E. Doering and T. C. Aschner, *J. Am. Chem. Soc.*, 71, 838 (1949).

hydride acceptor, in analogy to the alkoxide reduction of ketones, where the electropositive carbonyl carbon atom is the hydride acceptor; and (B) where the oxygen atom is the acceptor. There is, however, no evidence at this time in favor of either mechanism.

Scheme A:



Scheme B:



A mechanism essentially similar to the above could be written for the further reduction of azoxy and azo compounds to the corresponding hydrazoderivatives.

EXPERIMENTAL[24]

Azoxytoluene. In a 1-l. four-necked round bottom flask, equipped with a thermometer, condenser, addition funnel, and Trubore mechanical stirrer, were placed 80 g. of sodium hydroxide flakes and 80 g. of methanol. The reaction flask was heated to reflux; 5 g. of 9-fluorenone was added; the temperature was 85°. *o*-Nitrotoluene (137 g., 1 mole) was then added dropwise, over a period of 1 hr. 35 min.; during the addition the temperature rose to 102°. Heating and stirring were continued for 5 hr., at the end of which it was steam distilled to remove 9-fluorenone, *o*-toluidine, and any unreacted *o*-nitrotoluene. The temperature of the reaction mixture was not allowed to rise above 110°; this was accomplished by occasional addition of water.

The reaction mixture was cooled to 80° and extracted with 300 ml. of benzene, which was filtered in case insoluble tar was present. The benzene was evaporated on a steam bath by blowing with inert gas or it was distilled with vacuum. An oil was obtained which crystallized immediately on cooling to room temperature. The solid weighed 105.7 g. (93% yield); after one crystallization from benzene-hexane mixture, it melted at 58–60° (reported[25] m.p. 58.5°). Its infrared spectrum was identical with that of azoxytoluene.

(24) All melting points are corrected.

Catalysts other than 9-fluorenone used under the above conditions were: benzanthrone (3.5 g.), yield of azoxytoluene, 90%; anthrone (5 g.), yield, 84%; benzophenone (5 g.), yield, 78%; xanthone (5 g.), yield, 76%.

Hydrazotoluene. In a 1-l. three-necked round bottom flask equipped with condenser, thermometer, and Trubore stirrer, were placed azoxytoluene (140 g., 0.62 mole), sodium hydroxide (108 g.), methanol (192 g.), and 9-fluorenone (5 g.); the mixture was heated to reflux while agitating for 46 hr.; the temperature was 96–98°. At the end of the reaction time, the reaction mixture became tan in color, and after addition of 400 ml. of methanol, it was cooled to room temperature and filtered. The solid was washed thoroughly with water to free the solid hydrazotoluene from sodium formate and alkali. After drying the solid hydrazotoluene, it was crystallized from ethanol; it then weighed 110 g. (84% yield), m.p. 163–165° (reported m.p. 165°,[26] 150°[27]); its infrared spectrum showed it to be identical with hydrazotoluene. In addition to hydrazotoluene, a mixture of azoxy- and azotoluene was also isolated.

Hydrazobenzene. In a 1-l. three-necked, round bottom flask, equipped with condenser, thermometer, and Trubore mechanical stirrer, were placed azoxybenzene (140 g., 0.7 mole), sodium hydroxide (108 g.), methanol (192 g.), and 9-fluorenone or 9-fluorenol (5 g.); the mixture was heated to reflux while agitating for 46 hr; the temperature was 96–98°. At the end of the reaction time the reaction mixture became tan in color and 500 ml. of water were added dropwise to dissolve sodium formate and to precipitate the hydrazobenzene which was filtered with suction, washed thoroughly with about 1.5 l. of water, and dried thoroughly. The solid, after crystallization from ethanol, weighed 130 g., amounting to a quantitative yield, m.p. 126–128° (reported m.p. 131,°[28] 127°,[29] 124°[30]). Its infrared spectrum showed it to be identical with an authentic sample of hydrazobenzene.

9-Fluorenol. In a 500-ml. flask equipped with a thermometer, stirrer, and condenser were placed 54 g. of sodium hydroxide (A.R.), 96 g. of commercial methanol, and 5 g. of 9-fluorenone. The reaction mixture was heated to reflux with stirring for 5 hr; it was cooled and filtered. The solid containing sodium formate was washed thoroughly with water, dried, and found to weigh 5 g. (quantitative yield), m.p. 148–150° (reported m.p. 158°,[31] 153°[32]). Its infrared spectrum was identical with that of an authentic sample prepared according to Hochstein.[33]

Acknowledgment. This study was undertaken as the result of a discussion with Professor W. von E. Doering; the author wishes to thank him for his interest and the benefit of later helpful suggestions. The author also wishes to thank Messrs. F. Geremia and E. Foster for excellent technical assistance.

NORTH HAVEN, CONN.

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(26) *Chem. Zentr.*, **1935**, II, 2126; P. S. Varma and V. A. Rao, *J. Ind. Chem. Soc.*, **6**, 915 (1929).

(27) B. Rassow, *J. Prakt. Chem.*, **84**, 335 (1911).

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(31) J. Loevenich, W. Becker, and T. Schröder, *J. Prakt. Chem.*, **127**, 248 (1930).

(32) H. Staudinger and A. Gaule, *Ber.*, **49**, 1951 (1916).

(33) F. A. Hochstein, *J. Am. Chem. Soc.*, **71**, 305 (1949).

[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES, BROWN UNIVERSITY]

Synthesis of Dinitrobenzomorpholines and a New Ring System, Triazolobenzomorpholines[1]

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Picramides (and related compounds, 1b, 1c) of β-amino alcohols in which there are bulky groups on the α-carbon undergo ring closure with various bases to give substituted benzomorpholines (II). A nitro group in position 5 is reduced to an amine (III) and diazotization results in cyclization to a new ring system (IV), triazolobenzomorpholines.

An attempt to prepare the picryl ether of 2-amino-2-methyl-1-propanol by an adaptation of the method of Cope and Burg[3] for synthesis of sulfonate esters of amino alcohols, (1) resulted in a

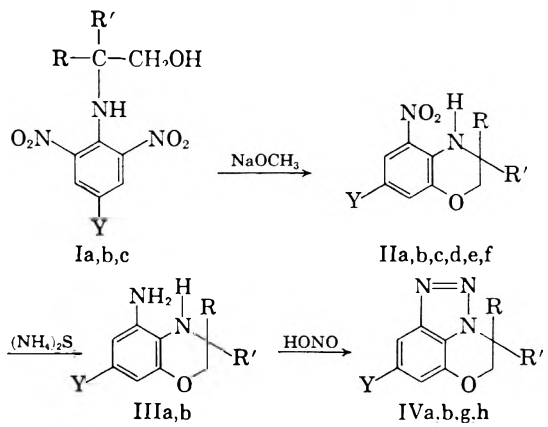
$$NaOCH_2CH_2NH_2 + C_6H_5SO_2Cl \longrightarrow C_6H_5SO_3CH_2CH_2NH_2 + NaCl \quad (1)$$

$$(CH_3)_2{-}CNH_2{-}CH_2ONa + (O_2N)_3C_6H_2Cl \longrightarrow IIa + NaCl \quad (2)$$

product in which the elements of nitrous acid had unexpectedly been lost. (2) The product was identified as 5,7-dinitro-3,3-dimethylbenzomorpholine, IIa (Chart I). This product could arise either from displacement of a nitro group by alkoxy (a well known reaction[4]) in a previously formed picramide(Ia to IIa) or from displacement of halogen by an amine in a previously formed ether. Neither reaction path has been used for benzomorpholine synthesis, where the simplest method appears to be ring closure on nitrogen, accomplished by reductive alkylation of a nitro group.[5,6] The mechanism of formation of the dinitrobenzomorpholines (II) is under study, but it will be assumed in the remainder of the present paper that the picramides (or I) are the starting compounds for the cyclization to benzomorpholines (II).

The benzomorpholine ring is only formed when compound I carries strong electron-withdrawing groups in the 4,6-positions and a nitro as leaving group in position 2. With nitro groups in positions 2 and 6, compound I will undergo ring closure when Y is $-NO_2$, $-CF_3$, $-CN$, but not when Y is $-COO^-$. With nitro groups in positions 2,4 and $-CF_3$ in position 6, ring closure could not be effected.

One arresting feature of the ring closure is that the group attached to the amino nitrogen must have a semblance to the shape or bulk of a *tert.*-butyl group which, of course, must include the β-hydroxy for the displacing group. The picramides of ethanolamine, 1-amino-2-propanol, 2-amino-3-butanol, 2-amino-1-butanol, and 1-amino-2-methyl-2-propanol[7] cannot be converted to benzomorpholines under the same conditions. Ring closures were effected in I (Y = NO_2) when R and R′ were both methyl, both hydroxymethyl, one methyl or ethyl and the other hydroxymethyl. This suggests that the present reaction is another manifestation of the unique character of geminal alkyl groups in accommodating ring closures.[8,9]



a. Y = NO_2, R = R′ = CH_3
b. Y = CF_3, R = R′ = CH_3
c. Y = CN, R = R′ = CH_3
d. Y = NO_2, R = C_2H_5, R′ = CH_2OH
e. Y = NO_2, R = CH_3, R′ = CH_2OH
f. Y = NO_2, R = R′ = CH_2OH
g. Y = NH_2, R = R′ = CH_3
h. Y = $NHCOC_6H_5$, R = R′ = CH_3

Chart I

A third factor not yet thoroughly investigated is the influence of base strength on ring closure. Sodium methoxide gave the best yields although excess of the amino alcohol (2-methyl-2-amino-1-propanol) gave a yield of 31% of IIa from the corresponding picramide, Ia. Sodium ethoxide, sodium hydride, and the sodium salts of the amino alcohols were less effective bases.

Identification of IIa as 5,7-dinitro-3,3-dimethyl-

(1) This work was supported in part by a grant from the Research Corporation.

(2) Allied Chemical and Dye Fellow, 1957–1958.

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(7) Mr. Glenn C. Morrison carried out these experiments.

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(9) C. K. Ingold, *J. Chem. Soc.*, 2676 (1922).

benzomorpholine precludes the possibility of rearrangement of the picramide Ia to an amino ether (β-amino-*tert.*-butyl 2,4,5-trinitrophenyl ether) before ring closure, as the amino ether would yield 6,8 - dinitro - 3,3 - dimethylbenzomorpholine. This pathway appeared to be in the realm of possibility as the conditions approximate those for the Smiles[10] rearrangement.

The proof of structure of IIa was accomplished by reduction of the 5-nitro group to an amine and diazotization of the 5-amino group (IIIa) to effect a second ring closure to a new ring system, IVa. Of necessity the amino group in III is in position 5 if the subsequent ring closure occurs. If a Smiles rearrangement had occurred, a nitro group at positions 6 or 8 could not be reduced and cyclized by diazotization.

Comparison of the infrared spectra of the triazolo compounds IVa, IVb, and IVg (Fig. 1)

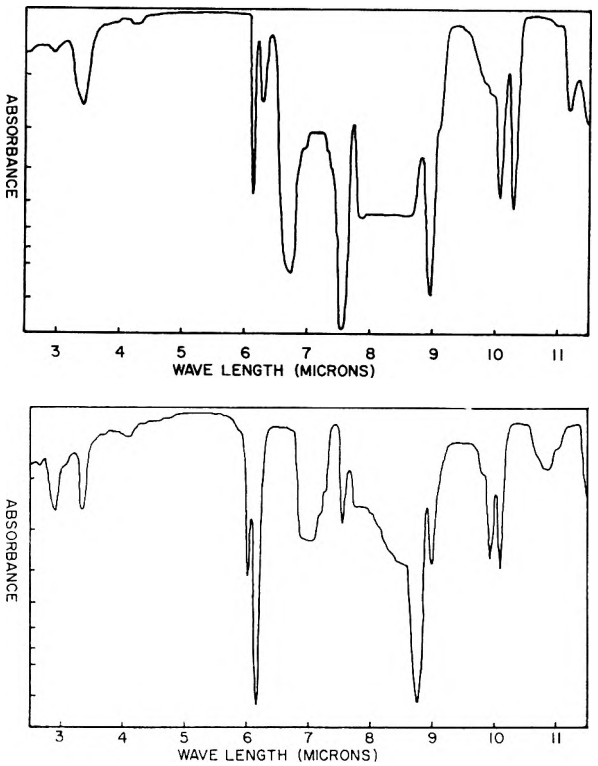

Fig. 1. Infrared spectra of 8-nitro-4,4-dimethyltriazolo-[1,5,4-d,e]benzomorpholine, IVa, and 8-amino-4,4-dimethyltriazolo[1,5,4-d,e]benzomorpholine, IVg, in chloroform (0.1% soln.) with sodium chloride prism. (Perkin-Elmer model 137 Infracord spectrophotometer)

with the aminobenzomorpholines IIIa and IIIb suggests that medium intensity bands at 10.1–10.2 μ may be characteristic of the triazolo ring in this three-ring system. Benzotriazole has a peak at 9.92 μ and Hartzel and Benson[11] suggest that characteristic absorption bands of the 4-alkyl-v-triazole ring system may lie between 9.8 and 10.3 μ.

The new triazolobenzomorpholine ring system compares in stability with the 4H-triazoloquinoline ring system, the nearest analog in the literature.[12] The triazolo ring system is aromatic in character and, indeed, very stable as is illustrated by the fact that oxidation of benzotriazoles cleaves the benzene ring in preference to the triazole ring, yielding triazoledicarboxylic acids.

The nitro group in IVa (the last one remaining from the original starting compound, picryl chloride) was easily reduced catalytically with hydrogen in the presence of platinum to give 8-amino-4,4-dimethyltriazolo [1,5,4-d,e] benzomorpholine[13] (IVg). The amino group was easily diazotized and coupled with various reagents to give a series of dyes (Table I) related to benzomorpholine dyes,[14] patented for use in dyeing cellulose acetate rayon and nylon.

The secondary nitrogen in the morpholine ring of IIa was not alkylated by methyl iodide and no derivative could be obtained with phenylisothiocyanate, Schotten-Baumann, or Hinsberg reagents. Nitrosation could not be effected with nitrous acid nor with nitrosyl chloride in pyridine. If the benzomorpholine IIa has the properties of a dinitroaniline, one might expect to cleave the ring to an amino ether. This could not be done in aqueous media and sodium ethoxide in ethanol gave a reaction in which no fragments could be identified. The ether linkage in the benzomorpholine was not cleaved by hydrochloric or hydrobromic acid under strenuous conditions while 57% hydriodic acid and pyridine hydrochloride (at 220°) gave profound decomposition.

EXPERIMENTAL[15]

Picramides. The picramides of ethanolamine,[16] m.p. 109.5–110.5°, 2-amino-1-butanol, m.p. 90–92°, 1-amino-2-propanol, m.p. 132.5–133.5°, 2-amino-3-butanol, m.p. 100–102.5°, diethanolamine, m.p. 138–139.5°, and 1-amino-2-methyl-2-propanol, m.p. 160.6–161.6°[17] were prepared by standard procedures except for the last (see ref. 17). Other picramides, Ib and Ic were not isolated but were used directly to prepare the corresponding benzomorpholine. Indeed, these picramides could not be isolated in pure form.

(10) J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, 49, 362 (1951).

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(15) Melting points are corrected. Analyses by S. M. Nagy, Microchemical Laboratory, M.I.T., Cambridge, Mass.

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TABLE I

COUPLING COMPOUNDS OF 8-AMINO-4,4-DIMETHYLTRIAZOLO[1,5,4-d,e]BENZOMORPHOLINE

Coupling Compound	M.P.	Color	Yield, %	Formula	Calcd. C	Calcd. H	Found C	Found H
Dimethylaniline	181–183[a]	or.-yel.	76	$C_{18}H_{20}N_6O$	64.26	5.99[b]	64.28	6.10
Diethylaniline	149–151	orange	82	$C_{20}H_{24}N_6O$	65.91	6.64	66.66	6.52
α-Naphthylamine	245–247	dk. red	70	$C_{20}H_{18}N_6O$	67.02	5.06[c]	67.03	5.21
Resorcinol	225 dec.	or.-red	20	$C_{16}H_{15}N_5O_3$	59.07	4.65	59.96	4.71

[a] Melting points uncorrected. [b] Calcd.: N, 24.99. Found: N, 25.10. [c] Calcd.: N, 23.45. Found: N, 22.80.

Various methods of recrystallization of compound Ia resulted in a product, m.p. 103–110°, whose nitrogen content lay between the value calculated for picramide, 18.7%, and dinitrobenzomorpholine, 16.6%. The carbon content of the product also lay between that of the picramide and the dinitrobenzomorpholine. When an attempt to prepare the picramide was made in the presence of excess amino alcohol, IIa, instead, was obtained in 31% yield.

5,7-Dinitro-3,3-dimethylbenzomorpholine, IIa. In a 2-l. three-necked flask fitted with a stirrer, dropping funnel, and a condenser carrying a calcium chloride tube was placed 60.0 g. (0.24 mole) of picryl chloride in 600 ml. of absolute methanol. To this was added 46.5 g. (0.52 mole) of 2-amino-2-methyl-1-propanol and the solution was refluxed 45 min. Thirty grams (0.55 mole) of sodium methoxide in 200 ml. of absolute methanol was added over a period of 10 min. from the dropping funnel. The mixture was stirred 30 min. longer at reflux, cooled in ice, and the product removed and washed thoroughly with water and dilute methanol. In several runs the product weighed 40.5–45.1 g., m.p. 173–175.5°. Recrystallization from 800 ml. of benzene gave 29.0–35.6 g., 47–58% yield, m.p. 174.5–176°.

Anal. Calcd. for $C_{10}H_{11}N_3O_5$: C, 47.40; H, 4.35; N, 16.61. Found: C, 47.73; H, 4.50; N, 16.21.

The compound took up the calculated amount of hydrogen in the presence of platinum oxide for two nitro groups but the product rapidly decomposed in air and was not further characterized.

7-Nitro-5-amino-3,3-dimethylbenzomorpholine, IIIa. A mixture of 31.1 g. (0.123 mole) of IIa in 400 ml. of 95% ethanol and 200 ml. of 28% ammonium hydroxide was stirred mechanically at 45–55° while a slow stream of hydrogen sulfide was introduced at the bottom of the suspension over a 2.5-hr. period. The red solution was cooled in ice and the red product removed by filtration. Concentration of the filtrate at reduced pressure to 250 ml. gave a total of 18 g. of product. The product was washed with carbon disulfide and recrystallized from toluene to yield 15.6g. (57%) of 7-nitro-5-amino-3,3-dimethylbenzomorpholine, m.p. 180.5–183.5° dec. The reaction was carried out with some dispatch since it oxidized rapidly in solution.

Vacuum sublimation gave an analytical sample and the compound was reasonably stable after purification; m.p. 182.5–184.5° dec.

Anal. Calcd. for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.83. Found: C, 53.65; H, 6.17; N, 18.67.

A benzal derivative was prepared by the method of Vogel[18] and recrystallized from 95% ethanol, m.p. 160–163°.

Anal. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.51; N, 13.50. Found: C, 65.32; H, 5.78; N, 13.64.

A monoacetyl derivative prepared by the method of Vogel[19] was sublimed *in vacuo* to give an analytical sample, m.p. 195–196.5°.

Anal. Calcd. for $C_{12}H_{15}N_3O_4$: C, 54.34; H, 5.70; N, 15.84. Found: C, 53.80; H, 5.58; N, 15.76.

8-Nitro-4,4-dimethyltriazolo[1,5,4-d,e]benzomorpholine, IVa. Five grams (0.022 mole) of 7-nitro-5-amino-3,3-dimethylbenzomorpholine (IIIa) was dissolved in 50 ml. of warm 20% sulfuric acid and then cooled to 0°. The solution was stirred mechanically during the addition of a solution of 1.7 g. (0.025 mole) of sodium nitrite in 10 ml. of water over a 10-min. period. The resulting mixture was stirred for 15 min. longer at 0–10°. Filtration and recrystallization from dilute ethanol yielded 4.9 g. (93%) of dark needles, m.p. 147–153°. Vacuum sublimation gave an analytical sample of yellow needles, m.p. 151.5–153.5°.

Anal. Calcd. for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.43; H, 4.51; N, 24.36.

Comparison of the infrared spectra of compounds IVa and IVg is afforded in Fig. 1.

8-Amino-4,4-dimethyltriazolo[1,5,4-d,e]benzomorpholine, IVg. A sample of 8-nitro-4,4-dimethyltriazolo[1,5,4-d,e]-benzomorpholine (0.92 g., 0.0039 mole) was dissolved in 30 ml. of absolute methanol and reduced with hydrogen at 1 atm. in the presence of 0.25 g. of platinum oxide (prereduced). The theoretical volume of hydrogen was taken up. Removal of the solvent gave a slightly discolored product but vacuum sublimation at 186° (1 mm.) gave 0.50 g. (62%) of white cubic crystals, m.p. 217.5–220.5° dec. (darkens 214°).

Anal. Calcd. for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.91; N, 27.43. Found: C, 59.17; H, 6.07; N, 27.39.

A benzoyl derivative, IVh, was recrystallized from dilute methanol and sublimed at 215° (1 mm.), m.p. 219.5–221.5°.

Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.28; H, 5.16; N, 18.01.

5-Nitro-7-cyano-3,3-dimethylbenzomorpholine, IIc. 3,5-Dinitro-4-chlorobenzoic acid was obtained in 95% yield from *p*-chlorobenzoic acid as described in the literature.[20] The acid was converted to an amide (m.p. 186°) by way of the acid chloride (m.p. 58°) according to directions of Lindemann and Wessel[21] in 83% yield.

A finely powdered mixture of 12.4 g. (0.051 mole) of 3,5-dinitro-4-chlorobenzamide was heated with 12 g. (0.084 mole) of phosphorus pentoxide for 15 min. in a metal bath at 300–350°. The resulting pale yellow nitrile was distilled from the reaction flask, b.p. 220–225° (15 mm.). Recrystallization of the solidified product from methanol gave 5.5 g. (48%) of short needles, m.p. 137–141°. The analytical sample by repeated recrystallizations from methanol melted at 143–144.5°.

Anal. Calcd. for $C_7H_2N_3O_4Cl$: C, 36.94; H, 0.89; N, 18.46. Found: C, 37.01; H, 1.35; N, 18.30.

Three grams (0.013 mole) of 3,5-dinitro-4-chlorobenzonitrile was refluxed for 0.5 hr. with 2.5 g. (0.028 mole) of 2-amino-2-methyl-1-propanol in 60 ml. of absolute methanol. Addition of 1.6 g. (0.028 mole) of sodium methoxide in 60 ml. of absolute methanol and refluxing 0.5 hr. longer gave 1.5 g. of orange product after evaporation of most of the solvent. Recrystallization from methanol yielded 1.2 g.

(18) A. I. Vogel, *A Textbook of Practical Organic Chemistry*, Longmans, Green and Co., New York (1951), 2nd Ed., p. 625.

(19) Ref. 12, pp. 556–7.

(20) F. Ullmann and N. Wosnessensky, *Ann.*, **366**, 92 (1909).

(21) H. Lindemann and W. Wessel, *Ber.*, 58B, 1221 (1925).

(39%) of 5-nitro-7-cyano-3,3-dimethylbenzomorpholine, fluffy orange crystals, m.p. 176–181°. A sublimed sample (160°, 1 mm.) was used for analysis, m.p. 180–181.5°.

Anal. Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.76; N, 18.02. Found: C, 56.47; H, 4.92; N, 17.82.

By a procedure similar to that described for compound IIa above, the following dinitrobenzomorpholines were obtained:

3-Hydroxymethyl-3-ethyl-5,7-dinitrobenzomorpholine, IId, orange crystals, m.p. 139.5–141°, 37%.

Anal. Calcd. for $C_{11}H_{13}N_3O_6$: C, 46.64; H, 4.63; N, 14.84. Found: C, 46.51; H, 4.78; N, 14.90.

3-Hydroxymethyl-3-methyl-5,7-dinitrobenzomorpholine, IIe, orange crystals, m.p. 147.2–148.6°, 47%.

Anal. Calcd. for $C_{10}H_{11}N_3O_6$: C, 44.61; H, 4.12; N, 15.61. Found: C, 44.84; H, 3.95; N, 15.80.

3,3-Dihydroxymethyl-5,7-dinitrobenzomorpholine, IIf, yellow powder, m.p. 158.5–160 dec., 31%.

Anal. Calcd. for $C_{10}H_{11}N_3O_7$: C, 42.11; H, 3.89; N, 14.73. Found: C, 41.93; H, 4.05; N, 14.64.

5-Nitro-7-trifluoromethyl-3,3-dimethylbenzomorpholine, IIb. Two nitro groups are best introduced into 4-chlorobenzotrifluoride one at a time as described by Friedrich and Schniepp.[22] The first nitration gave 3-nitro-4-chlorobenzotrifluoride in 84% yield[23] and the second 3,5-dinitro-4-chlorobenzotrifluoride[24] in 85% yield. Seven grams (0.026 mole) of the dinitro compound was dissolved in 50 ml. of absolute methanol. The solution was refluxed with 4.65 g. (0.05 mole) of 2-amino-2-methyl-1-propanol for a few minutes, 4.0 g. of sodium methoxide was added in 50 ml. of methanol, and refluxing was continued 10 min. The product was precipitated by adding 50 ml. of water and recrystallized from 90% methanol to yield 4.8 g. (67%) of 5-nitro-7-trifluoromethyl-3,3-dimethylbenzomorpholine, golden needles, m.p. 107–109°. A sublimed analytical sample melted at 108–109.5°.

Anal. Calcd. for $C_{11}H_{11}N_2O_3F_3$: C, 47.83; H, 4.01; N, 10.14. Found: C, 48.09; H, 4.19; N, 10.13.

5-Amino-7-trifluoromethyl-3,3-dimethylbenzomorpholine, IIIb. In the presence of 0.30 g. of platinum oxide (prereduced) 1 g. of 5-nitro-7-trifluoromethylbenzomorpholine was reduced quantitatively in 40 ml. of absolute methanol at 1 atm. of hydrogen pressure in 1 hr. After removal of solvent the product was sublimed at 70° (1 mm.) to give 0.80 g. (90%) of white 5-amino-7-trifluoromethyl-3,3-dimethylbenzomorpholine, m.p. 80–82°.

Anal. Calcd. for $C_{11}H_{13}N_2OF_3$: C, 53.65; H, 5.37; N, 11.38. Found: C, 53.88; H, 5.43; N, 11.30.

8-Trifluoromethyl-4,4-dimethyltriazolo[1,5,4-d,e]benzomorpholine, IVb. A sublimed sample (0.27 g., 0.0011 mole) of 5-amino-7-trifluoro-3,3-dimethylbenzomorpholine, IIIb, was dissolved in 30 ml. of warm 50% sulfuric acid and then cooled in ice. An ice-cold solution of 0.12 g. (0.0017 mole) sodium nitrite in 10 ml. of water was added slowly over a 10-min. period with stirring. The reaction mixture was poured into 100 ml. of water and the white precipitate was collected. Recrystallization from dilute methanol gave 0.10 g. (35%) of short white needles, m.p. 101–102.5°.

Anal. Calcd. for $C_{11}H_{10}N_3OF_3$: C, 51.36; H, 3.92; N, 16.34. Found: C, 51.16; H, 4.09; N, 16.01.

Azo Dyes from 8-Amino-4,4-dimethyltriazolo[1,5,4-d,e]-benzomorpholine, IVg. Standard procedures for diazotization of 8-amino-4,4-dimethyltriazolo[1,5,4-d,e]benzomorpholine and coupling with various compounds in sodium acetate solution were employed to obtain the dyes described in Table I. The dyes were all recrystallized from 95% ethanol.

PROVIDENCE 12, R. I.

(22) M. E. Friedrich and L. E. Schniepp, U. S. Patent 2,257,093 (1941).

(23) R. A. Benkeser and W. E. Buting, *J. Am. Chem. Soc.*, **74**, 3011 (1952).

(24) L. M. Yagupol'skii and V. S. Mospan, *Ukrain. Khim. Zhur.*, **21**, 81 (1955); *Chem. Abstr.*, **49**, 8866 (1955).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, M. S. UNIVERSITY]

Chloromethylation of Some Coumarin Derivatives

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Received March 28, 1960

Several coumarin derivatives have been chloromethylated and the structures of the chloromethyl derivatives established by direct comparison of the methyl derivatives, obtained on reduction, with the known compounds or authentic specimens synthesized for this purpose.

The chloromethylation of coumarins has not been studied so far. As chloromethyl derivatives are useful for the synthesis of a variety of compounds, the present work was undertaken. Coumarin, 4-methylcoumarin, 4′-methyl-1,2-naphtha-α-pyrone, and 7,8-dimethoxy-4-methylcoumarin on chloromethylation with paraformaldehyde and hydrogen chloride gave the corresponding 3-chloromethyl derivatives. Higher chloromethyl derivatives could not be obtained. The chloromethyl derivatives were reduced to the corresponding 3-methylcoumarin derivatives and directly compared with the authentic specimens.

7-Methoxy-4-methylcoumarin with one mole of paraformaldehyde gave a mixture from which only the 6-chloromethyl derivative could be isolated in a pure state. This was reduced to 7-methoxy-4,6-dimethylcoumarin. With 2.3 moles of paraformaldehyde a mixture was obtained from which both the 3,6- and the 3,8-dichloromethyl derivatives were isolated. These were reduced to the corresponding 3,4,6-trimethyl- and 3,4,8-trimethylcoumarin, which were synthesized for comparison by the Pechmann condensation of ethyl-α-methyl acetoacetate with 4-methyl- and 2-methylresorcinol respectively and subsequent methylation of the hydroxycoumarins formed. The 3,6,8-trichloromethyl derivative was obtained by the further chloromethylation of the above dichloromethyl derivatives and by the chloromethylation of 7-methoxy-4-methylcoumarin in ethylene dichloride in presence of zinc chloride.

TABLE I. CHLOROMETHYLCOUMARINS

No.	Substance	Product Obtained	M.P.	Yield, %	Formula	C, %		H, %		Cl, %	
						Found	Calcd.	Found	Calcd.	Found	Calcd.
1	Coumarin	3-Chloromethyl-	111	33	$C_{10}H_7O_2Cl$	61.51	61.69	3.51	3.59	17.99	18.30
2	4-Methylcoumarin	3-Chloromethyl-	139–140	73	$C_{11}H_9O_2Cl$	63.18	63.30	4.02	4.31	16.61	17.00
3	7-Methoxy-4-methylcoumarin	6-Chloromethyl-	246	10[a]	$C_{12}H_{11}O_3Cl$	60.81	60.37	4.73	4.61	14.52	14.88
		3,6-Dichloromethyl-	195	Poor[a]	$C_{13}H_{12}O_3Cl_2$	54.28	54.35	3.92	4.18	24.60	24.73
		3,8-Dichloromethyl-	199–200	Poor[a]	$C_{13}H_{12}O_3Cl_2$	54.36	54.35	4.06	4.18	24.79	24.73
		3,6,8-Trichloromethyl-	168	22	$C_{14}H_{13}O_3Cl_3$	50.13	50.06	3.82	3.87	32.02	31.74
4	Methyl 7-hydroxy-4-methylcoumarin-6-carboxylate	3,8-Dichloromethyl-	202	80	$C_{14}H_{12}O_5Cl_2$	51.26	50.75	3.63	3.62	21.41	21.45
5	7-Hydroxy-4-methylcoumarin-6-carboxylic acid	3,8-Dichloromethyl-	[b]	71	$C_{13}H_{10}O_5Cl_2$	49.70	49.21	3.12	3.15	22.16	22.39
6	Methyl 7-methoxy-4-methylcoumarin-6-carboxylate	3-Chloromethyl-coumarin-6-carboxylic acid	188–190	72	$C_{13}H_{11}O_5Cl$	55.64	55.22	4.01	3.88	12.07	12.56
7	7,8-Dimethoxy-4-methyl coumarin	3-Chloromethyl-	140–141	36	$C_{13}H_{13}O_4Cl$	58.48	58.10	5.16	4.84	13.68	13.22
8	4′-Methyl-1,2-naphtha-α-pyrone	3′-Chloromethyl-	205–206	33	$C_{16}H_{11}O_2Cl$	70.02	69.63	4.29	4.25	13.99	13.73

[a] Mixture of various products formed; hence the yield of the isolated product is poor. [b] The product decomposes at about 210° and swells up. The resulting solid does not melt even on strong heating.

On reduction 7-methoxy-3,4,6,8-tetramethylcoumarin was obtained as seen by direct comparison with the methyl ether of the product from the Pechmann condensation of 2,4-dimethylresorcinol and ethyl-α-methyl acetoacetate. Attempts to chloromethylate 7-hydroxy-4-methyl-, 7,8-dihydroxy-4-methyl-, and 5,7-dihydroxy-4-methylcoumarin and its dimethyl ether resulted in the formation of polymeric products from which it was difficult to isolate a product with definite melting point.

7-Hydroxy-4-methylcoumarin-6-carboxylic acid and its methyl ester could not be chloromethylated in aqueous solution but in glacial acetic acid using anhydrous zinc chloride the 3,8-dichloromethyl derivatives were obtained. These were reduced and the products compared with the authentic specimens. Methyl-7-hydroxy-3,4,8-trimethylcoumarin-6-carboxylate required for comparison was synthesized by the Pechmann condensation of methyl 2,4-dihydroxy-3-methylbenzoate with ethyl-α-methyl acetoacetate. This was hydrolyzed to the corresponding acid which on decarboxylation gave 7-hydroxy-3,4,8-trimethylcoumarin.

Methyl-7-methoxy-4-methylcoumarin-6-carboxylate on chloromethylation gave only 7-methoxy-3-chloromethyl-4-methylcoumarin-6-carboxylic acid, which was reduced to the corresponding 3,4-dimethyl derivative and compared with an authentic specimen.

All the chloromethylcoumarins have been converted into the acetoxymethyl and methoxymethylcoumarins.

EXPERIMENTAL

All melting points are uncorrected.

Chloromethylations. (a) 4-Methyl-, 7-methoxy-4-methyl-, and 7,8-dimethoxy-4-methylcoumarin, and 4′-methyl-1,2-naphtha-α-pyrone have been chloromethylated as follows: A mixture of the coumarin derivative (0.02 mole) in minimum quantity of acetic acid (80%) and paraformaldehyde (0.02 mole) was treated with hydrogen chloride at 60–70° for 1 hr. and the mixture was left overnight. Next day the product which separated as such or on dilution with water was filtered, washed with alcohol, and crystallized from benzene. When only monochloromethylation takes place, better yields of the products are obtained by using 2 to 3 moles of paraformaldehyde. 7-Methoxy-4-methylcoumarin on chloromethylation with 2.3 moles of paraformaldehyde gave a mixture which was separated by dissolving it in excess of hot benzene and allowing it to cool. The 3,8-dichloromethyl derivative started separating in the form of needles. After a time when the other isomer, which crystallized in the form of buds, started separating, the solution was filtered. The residue on further crystallization from benzene yielded the pure 3,8-dichloromethyl derivative. The filtrate on further cooling yielded the 3,6-isomer in a pure form.

(b) Coumarin, 7-hydroxy-4-methylcoumarin-6-carboxylic acid, its methyl ester and methoxy methyl ester were chloromethylated as follows: A mixture of coumarin derivative (0.01 mole) in glacial acetic acid (50 ml.), paraformaldehyde (excess) and zinc chloride (0.01 mole) was heated on a steam bath and dry hydrogen chloride passed through it for 1 hr. The chloromethyl derivative which separated on cooling as such or on dilution with water was further crystallized from benzene.

TABLE II

REDUCTION PRODUCTS FROM CHLOROMETHYLCOUMARINS DESCRIBED IN TABLE I

No.	Coumarin[a]	M.P.	Formula	C, % Found	C, % Calcd.	H, % Found	H, % Calcd.
1	3-Methyl-[a]	92	—	—	—	—	—
2	3,4-Dimethyl-[b]	115	—	—	—	—	—
3	7-Methoxy-4,6-dimethyl-[c]	181	$C_{12}H_{12}O_3$	70.08	70.58	5.68	5.88
	7-Methoxy-3,4,6-trimethyl-[d]	190	$C_{13}H_{14}O_3$	70.95	71.55	6.68	6.42
	7-Methoxy-3,4,8-trimethyl-[d]	188–190	$C_{13}H_{14}O_3$	71.15	71.55	6.06	6.42
	7-Methoxy-3,4,6,8-tetramethyl-[d]	131	$C_{14}H_{16}O_3$	72.40	72.39	6.51	6.94
4	7-Hydroxy-3,4,8-trimethyl-6-carbomethoxy-[e]	187	$C_{14}H_{14}O_5$	64.30	64.12	5.28	5.34
5	7-Hydroxy-3,4,8-trimethyl-6-carboxy-[f]	280	$C_{13}H_{12}O_5$	62.80	62.90	4.62	4.83
6	7-Methoxy-3,4-dimethyl-6-carboxy-[g]	248	$C_{14}H_{14}O_5$	64.22	64.12	5.38	5.34
7	7,8-Dimethoxy-3,4-dimethyl-[h]	109	$C_{13}H_{14}O_4$	66.85	66.60	5.96	6.00
8	3′,4′-Dimethyl-1,2-naphtha-α-pyrone-[i]	199–200	—	—	—	—	—

[a] The products described here have been directly compared with the authentic specimens synthesized as indicated for each product. C. Mentzer and P. Meunier, *Bull. Soc. Chim.*, 10, 356 (1943) [*Chem. Abstr.*, 38, 2649 (1944)]. [b] Peters and Simonis, *Ber.*, 41, 830 (1908). [c] Methylation of 7-hydroxy-4,6-dimethylcoumarin prepared according to Yanagita, *Ber.*, 71, 2269 (1938). [d] Methylation of the corresponding hydroxy derivative described in Table IV. [e] Pechmann condensation of methyl 2,4-dihydroxy-3-methylbenzoate with ethyl-α-methyl acetoacetate (described in Table IV). [f] Hydrolysis of 4. [g] Hydrolysis of methyl 7-methoxy-3,4-dimethylcoumarin-6-carboxylate prepared according to Sethna and Shah, *J. Indian Chem. Soc.*, 15, 383 (1938). [h] Methylation of 7,8-dihydroxy-3,4-dimethylcoumarin prepared according to Canter, Martin and Robertson, *J. Chem. Soc.*, 1877 (1931). [i] Chakravarti, *J. Indian Chem. Soc.*, 8, (407 1931).

TABLE III

ACETOXY AND METHOXYMETHYLCOUMARINS FROM THE CHLOROMETHYLCOUMARINS DESCRIBED IN TABLE I

S No.	Derivative Prepared	M.P.	Formula	C, % Found	C, % Calcd.	H, % Found	H, % Calcd.
1	A[a]	105–107	$C_{12}H_{10}O_4$	66.17	66.05	4.19	4.58
	B[a]	126	$C_{11}H_{10}O_3$	69.11	69.47	5.20	5.26
2	A	128	$C_{13}H_{12}O_4$	67.72	67.24	5.07	5.17
	B	72	$C_{12}H_{12}O_3$	70.80	70.58	5.76	5.88
3	A	191	$C_{14}H_{14}O_5$	63.86	64.12	5.47	5.34
	B	136	$C_{13}H_{14}O_4$	66.42	66.65	5.91	6.02
	A	180	$C_{17}H_{18}O_7$	60.72	61.07	5.67	5.38
	B	169	$C_{16}H_{18}O_5$	64.32	64.73	6.48	6.52
	A	174	$C_{17}H_{18}O_7$	61.40	61.07	4.98	5.38
	B	174	$C_{15}H_{18}O_5$	64.50	64.73	6.58	6.52
	A	203	$C_{20}H_{22}O_9$	59.02	59.11	5.22	5.46
	B	182	$C_{17}H_{22}O_6$	63.80	64.34	6.48	6.88
4	A	198	$C_{18}H_{18}O_9$	57.29	57.14	4.36	4.76
	B	138	$C_{16}H_{18}O_7$	59.42	59.62	5.48	5.59
5	B	138	$C_{16}H_{18}O_7$		Same as 4 B		
6	B[b]	175	$C_{15}H_{16}O_6$	61.37	61.64	5.13	5.47
7	A	148	$C_{15}H_{16}O_6$	61.48	61.50	5.16	5.48
	B	96	$C_{14}H_{16}O_5$	63.46	63.63	5.75	6.06
8	A	172	$C_{17}H_{14}O_4$	71.85	72.30	5.10	4.96
	B	116	$C_{16}H_{14}O_3$	75.83	75.59	5.37	5.51

[a] A = Acetoxymethyl; B = Methoxymethyl. [b] The product obtained is methyl 7-methoxy-3-methoxymethyl-4-methylcoumarin-6-carboxylate.

TABLE IV

COUMARINS SYNTHESIZED BY THE PECHMANN CONDENSATION OF ETHYL-α-METHYL ACETOACETATE WITH VARIOUS PHENOLS

No.	Phenol	Coumarin Obtained	M.P.	Formula	C, % Found	C, % Calcd.	H, % Found	H, % Calcd.
1	4-Methylresorcinol	7-Hydroxy-3,4,6-trimethyl-	266	$C_{12}H_{12}O_3$	70.27	70.58	5.39	5.88
2	2-Methylresorcinol	7-Hydroxy-3,4,8-trimethyl-	274	$C_{12}H_{12}O_3$	70.54	70.58	5.71	5.88
3	2,4-Dimethylresorcinol	7-Hydroxy-3,4,6,8-tetramethyl-	232	$C_{13}H_{14}O_3$	71.20	71.54	6.12	6.47
4	Methyl 2,4-dihydroxy-3-methylbenzoate	7-Hydroxy-3,4,8-trimethyl-6-carbomethoxy-	187		See Table II, No. 4			

The chloromethyl derivatives deteriorate when heated in aqueous or aqueous acetic acid solutions.

General reduction procedure. The chloromethyl derivative (0.5 g.) in acetic acid (8 ml.) and water (2 ml.) was treated during 0.5 hr. with zinc dust (0.5 g.) and the reaction mixture heated on a steam bath for 2 hr. in all. The reaction mixture was then filtered and poured into cold water. The methyl derivative which separated was crystallized from dilute acetic acid. It was necessary to add hydrochloric acid (0.5 ml.) in the case of 7-methoxy-3,6-dichloromethyl-4-methylcoumarin to prevent the formation of the diacetoxymethyl derivative, and in the case of 7-hydroxy-3,8-dichloromethylcoumarin and 7-methoxy-3-chloromethyl-4-methylcoumarin-6-carboxylic acid to precipitate the product.

Pechmann condensations. Equimolar proportions of ethyl-α-methyl acetoacetate and the required phenol were treated with sulfuric acid (80%) and kept for 24 hr. The next day the mixture was poured into water and the product obtained crystallized from rectified spirit (see Table IV).

Acetoxy methylcoumarins were prepared by refluxing the chloromethylcoumarin in glacial acetic acid with fused sodium acetate for 2 hr. (see Table III).

Methoxymethylcoumarins were prepared by refluxing the chloromethylcoumarin with methyl alcohol in the presence of fused potassium carbonate for 6 hr. (Table III).

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Pyridine 1-Oxides. VII. 3-Nitropyridine 1-Oxide[1a]

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3-Aminopyridine was converted to 3-nitropyridine 1-oxide by three different routes, the preferable one being preliminary oxidation with peroxysulfuric acid to 3-nitropyridine, followed by *N*-oxidation with 40% peracetic acid. In agreement with expectation, the nitro group of 3-nitropyridine 1-oxide could not be displaced by nucleophilic reagents such as methoxide ion and was inert toward acetyl chloride. Treatment of 3-nitropyridine 1-oxide with phosphorus oxychloride gave a mixture of 2-chloro-3-nitropyridine and 6-chloro-3-nitropyridine, and treatment with acetic anhydride gave 3-nitro-2-pyridone.

The usefulness and versatility of pyridine-1-oxides as synthetic intermediates is due both to the facility with which the *N*-oxide grouping can be introduced and selectively removed and to its unique amphoteric ability to facilitate both nucleophilic substitution and displacement reactions and electrophilic substitution reactions.[2] For example, the ready accessibility of 4-nitropyridine 1-oxides by direct nitration of the *N*-oxides,[3,4] and the ease with which such intermediates can be converted into other 4-substituted pyridine derivatives by reductive and nucleophilic displacement reactions of the 4-nitro group have been extensively exploited by organic chemists concerned with synthetic manipulations in the pyridine field.[2] The versatility of 4- (or 2-) nitropyridine-1-oxides as synthetic intermediates is due in part to conjugation of the nitro group with the *N*-oxide function, and a consequent ready displacement of the nitro group by attacking nucleophiles. With the unconjugated isomer, 3-nitropyridine 1-oxide, however, such nucleophilic displacements of the nitro group would not be expected, but facilitation of nucleophilic substitution in the 2-,4- and 6-positions should be observed. Preference for the 2-position would be anticipated by analogy, as nicotinamide-1-oxide upon treatment with phosphorus oxychloride and phosphorus pentachloride yields exclusively 2-chloronicotinonitrile,[5] and 3-halopyridine 1-oxides upon treatment with acetic anhydride give only 3-halo-2-pyridones.[6] An investigation of the chemistry of 3-nitropyridine 1-oxide thus appeared to be of both theoretical and possible synthetic interest.

3-Nitropyridine 1-oxide (III) has previously been prepared by the action of benzoyl nitrate on pyridine 1-oxide (very low yield)[7] and by direct oxidation of 3-nitropyridine with hydrogen peroxide in acetic acid (34% yield[7] and 40% yield[8]). The use of commercially available 40% peracetic acid is a convenient alternative to the above conditions and affords comparable yields (40.5%). Alternative routes were investigated but were much less satisfactory. For example, direct oxidation of 3-aminopyridine with peroxytrifluoroacetic acid gave a mixture of 3-nitropyridine (II) (21%) and 3-nitropyridine 1-oxide (III)(22%). An adaptation (I→IV→V→VI→III) of the procedure previously described by Brown[9] for the preparation of 2-nitropyridine 1-oxide from 2-

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(2) For a recent review of pyridine-1-oxide chemistry, see A. R. Katritzky, *Quart. Rev.*, **10**, 395 (1956).

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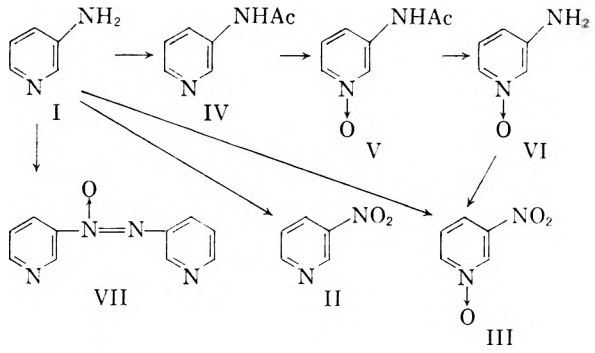
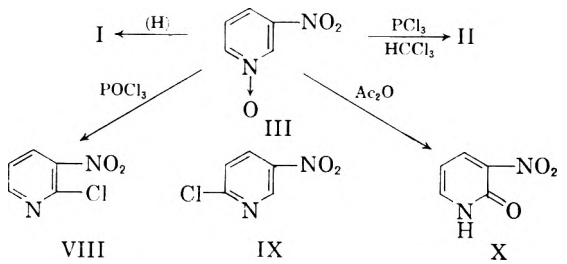


aminopyridine gave 3-nitropyridine 1-oxide (III) in only 14% overall yield.

Kimura and Takano[10] have recently reported that an attempt to prepare 3-nitropyridine (II) by oxidation of 3-aminopyridine with peroxysulfuric acid according to the method of Schickh[11] yielded only 3,3′-azoxypyridine (VII), and that further oxidation of VII was unsuccessful. Although no experimental procedure was reported, it was mentioned that Shindo[12] was able to prepare II by Schickh's method, in which the 3-aminopyridine was added to the peroxysulfuric acid. In this connection, Wiley and Hartman[13] have reported that addition of peroxysulfuric acid to a solution of 3-aminopyridine in sulfuric acid yields 3,3′-azoxypyridine and not 3-nitropyridine, and we have confirmed this result, even when 90% rather than 30% hydrogen peroxide was used. Thus, although 2- and 4-aminopyridines can be oxidized to the corresponding nitropyridines by either mode of addition,[13–15] 3-aminopyridine can be converted to 3-nitropyridine only by using the mode of addition originally specified by Schickh; namely, by addition of 3-aminopyridine to the peracid.

Treatment of 3-nitropyridine 1-oxide (III) with phosphorus trichloride resulted in smooth deoxygenation to 3-nitropyridine (II), and catalytic reduction of III gave 3-aminopyridine (I). No apparent reaction took, place when III was heated under reflux with acetyl chloride, and over 80% of the starting material was recovered unchanged. By contrast, 2- and 4-nitropyridine 1-oxides react violently with acetyl chloride at room temperature with copious evolution of nitrogen dioxide.[4,9] Refluxing III with methanolic sodium methoxide gave only a dark brown, tarry solid which rapidly absorbed water from the air and was not characterized. Analogous results were obtained when 2,6-dimethyl-3-nitropyridine 1-oxide was treated with sodium ethoxide.[16] In view of the failure of these attempts to effect nucleophilic displacement of the 3-nitro group in III, it is interesting that Katritzky, *et al.*[3] have reported the successful synthesis of 3-ethoxy- and 3-methoxypyridine 1-oxide by the action of the respective alkoxide on 3-chloropyridine 1-oxide.

A mixture of 2-chloro-3-nitropyridine (VIII) and 6-chloro-3-nitropyridine (IX) was obtained when 3-nitropyridine 1-oxide (III) was heated under reflux with phosphorus oxychloride. 3-Nitropyridine 1-oxide rearranges in 50% yield to 3-nitro-2-pyridone (X) upon heating with acetic anhydride.



Procedures have been recently described for the direct introduction of a nitrile group into the pyridine nucleus by nucleophilic attack of cyanide ion on an *O*-methyl salt of the *N*-oxide.[17,18] Although 3-nitropyridine(pK 0.90 ± 0.1) is reported to give a methiodide,[19] we have experienced difficulty in preparing the methiodide of 3-nitropyridine-1-oxide (pK − 1.2 ± 0.1).[20] Nevertheless, preliminary results indicate that cyanonitropyridines are formed in small amounts when III is subjected to this reaction. This work is still in progress.

EXPERIMENTAL[21]

3-Aminopyridine (I) was obtained from The Reilly Tar and Chemical Co. and sublimed at 60°/0.1 mm. to give clear hydroscopic plates, m.p. 63–65° (lit.,[22] m.p. 64°), which turn white upon exposure to air; *picrate*, m.p. 201–202°.

3-Acetamidopyridine (IV) was prepared as previously described[23]: m.p. 133–135° (lit. m.p. 133°).

3-Acetamidopyridine 1-oxide (V). To a solution of 14.0 g. of 3-acetamidopyridine in 15 ml. of acetic acid was slowly added 15 ml. of 40% peracetic acid, and the mixture was heated at 55° for 3 hr. and then at 65° for 4 hr. A catalytic amount of charcoal was added and the mixture heated 30

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(20) The lower pK of III as compared with II is in agreement with previous observations that heterocyclic *N*-oxides are weaker bases than their parent bases (a) C. C. J. Culvenor, *Rev. Pure and Applied Chem.*, **3**, 83 (1953); (b) H. H. Jaffé and G. O. Doak, *J. Am. Chem. Soc.*, **77**, 4441 (1955).

(21) All melting points are uncorrected.

(22) F. Friedl, *Ber.* **45**, 428 (1912).

(23) R. Camps, *Archiv. Pharm.*, **240**, 345 (1902).

min. at 50° to destroy residual peroxide. The acetic acid solution was then evaporated under reduced pressure and the yellow residue extracted with cold acetone to remove the last traces of acetic acid. The remaining almost colorless solid (11.7 g., 75%, m.p. 210–215°) was recrystallized from acetone to give colorless crystals, m.p. 216° (lit.,[20b] 215.5–216.5°).

3-Aminopyridine 1-oxide (VI). A mixture of 10 ml. of 10% aqueous sodium hydroxide, 50 ml. of 3% hydrogen peroxide, and 1.0 g. of 3-acetaminopyridine-1-oxide was heated under reflux for 1 hr., cooled to room temperature, an additional 25 ml. of 3% hydrogen peroxide added, and refluxing continued for an additional hour. The solution was then acidified with dilute hydrochloric acid to *p*H 6 and evaporated to dryness under reduced pressure. The residual tan solid was extracted with 100 ml. of boiling ethanol and the filtered extract evaporated to dryness. The residue was then extracted with 150 ml. of chloroform. Evaporation of the chloroform extract under reduced pressure yielded 0.51 g. (71%) of light yellow crystals, m.p. 121–124° (lit.,[24] m.p. 124–125°).

3-Nitropyridine 1-oxide (III). *Method A.* To 25 ml. of dichloromethane cooled to 2° in an ice bath was added with stirring 1.88 ml. of 90% hydrogen peroxide followed by 12.5 ml. of trifluoroacetic anhydride. The solution was stirred for 10 min. and then 1.5 g. of 3-aminopyridine dissolved in 15 ml. of dichloromethane was added dropwise over a period of 10 min. During the addition, the solution turned light green. The ice bath was removed and the solution was refluxed gently for 1 hr., during which time the color changed to light yellow. After cooling to room temperature, the solution was washed with two 100-ml. portions of water, and then with two 75-ml. portions of 10% aqueous sodium carbonate, the washings were extracted with four 200-ml. portions of chloroform, and the chloroform extracts were combined and dried over anhydrous sodium sulfate. Evaporation to dryness under reduced pressure gave 0.50 g. (22.4%) of yellow needles, m.p. 165–167°. Recrystallization from ethanol raised the melting point to 172–173° (lit.,[8] m.p. 169–169.5°).

Anal. Calcd. for $C_5H_4N_2O_3$: C, 42.9; H, 2.9; N, 20.0. Found: C, 42.9; H, 3.0; N, 20.1.

The dichloromethane solution above was dried over anhydrous sodium sulfate and evaporated to dryness to give 0.42 g. (21.2%) of 3-nitropyridine as an oil which solidified upon trituration to yellow needles, m.p. 38–39° (lit.[22] m.p. 41°).

Method B. Over a period of 90 min. 50 ml. of 40% peracetic acid was added dropwise to a stirred solution of 21.5 g. of 3-nitropyridine in 50 ml. of glacial acetic acid. The temperature of the reaction mixture rose to 100° during the addition. The dark red solution was stirred at room temperature for 4 hr. and then at 75° (oil bath temperature) for 5 hr. It was evaporated to one-half its volume under reduced pressure, 225 ml. of water added, sodium carbonate added to *p*H 8, and the resulting dark brown solution extracted with eight 250-ml. portions of chloroform. The combined extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure to give 14.4 g. of a yellow solid, m.p. 135–158°. Recrystallization from ethanol then gave 9.8 g. (40.5%) of 3-nitropyridine-1-oxide, m.p. 169–171°.

Method C. To a stirred solution of 5 ml. of chloroform, 0.43 ml. of 90% hydrogen peroxide, and 3.1 ml. of trifluoroacetic anhydride prepared as described above in Method A was added slowly a solution of 0.35 g. of 3-aminopyridine-1-oxide in 25 ml. of chloroform. After addition was complete, the reaction mixture was heated under reflux for 1 hr., cooled to room temperature, and extracted with two 50-ml. portions of water followed by two 40-ml. portions of 10% aqueous sodium carbonate. The combined aqueous extracts were extracted with chloroform, and the combined chloroform solutions and extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure to give 0.15 g. (34%) of 3-nitropyridine-1-oxide, m.p. 169–171°, identical in all respects with the product obtained by Methods A and B.

Reduction of 3-nitropyridine 1-oxide to 3-nitropyridine. To a stirred solution of 0.5 g. of 3-nitropyridine 1-oxide in 10 ml. of chloroform at 0° was added 0.8 ml. of phosphorus trichloride, and the mixture was stirred at 0° for 5 min. and then at 70–80° for 1 hr. It was then cooled to room temperature, added to 125 ml. of ice water, and the aqueous layer separated and made alkaline (*p*H 10) with 10% sodium hydroxide. The alkaline solution was extracted with 100 ml. of chloroform, and the chloroform solutions were combined, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give 0.19 g. (43%) of 3-nitropyridine, m.p. 38–40°, identical in all respects with an authentic sample.

Reduction of 3-nitropyridine 1-oxide to 3-aminopyridine. A solution of 1.0 g. of 3-nitropyridine-1-oxide in 150 ml. of absolute ethanol containing 0.2 g. of platinum oxide catalyst was hydrogenated at room temperature for 16 hr. at 40 p.s.i. of hydrogen. Filtration of the catalyst and evaporation of the filtrate gave 3-aminopyridine as a tan oil in quantitative yield; *picrate*, m.p. 201–202°.

Reaction of 3-nitropyridine 1-oxide with phosphorus oxychloride. A mixture of 2.0 g. of 3-nitropyridine-1-oxide and 30 ml. of phosphorus oxychloride was stirred and heated slowly to reflux over a period of 1.5 hr. The solution was then heated under reflux for 1 hr. and the excess phosphorus oxychloride removed by distillation under reduced pressure to give 1.53 g. of a brown solid, m.p. 73–92°. Continuous sublimation at 50–60°/0.1 mm. over a period of 2 weeks first yielded 0.68 g. (30%) of cubic crystals of 2-chloro-3-nitropyridine, m.p. 103–104° (lit.,[25] m.p. 101–102°), followed by 0.19 g. (8.4%) of 6-chloro-3-nitropyridine, m.p. 110° (lit.,[26] m.p. 108–110°). A mixture of 2-chloro and 6-chloro-3-nitropyridine melted at 85–94°.

Anal. Calcd. for $C_5H_3N_2O_2Cl$: C, 37.9; H, 1.9; 17.7. Found (for VIII): C, 37.9; H, 2.05; N, 17.4.

3-Nitro-2-pyridone (X). A mixture of 1.0 g. of 3-nitropyridine-1-oxide and 25 ml. of acetic anhydride was heated under reflux for 24 hr. and then evaporated under reduced pressure to near dryness. The residue was heated with 40 ml. of water for 1.5 hr. the mixture filtered to remove a small amount of an insoluble, high-melting solid, and the filtrate evaporated to dryness under reduced pressure. The residue was suspended in 10 ml. of chloroform and the mixture filtered to give 0.52 g. of crude 3-nitro-2-pyridone, m.p. 200–210°. This was refluxed in xylene for several hours, the solution filtered, and the filtrate concentrated under reduced pressure. Cooling gave 0.50 g. (50%), m.p. 220°. An additional recrystallization from boiling xylene raised the melting point to 224–225.5° (lit.,[25] m.p. 224°).

Anal. Calcd. for $C_5H_4N_2O_3$: C, 42.9; H, 2.9; N, 20.0. Found: C, 43.0; H, 3.0; N, 20.1.

Acknowledgment. We are indebted to Dr. Wolfgang Pfleiderer, Institut für organische Chemie der Technischen Hochschule, Sutttgart, Germany, for carrying out the *p*K determinations.

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[CONTRIBUTION FROM THE AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

β,γ-Dihalopropylamines. II. 1-Amino-2,3-dichloro-3-phenylpropanes and Bis(β,γ-dichloropropyl)amines

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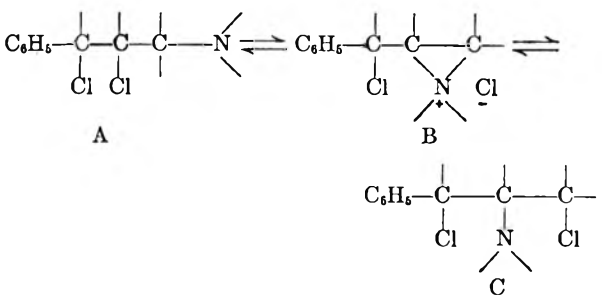
The hydrochlorides of 1-piperidino-, 1-dimethylamino-, 1-dibenzylamino-, 1-methylbenzylamino-, and 1-morpholino-2,3-dichloro-3-phenylpropane have been prepared by chlorine addition to the corresponding cinnamylamine hydrochlorides, obtained from the reaction of cinnamyl bromide with the corresponding secondary amine. These β,γ-dichloropropylamine hydrochlorides react very slowly with piperidine to produce triaminopropanes. The hydrochlorides of bis-*N*,*N*-(2,3-dichloro-3-phenylpropyl)-1-benzylamine and the 1-methylamine analogue were prepared by chlorination of the corresponding *N*,*N*-dicinnamylamines. *N*-(2,3-Dichloro-3-phenylpropyl)-*N*-(2,3-dichloropropyl)-1-benzylamine hydrochloride was also prepared by chlorination of *N*-allyl-*N*-benzylcinnamylamine hydrochloride. These compounds have been synthesized for pharmacological testing as antitumor agents, etc.

As a continuation of a general program concerned with the synthesis of potential anticancer agents, it seemed of interest to obtain for pharmacological testing a series of compounds having the functional group arrangement represented by the general formulas A and/or C.[1]



The relationship of the structural arrangements of A and C to that present in the nitrogen mustards is apparent. Compounds of type A and C might be expected to be converted to the potentially pharmacologically important[2,3] intermediate quaternary ethylenimmonium chloride (B) in neutral or basic media.

A possible method of synthesis for compounds of structure A and/or C involves the addition of chlorine to cinnamylamines. It has been shown from a series of melting point experiments that a compound of type C may rearrange to the isomeric type A on heating to its melting point.[1] The structures of type A seem to be thermodynamically more stable than those of type C.

The necessary cinnamylamines were prepared readily by the reaction of cinnamyl bromide with two equivalents of the respective secondary amine in ether or on refluxing in benzene solution. The conditions of reaction and the isolation techniques were varied somewhat in each case to obtain optimum yields of pure materials where possible. In this way the *N*-cinnamylpiperidine, morpholine, dimethylamine, methylbenzylamine, and dibenzylamine hydrochlorides were usually obtained in good yields.

N,*N*-Dimethylcinnamylamine hydrochloride had previously been prepared by Mannich and Chang,[4] and later by Braun and Kohler,[5] by heating cinnamyl bromide, and dimethylamine. *N*-Benzyl-*N*-cinnamylmethylamine hydrochloride had also been previously prepared from benzyl bromide and *N*-methylcinnamylamine by Blicke and Zienty,[6] who found this compound to possess weak antispasmodic activity.

Because of the hygroscopic nature of the hydrochloride salt of *N*,*N*-dibenzylcinnamylamine, this compound resisted purification and could not be isolated in the solid state, but remained as an oil. In the case of the less reactive cinnamyl chloride, a reaction temperature 50° higher was necessary to obtain a comparable yield of *N*-cinnamylpiperidine hydrochloride.

Chlorine was added to the cinnamylamine hydrochlorides in chloroform solution to produce the 1-amino-2,3-dichloro-3-phenylpropane hydrochlorides. In this way 1-piperidino, 1-dimethylamino, 1-morpholino, 1-dibenzylamino, and 1-methylbenzylamino-2,3-dichloro-3-phenylpropane hydrochlorides were obtained in good yields.

The relatively low level of reactivity of the halogen atoms in the 1-amino-2,3-dichloro-3-phenylpropanes is indicated by the fact that the free bases can be isolated from their hydrochloride salts in the presence of sodium hydroxide, and also by the severity of the conditions required to obtain their

(1) N. H. Cromwell and A. Hassner, *J. Am. Chem. Soc.*, **77**, 1568 (1955).

(2) The vesicant properties of tris(β-chloroethyl)amine and methylbis-(β-chloroethyl)amine are well known, see: (a) K. Ward, *J. Am. Chem. Soc.*, **57**, 914 (1935); (b) O. Eisleb, *Ber.*, **74**, 1433 (1941); (c) K. A. Jensen and F. Lundquist, *Dansk. Tidsskr. Farm.*, **15**, 201 (1941). These compounds have been called "nitrogen mustards" because of their relationship structurally and biologically with mustard gas.

(3)(a) A. Gilman and F. S. Philips, *Science*, **103**, 409 (1946); (b) E. Boyland, *Brit. J. Pharmacol.*, **1**, 247 (1946).

(4) C. Mannich and Fu Tsong Chang, *Ber.*, 66B, 419 (1933).

(5) J. von Braun and Z. Köhler, *Ber.*, 51, 85 (1918).

(6) F. Blicke and F. B. Zienty, *J. Am. Chem. Soc.*, 61, 775 (1939).

reaction with piperidine.[7] When 1-piperidino-2,3-dichloro-3-phenylpropane hydrochloride was refluxed for two days with five molar equivalents of piperidine in absolute ethanol, a low yield of the 1,2,3-tripiperidino-3-phenylpropane was obtained as shown by an ionic chlorine analysis of the isolated trihydrochloride salt.

To obtain another series of analogous materials for pharmacological testing, certain bis (β,γ-dichloropropyl)amine hydrochlorides were made by adding chlorine to the respective unsaturated amine. In general, methods for preparation of the unsaturated amine similar to those reported by previous workers, in which an aqueous medium was employed, failed to proceed satisfactorily.[8] Even in anhydrous ether the reaction products of cinnamyl bromide with the primary amine were often brown colored oils which resisted further purification and were consequently used as such in the chlorination reaction. In this manner the hydrochloride salt of *N,N*-dicinnamylmethylamine and the free base *N,N*-dicinnamylbenzlamine were prepared in fair yields.

N-Allyl-*N*-cinnamylbenzylamine hydrochloride was obtained by reacting cinnamyl bromide in ether solution with *N*-allylbenzylamine formed by the action of allyl bromide with benzylamine at room temperature. The hydrochloride salt of *N,N*-dicinnamylmethylamine had been previously prepared for antispasmodic studies by Blicke and Zienty.[6]

The preparation of the tetrachloro derivatives of the *N,N*-dicinnamyl- and *N*-allyl-*N*-cinnamylamines was a relatively simple procedure because the unsaturated amine hydrochloride salts were quite soluble in chloroform. Thus, by adding chlorine to the unsaturated amine hydrochloride dissolved in cold chloroform, the hydrochloride salts of bis(2,3-dichloro-3-phenylpropyl)-1-methylamine, bis(2,3-dichloro-3-phenylpropyl)-1-benzylamine, and *N*-(2,3-dichloropropyl)-*N*-(2,3-dichloro-3-phenylpropyl)-1-benzylamine were obtained.

When the oily material from the reaction of allyl bromide with benzylamine in refluxing benzene, which was assumed to be *N,N*-diallylbenzylamine hydrochloride, was chlorinated in chloroform, a material was isolated which possessed analytical percentages which could possibly be accounted for by the elimination of the benzyl group. Earlier reports state that dealkylation sometimes occurs with tertiary amines in carbon tetrachloride on adding bromine,[9] with the possibility of hydrolysis not being excluded.

Several of the β,γ-dichloroamines reported here either have been or are being tested in mice for anti-tumor activity by the Cancer Chemotherapy, National Service Center, National Institutes of Health, Bethesda, Maryland. They are also being tested for antihistaminic, anticonvulsant, adrenolytic and preganglionic blockade activity by Smith, Kline and French Laboratories, Philadelphia, Pennsylvania. The results of these tests will be reported elsewhere.

EXPERIMENTAL[10]

Cinnamyl bromide.[11] This material was prepared in 82–90% yields from cinnamyl alcohol and 48% hydrobromic acid by stirring at room temperature for 3 hr. Suitable purification was attained by separating and thoroughly mixing the greenish-oily layer with methanol, then discarding the methanol layer. Washing an ethereal solution of the bromide with water followed by drying and distillation gave a pure production, b.p. 91° (0.75 mm); n_D^{25} 1.6100.

N-Cinnamyldimethylamine hydrochloride. The preparation of this amine was accomplished by slowly adding 2 molar equivalents of anhydrous dimethylamine dissolved in ether to a cooled ethereal solution of cinnamyl bromide. The dimethylamine hydrobromide was removed by filtration after stirring overnight. The ether solution was washed with water, dried, and saturated with dry hydrogen chloride gas. The resulting colorless solid hydrochloride was removed and recrystallized from ethanol-ether in 82.5% yield, m.p. 189–191° (lit.,[12] m.p. 188°).

Anal. Calcd. for $C_{11}H_{16}NCl$: C, 66.82; H, 8.16; N, 7.08; Cl^-, 17.94. Found: C, 67.46; H, 8.03; N, 6.93; Cl^-, 18.38.[13]

1-Dimethylamino-2,3-dichloro-3-phenylpropane hydrochloride. A 3.0-g. sample of the recrystallized hydrochloride of *N*-cinnamyldimethylamine was dissolved in 100 ml. of dry chloroform and tank chlorine gas passed into the cooled solution over a period of 30 min. After standing at room temperature for 3 hr. partial evaporation of the solvent gave the colorless product, 3.25 g. (80% yield); recrystallized from ethanol-ether, m.p. 171–172.5°.

Anal. Calcd. for $C_{11}H_{16}NCl_3$: C, 49.18; H, 6.00; N, 5.22; Cl^-, 13.07. Found: C, 48.85; H, 6.16; N, 4.94; Cl^-, 12.96.

N-Cinnamylpiperidine hydrochloride. This material was prepared from cinnamyl bromide and 2 molar equivalents of piperidine in ether solution at room temperature. The reaction mixture was worked up in the usual manner to give 74–75% yields of the colorless hydrochloride salt, m.p. 207–209°; recrystallized from ethanol-ether, m.p. 207–208.5°.

Anal. Calcd. for $C_{14}H_{20}NCl$: C, 70.73; H, 8.48; N, 5.89; Cl^-, 14.91. Found: C, 70.78; H, 8.35; N, 5.81; Cl^-, 14.82.

The amine hydrochloride was also prepared from cinnamyl chloride (Eastman-3286) and 2 molar equivalents of piperidine, both in ether, (46.5% yield) by stirring at room temperature overnight, and in a 60% yield in refluxing benzene, m.p. 208.5–210°.

1-Piperidino-2,3-dichloro-3-phenylpropane hydrochloride. This dichloro compound was prepared by dissolving *N*-cinnamylpiperidine hydrochloride in chloroform and saturating with dry chlorine gas. The colorless hydrochloride salt was removed in an 85–95% yield by filtration after warming the chloroform solution and adding ether to induce crys-

(7) This property had been demonstrated with 1-amino-2,3-dichloropropanes, see Ref. 1.

(8) A. Parthiel and H. von Broich, *Ber.*, **30**, 618 (1897).

(9) H. Böhme and W. Krause, *Ber.*, **84**, 170 (1951).

(10) All melting points reported here are those obtained by heating the sample at the rate of 3° per min. unless otherwise stated.

(11) L. Claisen and E. Tietze, *Ber.*, **58**, 279 (1925).

(12) *Beilstein*, **12**, 1189.

(13) Direct Volhard titration was employed for the determination of ionic halogen.

tallization; recrystallized from ethanol-ether, m.p. 171–172.5°.

Anal. Calcd. for $C_{14}H_{20}NCl_3$: C, 54.48; H, 6.54; N, 4.54; Cl^-, 11.46. Found: C, 54.58; H, 6.55; N, 4.39; Cl^-, 11.51.

N-Benzyl-N-cinnamylmethylamine hydrochloride.[6] The hydrochloride salt of this amine was prepared in an analogous manner from cinnamyl bromide and 2 molar equivalents of *N*-benzylmethylamine in an ether solution at room temperature. The product was exceedingly hygroscopic and recrystallization from ethanol-ether resulted in a colorless solid in 38.2% yield, m.p. 142–144° (Lit.,[6] m.p. 141–142°).

Anal. Calcd. for $C_{17}H_{20}NCl$: C, 74.57; H, 7.36; N, 5.12; Cl^-, 12.95. Found: C, 74.11; H, 7.40; N, 5.33; Cl^-, 12.83.

1-(N)-Benzylmethylamino-2,3-dichloro-3-phenylpropane hydrochloride. The dichloro derivative was made by dissolving *N*-benzyl-*N*-cinnamylmethylamine hydrochloride in chloroform and saturating the cooled solution with dry chlorine gas. Evaporation of the solvent gave an 84.6% yield of a colorless oil which was very difficult to purify. After trying a variety of solvents a colorless solid in 47.6% yield was finally obtained from *n*-butyl alcohol-ether after cooling for 1 month; m.p. 122–124°.

Anal. Calcd. for $C_{17}H_{20}NCl_3$: C, 59.23; H, 5.85; Cl, 30.86. Found: C, 59.47; H, 5.89; Cl, 30.79.

N-Cinnamyldibenzylamine hydrochloride. The crude hydrochloride of this amine was prepared by dissolving dibenzylamine (19.7 g.) and cinnamyl bromide (9.8 g.) in 150 ml. of dry benzene and refluxing for 4 hr. The dibenzylamine hydrobromide was removed by filtration, after which the benzene solution was washed with water, dried, and saturated with dry hydrogen chloride gas. The hygroscopic hydrochloride resisted purification and was therefore used as such in the following chlorination reaction.

1-(N)-Dibenzylamino-2,3-dichloro-3-phenylpropane hydrochloride. A cooled, chloroform solution of *N*-cinnamyldibenzylamine was saturated with dry chlorine gas. Evaporation of the solvent resulted in 12.2 g. of a viscous brown colored oil, recrystallized successively from *n*-butyl alcohol-ether and ethanol-ether; 4.1 g. (31.8% yield), m.p. 93–95°.

Anal. Calcd. for $C_{23}H_{24}NCl_3$: C, 65.65; H, 5.75; N, 3.33. Found: C, 65.51; H, 6.10; N, 3.34.

N-Cinnamylmorpholine hydrochloride. The procedure used was identical with that for *N*-cinnamylpiperidine hydrochloride, using cinnamyl bromide and morpholine. The hydrochloride salt was a colorless solid obtained in 78.4% yield, m.p. 209–210.5°.

Anal. Calcd. for $C_{13}H_{18}NClO$: C, 65.12; H, 7.57; N, 5.84. Found: C, 65.18; H, 7.60; N, 5.86.

1-Morpholino-2,3-dichloro-3-phenylpropane hydrochloride. Purified *N*-cinnamylmorpholine hydrochloride was dissolved in chloroform, saturated with chlorine, and ether added to crystallize the colorless solid in 99% yield, m.p. 163.5–165°.

Anal. Calcd. for $C_{13}H_{18}NCl_3O$: C, 50.26; H, 5.84; Cl, 34.24. Found: C, 50.05; H, 5.88; Cl, 34.54.

N-Allylbenzylamine hydrochloride. This amine was obtained while attempting to prepare *N,N*-diallylbenzylamine hydrochloride by treating allyl bromide (0.2 mole) with benzylamine (0.3 mole) in ether solution and stirring at room temperature for 3 days. The benzylamine hydrobromide was filtered and the ether extract washed with water, dried, and saturated with hydrogen chloride gas to give a 47.5% yield of a cream colored solid, recrystallized from ethanol-ether, m.p. 143.5–144°.

Anal. Calcd. for $C_{10}H_{14}NCl$: C, 65.37; H, 7.67; N, 7.63. Found: C, 65.64; H, 7.36; N, 7.44.

N-Allyl-N-cinnamylbenzylamine hydrochloride. A 2.3-g. sample of *N*-allylbenzylamine hydrochloride was dissolved in 10% sodium carbonate and extracted with ether. The ether filtrate was dried and to it was slowly added 1.23 g. of cinnamyl bromide. The mixture was warmed to reflux and stirred overnight. Filtration of the amine hydrobromide indicated 71% reaction. The ether filtrate was washed with water, dried, and saturated with dry hydrogen chloride gas to give 68.7% yield of a hygroscopic colorless solid which resisted purification and was used as such in the chlorination reaction.

N-(2,3-Dichloro-3-phenylpropyl)-N-(2,3-dichloropropyl)-1-benzylamine hydrochloride. The crude oily hydrochloride of *N*-allyl-*N*-cinnamylbenzylamine from the above reaction was dissolved in chloroform, cooled, and saturated with chlorine gas. Adding ether precipitated 1.2 g. of a colorless solid, m.p. 139.5–141.5°.

Anal. Calcd. for $C_{19}H_{22}NCl_5$: C, 51.67; H, 5.02; Cl, 40.14. Found: C, 51.53; H, 4.69; Cl, 39.95.

N,N-Dicinnamylbenzylamine. Stirring 2 molar equivalents of cinnamyl bromide and three molar equivalents of benzylamine in ether for 40 hr. at room temperature precipitated 99% of the expected by-product. The ether solution was washed with water, dried and evaporated to give a 66% yield of a light orange colored oil, which was mixed with petroleum ether (b.p. 60–70°) and cooled to give a colorless solid, m.p. 62–64°; recrystallized from methanol, m.p. 64–65°; hydrochloride, m.p. 211–214°.

Anal. Calcd. for $C_{25}H_{25}N$: C, 88.45; H, 7.42; N, 4.13. Found: C, 88.40, H, 7.31; N, 4.18.

Bis-N,N-(2,3-dichloro-3-phenylpropyl)-1-benzylamine hydrochloride. A cooled solution of *N,N*-dicinnamylbenzylamine hydrochloride in chloroform was saturated with chlorine gas. Partial evaporation of the solvent resulted in a yellow solid which was recrystallized from ethanol-ether to give an 87.2% yield of a colorless solid, m.p. 165–166°.

Anal. Calcd. for $C_{25}H_{26}NCl_5$: C, 57.99; H, 5.06; Cl, 34.24. Found: C, 58.15; H, 5.52; Cl, 34.04.

N,N-Dicinnamylmethylamine hydrochloride. A gummy hygroscopic material which was used in the following chlorination reaction was obtained when 0.15 mole of a standard monomethylamine-ether solution and 0.1 mole of cinnamyl bromide in ether were allowed to stir 12 hr. at room temperature. Working up by the usual procedure and saturating with hydrogen chloride gas developed the product.

Bis-N,N-(2,3-dichloro-3-phenylpropyl)-1-methylamine hydrochloride. The crude amine hydrochloride was saturated with chlorine in chloroform and the addition of ether precipitated 3.6 g. (58%) of a colorless solid melting at 179–181°, after recrystallization from acetone-ether.

Anal. Calcd. for $C_{19}H_{22}NCl_5$: C, 51.67; H, 5.02; Cl, 40.14. Found: C, 51.24; H, 5.11; Cl, 39.93.

N,N-Diallylbenzylamine hydrochloride. To a solution of allyl bromide (0.2 mole) in refluxing benzene was slowly added benzylamine (0.3 mole). After filtration the benzene filtrate was washed, dried, and saturated with hydrogen chloride gas, resulting in a dark brown oily hydrochloride (yield 55%) which was used as such in the subsequent chlorination reaction.

Bis-N,N-(2,3-dichloropropyl)amine hydrochloride. The crude dark brown colored unsaturated amine hydrochloride from the previous experiment was chlorinated in the usual manner, except that the temperature was raised to 16°. Standing overnight, followed by evaporation, gave 17.1 g. of a light tan colored oil. Recrystallization from ethanol-ether resulted in 3.5 g. of a colorless solid, m.p. 178–179°.

Anal. Calcd. for $C_{13}H_{16}NCl_5$: C, 42.71; H, 4.96; $C_6H_{12}NCl_5$; C, 26.16; H, 4.39; Found: C, 26.24; H, 4.26.

1,2,3-Tri(N-piperidino)-1-phenylpropane trihydrochloride. To a solution of 27.6 g. of redistilled piperidine in 300 ml. of absolute ethanol was slowly added 20.0 g. of 3-phenyl-2,3-dichloro-1-piperidinopropane hydrochloride. The mixture was heated at reflux under nitrogen for 2 days. Evaporation of the ethanol solvent and addition of dry ether resulted in the by-product, piperidine hydrochloride. Filtration followed by drying of the ether filtrate and saturation with dry hydrogen chloride gas gave a light tan colored solid. This was shaken in water and the insoluble residue removed by filtration, after which 10% sodium carbonate solution was added to liberate the free amine. The precipitated oil was extracted with ether and saturated with hydrogen chloride gas, yield-

ing a light yellow colored salt, m.p. 188–192° after losing gas from 150–170°.

An ionic chlorine analysis indicates this material to be the trihydrochloride salt.

Anal. Calcd. for $C_{23}H_{42}N_3Cl_4$; Cl^-, 22.70. Found: Cl^-, 22.33.

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LINCOLN, NEB.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, UNIVERSITY OF CHICAGO]

New Heteroaromatic Compounds. VII. Chloro and Bromo Derivatives of 10-Hydroxy-10,9-borazarophenanthrene

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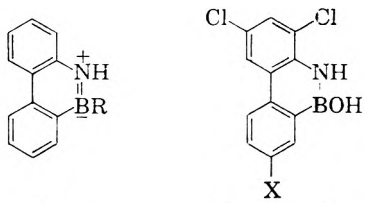
Chlorination or bromination of 10-hydroxy-10,9-borazarophenanthrene gave the 6,8-dichloro or dibromo derivatives. Further chlorination of 6,8-dichloro-10-hydroxy-10,9-borazarophenanthrene gave the 2,6,8-trichloro derivative. Syntheses of the ethers from 2- and 6-chloro-10-hydroxy-10,9-borazarophenanthrene are described.

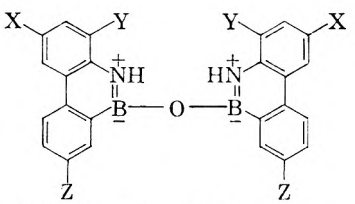
In a previous paper[1] we reported the nitration and chlorination of 10-methyl-10,9-borazarophenanthrene (Ia) and the nitration of 10-hydroxy-10-9-borazarophenanthrene (Ib). We have now examined the chlorination and bromination of Ib.

Chlorination of Ib with two moles of chlorine at room temperature gave, in good yield, a dichloro derivative which was shown to be 6,8-dichloro-10-hydroxy-10,9-borazarophenanthrene (IIa) by degradation to 3,5-dichloro-2-aminodiphenyl with cold concentrated sulfuric acid.[1]



Ia. R = Me
Ib. R = OH

IIa. X = H
IIb. X = Cl



IIIa. X = Y = H, Z = Cl
IIIb. X = Cl, Y = Z = H
IIIc. X = Y = Z = Cl
IIId. X = Y = Br, Z = H

When the chlorination was repeated with one mole of chlorine, IIa remained the sole isolable product. All attempts to obtain monochloro derivatives failed, even when less than one mole of chlorine was used. Since we had hoped to obtain a mixture of monochloro derivatives we began work on the synthesis of possible isomers; 2- and 6-chloro-10-hydroxy-10,9-borazarophenanthrene were readily obtained by hydrolysis of the corresponding 10-chloro derivatives[1] and isolated as their anhydrides, IIIa and IIIb, respectively. Since no monochloro derivatives could be obtained from Ib and since the necessary starting material (2-amino-3-chlorodiphenyl) is inaccessible we did not synthesise the 8-chloro derivative.

Chlorination of Ib with three moles of chlorine at a higher temperature gave 2,6,8-trichloro-10-hydroxy-10,9-borazarophenanthrene (IIb) which on standing at room temperature lost water to form the corresponding ether (IIIc). The structure of IIIc was indicated by its synthesis from IIIa by chlorination.

Bromination of Ib with two moles of bromine in acetic acid gave 6,8-dibromo-10-hydroxy-10,9-borazarophenanthrene which was isolated as the corresponding ether (IIId). The structure of IIId was shown by degradation to 2-amino-3,5-dibromodiphenyl with concentrated sulfuric acid and by synthesis from 2-amino-3,5-dibromodiphenyl by the method previously described.[2] The ultraviolet absorption spectra of these compounds in 95% ethanol solution are indicated in Table I.

DISCUSSION

Theory suggests[1] that the 8-position in 10,9-borazarophenanthrene should be the most reactive towards electrophilic substitution, followed closely by the 6-position. This was shown to be the case for nitration of Ia and Ib while chlorination of Ia gave almost exclusively the 8-chloro derivative. Here we have shown that the 6- and 8-positions of Ib are also the most reactive for chlorination and bromination.

The effect of a $-E$ substituent (such as hydroxyl)

(1) M. J. S. Dewar and Ved P. Kubba, *Tetrahedron*, **7**, 213 (1959).

(2) M. J. S. Dewar, V. P. Kubba, and R. Pettit, *J. Chem. Soc*, 3073 (1958).

TABLE I

ULTRAVIOLET ABSORPTION

Compound	λ_{max}	Log ϵ_{max}	λ_{min}	Log ϵ_{min}
IIa	222	4.5489	214	4.4693
	234	4.6240	224	4.5448
	242	4.5550	238	4.4593
	268	4.0355	264	4.0254
	276	4.0648	272	3.9428
	326	3.8739	294	3.2138
	338	3.8661	332	3.8114
			350	2.7908
IIb	218	4.5077	216	4.4926
	224	4.5325	220	4.5031
	228	4.5395	226	4.5204
	282	4.1388	276	4.0762
	328	3.9183	298	3.4516
	342	3.9333	336	3.8881
			356	2.9160
IIIa	220	4.8607	216	4.8511
	226	4.8644	222	4.8511
	230	4.8700	228	4.8607
	266	4.3910	262	4.3533
	276	4.4154	270	4.2913
	316	4.2150	286	3.7031
	328	4.2354	320	4.1598
			340	2.9761
IIIb	220	4.8665	216	4.8488
	224	4.8524	222	4.8488
	238	4.7949	234	4.7866
	244	4.7700	242	4.7652
	272	4.4056	268	4.2679
	324	4.1928	284	3.4897
	336	4.2073	330	4.1425
			348	3.3259
IIId	222	4.8599	216	4.8349
	236	4.8711	226	4.8501
	268	4.3861	266	4.3738
	278	4.3897	274	4.2800
	326	4.1877	294	3.4830
	340	4.2171	332	4.1457
			350	3.3980

on the reactivity of an alternant hydrocarbon (such as phenanthrene) should be similar to that of replacing the corresponding ring carbon atom by a less electronegative atom (such as boron). Introducing a hydroxyl group into the 10-position of phenanthrene should therefore accelerate electrophilic substitution in the 2-, 4-, 6-, and 8-positions.[3] The 6- and 8-positions in 10-hydroxy-10,9-borazarophenanthrene should therefore be much the most reactive, the difference between them and the other positions being even greater than for 10,9-borazarophenanthrene itself.

Calculation[1] suggests that the 2- and 4-positions should be the next in reactivity, the former probably being the more reactive. (This should definitely be so if, as seems likely, the difference in electronegativity between B^- and C is similar to that between C and N^+). Since the 4-position in phenanthrene seems to be sterically hindered to substitution[4] and since the orientational effects of the hydroxyl in Ib should be similar to those of the boron, we can predict with assurance that the 2-position in Ib should be the third in reactivity. It is therefore satisfactory that further chlorination of IIa gave the 2,6,8-trichloro derivative (IIb).

We had hoped to compare the reactivities of the 6- and 8-positions of Ib to chlorine by determining the proportions of monochloro derivatives formed by chlorination. We were, however, unable to isolate any monochloro derivatives from the reactions; even when a deficiency of chlorine was used the dichloro derivative (IIa) was the sole isolable product. This was surprising; for the monochloro derivatives of Ib must be less reactive to electrophiles than Ib itself, and Ia can be readily monochlorinated. The only reasonable explanation seems to be that the reactivity of Ib is so great that the chlorination does not take place homogeneously. The chlorination was carried out by bubbling chlorine into a solution of Ib in acetic acid; if under these conditions both Ib and its monochloro derivatives react sufficiently rapidly with chlorine, the reation could be diffusion-controlled. The material in a layer of solution round each bubble of chlorine would then be completely chlorinated, the rest being unaffected. This explanation seems reasonable, for theory suggests that the 6- and 8-positions in Ib should be much the most reactive, and also much more reactive than the corresponding positions in Ia. It seems quite feasible that Ib should undergo a diffusion-controlled chlorination to IIa, while under similar conditions Ia reacts normally to give a monochloro derivative in good yield.

EXPERIMENTAL

Bis(2-chloro-10,9-borazaro-10-phenanthryl) ether (IIIa). A solution of 2-amino-4'-chlorodiphenyl (3.5 g.) in dry benzene (50 ml.) was added dropwise with vigorous stirring to one of boron trichloride (2.8 g.) in dry benzene (250 ml.) and the mixture boiled under reflux for 4 hr. After removing the solvent, anhydrous aluminum chloride (0.5 g.) was added and the mixture heated to 190° for 3 hr. The resulting 2,10-dichloro-10,9-borazarophenanthrene was taken up in ether and washed with water. Evaporation of the dried organic layer gave IIIa which crystallized from benzene in light brown needles (2.8 g., 75%) m.p. 192–193°.

Anal. Calcd. for $C_{24}H_{16}ON_2Cl_2B_2$: C, 65.3; H, 3.6; N, 6.4; Cl, 16.1. Found: C, 65.2; H, 3.9; N, 6.6; Cl, 16.0.

Bis(6-chloro-10,9-borazaro-10-phenanthryl) ether (IIIb) was prepared likewise in 69% over-all yield from 2-amino-5-chlorodiphenyl; the compound was crystallized from benzene in light brown prisms, m.p. 205–206°.

Anal. Calcd. for $C_{24}H_{16}ON_2Cl_2B_2$: N, 6.4; Cl, 16.1. Found: N, 6.6; Cl, 16.0.

6,8-Dichloro-10-hydroxy-10,9-borazarophenanthrene (IIa). Chlorine, prepared from potassium permanganate (2.14 g.) and concd. hydrochloric acid (13.3 ml.) was passed slowly into a solution of Ib (3.3 g.) in glacial acetic acid at room temperature. The solution was then poured into water, neutralized with sodium carbonate, and extracted with ether. Evaporation of the ether left crude IIa (3.35 g., 76%), which was chromatographed on Peter Spence alumina, type

(3) M. J. S. Dewar, *J. Am. Chem. Soc.*, **74**, 3341 *et seq.* (1952).

(4) M. J. S. Dewar and E. W. T. Warford, *J. Chem. Soc.*, 3570 (1956).

H, 100/200 mesh, from benzene/chloroform. Only one band could be detected by ultraviolet fluorescence; elution of this gave IIa which crystallized from benzene in needles, m.p. 263–264°.

Anal. Calcd. for $C_{12}H_8ONCl_2B$: N, 5.3; Cl, 26.9. Found: N, 5.2; Cl, 26.2.

Degradation of 6,8-dichloro-10-hydroxy-10,9-borazarophenanthrene. The chloro compound (0.5 g.) was added to concd. sulfuric acid (25 ml.). After 3 hr. at room temperature the solution was poured on ice, made basic with sodium hydroxide, and extracted with ether. Evaporation of the ether left 2-amino-3,5-dichlorodiphenyl which crystallized from aqueous alcohol in white needles (0.27 g., 60%), m.p. and mixed m.p. 50–51°.

2,6,8-Trichloro-10-hydroxy-10,9-borazarophenanthrene (IIb). Chlorine, prepared from potassium permanganate (3.92 g.) and concd. hydrochloric acid (24.4 ml.), was passed slowly into a solution of Ib (4.0 g.) in glacial acetic acid at 90–100°. The solution was poured into water, neutralized with sodium carbonate, and extracted with ether. Evaporation of the ether gave IIb which crystallized from benzene in white needles (4.9 g., 80%), m.p. 283–284°.

Anal. Calcd. for $C_{12}H_7ONCl_3B$: C, 48.3; H, 2.3; N, 4.7; Cl, 35.7. Found: C, 48.6; H, 2.3; N, 4.5; Cl, 35.9.

Bis(2,6,8-trichloro-10,9-borazaro-10-phenanthryl) ether (IIIc). (a) Chlorination of IIIa (2.0 g.) as above with chlorine prepared from potassium permanganate (1.3 g.) and concd. hydrochloric acid (10 ml.) gave IIIc (1.6 g., 61%) which, after crystallization from benzene, melted at 285–286°. (b) The same compound was obtained by allowing IIb to stand in air for 8 weeks at room temperature.

Anal. Calcd. for $C_{24}H_{12}ON_2Cl_6B_2$: N, 4.8; Cl, 36.7. Found: N, 4.6; Cl, 36.8.

Bis(6,8-dibromo-10,9-borazaro-10-phenanthryl) ether (IIId). (a) Bromine (4.8 g.) in glacial acetic acid (15 ml.) was added to a solution of Ib (3.0 g.) in glacial acetic acid (100 ml.) at 50°. After 2 hr. at 80° water was added and the crude dibromo compound (4.3 g., 80%) collected and crystallized from acetic acid, m.p. 295–296°. (b) The dibromo compound was synthesized as above from 2-amino-3,5-dibromodiphenyl (2.5 g.) by successive treatment with boron trichloride and aluminum chloride, the yield of material, melting point, and mixed melting point 295°, being 1.6 g. (61%).

Anal. Calcd. for $C_{24}H_{14}ON_2Br_4B_2$: N, 4.1; Br, 46.5. Found: N, 4.2; Br, 46.4.

CHICAGO 37, ILL.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CHICAGO]

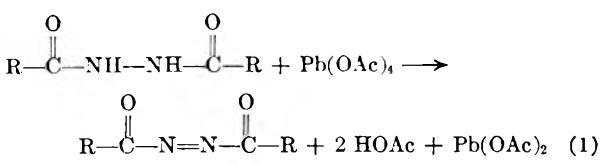
The Oxidation of 2,3-Dihydrophthalazine-1,4-dione with Lead Tetraacetate. Phthalazine-1,4-dione and 1,4-Dihydropyridazino[1,2-*b*]-phthalazine-6,11-dione

ROBERT A. CLEMENT

Received March 16, 1960

Evidence is presented that the oxidation of 2,3-dihydrophthalazine-1,4-dione (phthalhydrazide) with lead tetraacetate produces, as the initial and unstable product of oxidation, phthalazine-1,4-dione. By taking advantage of its extraordinary reactivity as a dienophile, this compound was intercepted with butadiene as 1,4-dihydropyridazino[1,2-*b*]phthalazine-6,11-dione, the structure of which was firmly established.

We have found[1] that the oxidation of diacyl hydrazides with lead tetraacetate according to equation 1 is a convenient method for the preparation of diacyl diimides, generally superior to the methods heretofore employed.[2] However, when the reaction was applied to 2,3-dihydrophthalazine-1,4-dione (I) (phthalhydrazide), the expected product, phthalazine-1,4-dione(II), was not isolated. Contrary to our experience with other diacyl hydrazides, gas was evolved during the oxidation and the initially highly-colored solution[3] became quite colorless during the isolation procedure.



$$R{-}C(=O){-}NH{-}NH{-}C(=O){-}R + Pb(OAc)_4 \longrightarrow R{-}C(=O){-}N{=}N{-}C(=O){-}R + 2\,HOAc + Pb(OAc)_2 \quad (1)$$

This paper is concerned with the results of an examination of the reaction of I with lead tetraacetate and provides evidence that the initial product of oxidation is, indeed, the expected diimide II which, however, is too unstable to be isolated or even to be preserved in solution. In the course of the investigation, there were prepared 1,4-dihydropyridazino[1,2-*b*]phthalazine-6,-11-dione (III) and 1,2,3,4-tetrahydropyridazino-[1,2-*b*]phthalazine-6,11-dione (IV), representatives of a heterocyclic ring system which, to the best of our knowledge, has not previously been described. Some of the transformations involved in this study are summarized in Fig. 1.

RESULTS

When the oxidation of 2,3-dihydrophthalazine-1,4-dione (I) with one mole of lead tetraacetate was carried out in acetonitrile, there was obtained, initially, a lime-green solution which very rapidly deposited a fine, white, amorphous solid and which

(1) Unpublished results, this laboratory.

(2) E. Mohr, *J. prakt. Chem.*, II, **70**, 281 (1904); R. Stolle *Ber.*, **45**, 273 (1912); L. Horner and W. Naumann, *Ann.*, **587**, 93 (1954); J. E. Leffler and W. B. Bond, *J. Am. Chem. Soc.*, **78**, 335 (1956).

(3) Diacyl hydrazides are intensely colored, generally red in solution.

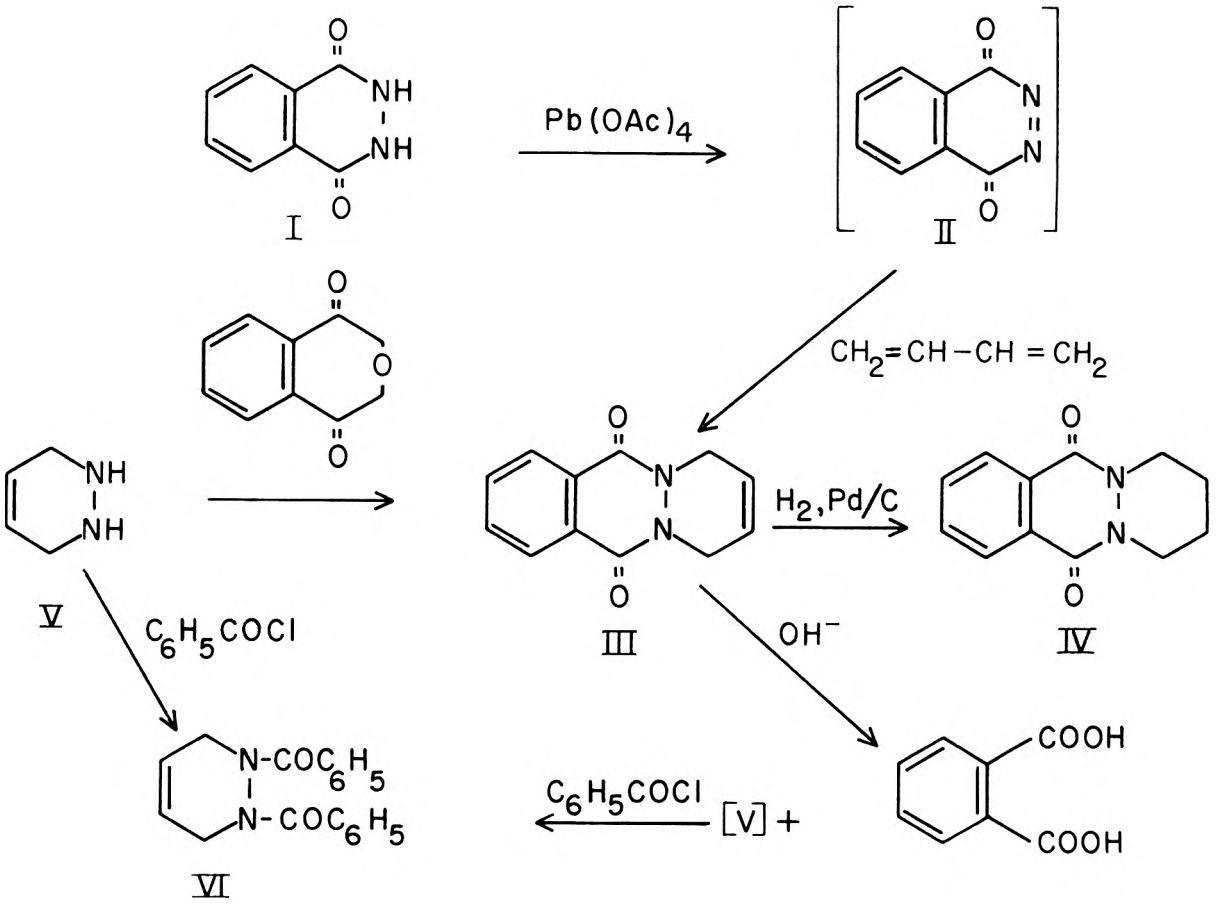
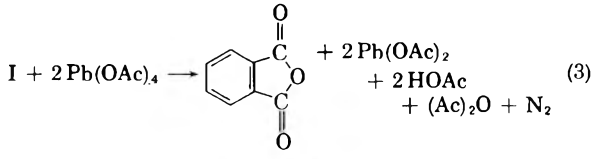


Fig. 1. Some transformations with 2,3-dihydrophthalazine-1,4-dione

became colorless in the course of a few hours. The amorphous solid was an intractable substance which was insoluble in all common solvents and which decomposed, usually explosively, when heated. Although this material could not be purified, it yielded an approximate analysis for phthalazine-1,4-dione (II) and in view of its intractable nature and its lack of color it was formulated as a polymer $(II)_n$ of that compound. Closer inspection of the reaction mixture revealed the presence, in roughly equivalent amounts, of phthalic anhydride and unchanged I. At this point it appeared that oxidation of I was proceeding, simultaneously, according to Equations 2 and 3, that II was responsible for the color of the solution, and that because of its instability, II was being removed rather rapidly according to Equation 4 to form the polymer $(II)_n$.

$$I + Pb(OAc)_4 \longrightarrow II + 2\,HOAc + Pb(OAc)_2 \quad (2)$$



(3)

$$n\,II \longrightarrow (II)_n \quad (4)$$

Confirmation of the validity of equation 3 was obtained in the oxidation of I with two moles of lead tetraacetate. Phthalic anhydride and nitrogen gas were produced in essentially quantitative yield.

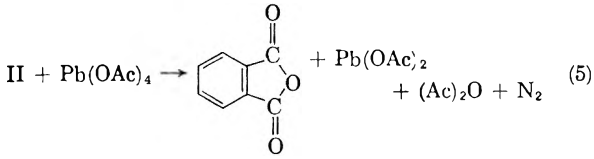
In view of the certain reactivity of II as reflected by Equation 4, and in view of the known reactivity of diacyl diimides as dienophiles,[4,5] it seemed feasible to attempt the interception of II with butadiene. In fact, when butadiene was added to the clear green solution, the green color disappeared immediately and there was produced 1,4-dihydropyridazino[1,2-*b*]phthalazine-6,11-dione (III), the structure proof for which is outlined below. III was produced in an amount roughly equivalent to that of the polymer $(II)_n$ formed from the green solution in the absence of butadiene, and the amounts of unchanged I and phthalic anhydride obtained in the two experiments were also roughly equivalent. These observations indicated that III and $(II)_n$ were derived from an identical precursor which most likely was II and which was responsible for the green color.

When the oxidation was carried out with buta-

(4) P. Baranger and J. Levisalles, *Bull. soc. chim. France*, 704 (1957).

(5) O. Diels, J. H. Blom, and W. Koll, *Ann.*, **443**, 242 (1925); O. Diels and K. Alder, *Ann.*, **450**, 237 (1926); O. Diels, S. Schmidt, and W. Witte, *Ber.*, **71**, 1186 (1938); K. Alder and H. Niklas, *Ann.*, **585**, 81 (1954).

diene present from the start, III was obtained in a 90% yield. This result showed, beyond doubt, that the initial product of oxidation is II as defined by Equation 2. Because of its instability, however, II disappears according to equations 4 and 5, reaction by the latter route consuming additional oxidant and, with a molar amount of oxidant, requiring one mole of I to remain unchanged for each mole of phthalic anhydride produced. The reactivity of II as a dienophile, however, is greater than its reactivities according



to Equations 4 and 5, and in the presence of butadiene, II is intercepted by butadiene essentially as rapidly as it is formed.

The structure of III is of some interest since it is a representative of the heretofore-unknown pyridazino[1,2-*b*]phthalazine heterocyclic ring system. As expected from its structure, III readily absorbed one mole of hydrogen to yield a dihydro derivative which is formulated as 1,2,3,4-tetrahydropyridazino[1,2-*b*]phthalazine-6,11-dione (IV). The structure of III was proved by an alternative synthesis from phthalic anhydride and 1,2,3,6-tetrahydropyridazine (V). Further confirmation of structure III was obtained by its hydrolysis to phthalic acid and V, identified as its derivative, 1,2-dibenzoyl-1,2,3,6-tetrahydropyridazine (VI).

The extraordinary reactivity of phthalazine-1,4-dione (II) as a dienophile is worthy of note. Its reaction with butadiene was instantaneous even at 0° and at a concentration of *ca.* 0.05*M*. The reaction of II with other dienes is currently under investigation as is the possiblity that it may undergo reaction with simple olefins by 1,2-cycloaddition.

EXPERIMENTAL[6]

Oxidation of 2,3-dihydrophthalazine-1,4-dione (I) *with lead tetraacetate. A. With one mole of lead tetraacetate.* To a slurry of I[7] (4.59 g., 28.4 mmoles) and purified acetonitrile[8] (150 ml.) in a flask provided with a loose-fitting stopper and cooled in an ice bath, was added lead tetraacetate[9] (12.6 g., 28.4 mmoles), and the heterogeneous mixture was stirred magnetically. As reaction proceeded, some gas was evolved, the solution became thick with precipitated lead acetate, and the color of the solution changed from golden brown to lime green. At the end of 1.33 hr. a test for lead tetraacetate was negative,[10] and the reaction mixture was immediately filtered and the filter cake washed with 50 ml. of acetonitrile to give an off-white precipitate and a clear, intense green filtrate.

The precipitate was stirred vigorously with 100 ml. of 1*N* nitric acid, filtered, and washed with water. It was then suspended in 100 ml. of water, and sufficient 2*N* sodium hydroxide was added to dissolve most of the precipitate and to bring the solution to *p*H 10. The solution was then filtered and the filtrate was added to a mixture of 25 ml. of glacial acetic acid and 25 ml. of water. The resulting precipitate was isolated by filtration and, after being dried at 110°, amounted to 1.41 g. (8.70 mmoles) of unchanged I, identified by its infrared spectrum.

The clear green filtrate from the initial filtration became cloudy with precipitate within 3 min., and after 3 hr. the solution was virtually colorless and had deposited a fine, white, amorphous precipitate which was collected by centrifugation and amounted to 0.71 g. [4.44 mmole of phthaloyl units on the basis of polymer $(II)_n$]. The analytical sample was prepared by washing this material with 100 ml. of acetonitrile and possessed absorption in the infrared (potassium bromide pellet) at 1700 (broad, carbonyl) and 1595 (carbonyl-conjugated unsaturation) cm^{-1}. It was insoluble in all the common organic solvents and in water, and decomposed in the range, 190–290°, usually explosively.

Anal. Calcd. for $(C_8H_4N_2O_2)_n$: N, 17.50. Found: N, 16.01.

The mother liquors from the isolation of the polymer $(II)_n$ were evaporated to dryness under reduced pressure and the gummy residue was sublimed at 100° and 1 mm. to yield 1.46 g. (9.74 mmoles) of phthalic anhydride, m.p. 125–131°, identified by the criteria of mixture melting point and infrared spectral comparison.

B. With two moles of lead tetraacetate. A slurry of I (0.47 g., 2.90 mmoles) in 40 ml. of acetonitrile was placed in a flask which was provided with a magnetic stirrer and a dumping arm which contained 2.60 g. (5.87 mmoles) of lead tetraacetate. The flask was attached to a manometric system which was flushed with nitrogen and maintained at atmospheric pressure and 28°. Reaction was initiated by dumping the lead tetraacetate into the acetonitrile solution. As reaction proceeded, the solution changed color from golden brown to green to colorless. After 1.5 hr. there was no further change in volume which, after correction for the partial pressure of acetonitrile and reduction to S.T.P., amounted to 68 ml. (103% of theory according to Equation 3).

The solution was then filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was sublimed at 100° and 1 mm. to yield 0.41 g. (95% of theory according to Equation 3) of phthalic anhydride, m.p. 123–131°, identified by the criteria of mixture melting point and infrared spectral comparison.

C. With one mole of lead tetraacetate and subsequent addition of butadiene. The reaction was run as in *A* with 4.86 g. (30.0 mmoles) of I, 150 ml. of acetonitrile, and 13.3 g. (30.0 mmoles) of lead tetraacetate. Unchanged I, isolated and identified as in *A*, amounted to 1.56 g. (9.63 mmoles).

Immediately after filtration and before any precipitate had appeared, the clear green filtrate from the removal of unchanged I and lead acetate was stirred while a stream of butadiene was directed onto the solution. Within *1 min.* after initiation of the operation (within 3 min. after filtration) the solution had become colorless and a white pre-

(6) Melting points were determined on a calibrated Fisher-Johns block. Infrared spectra were recorded on a Perkin-Elmer Model 21 Infrared Spectrophotometer. We are indebted to Mr. W. Saschek of this Department for the analyses.

(7) H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.*, 16 (1937).

(8) A. R. Ronzio and W. B. Cook, *Org. Syntheses*, Coll. Vol. III, 72 (1955).

(9) J. C. Bailar, Jr., *Inorg. Syntheses*, 1, 47 (1939).

(10) To test for lead tetraacetate, *ca.* 0.1 ml. of the reaction mixture was added to *ca.* 5 ml. of dilute sulfuric acid, swirled for 1 min., and then poured into an aqueous solution of potassium iodide and starch. If lead tetraacetate (at this point, lead dioxide) were present, the characteristic deep blue color of the iodine-starch complex appeared. It was necessary to destroy II with aqueous acid prior to addition to the iodide-starch solution, as it oxidizes iodide to iodine, instantly. In fact, all diacyl diimides we have tested give an intense blue color when added directly to an acidic solution of potassium iodide and starch.

cipitate had appeared. The reaction mixture was immediately connected to the water aspirator, and solvent was removed at reduced pressure to yield a white solid which was suspended in 100 ml. of water and stirred while the solution was adjusted to *p*H 10 with 2*N* sodium hydroxide. Filtration gave a pale orange solid which was stirred vigorously for 1 hr. in a mixture of 50 ml. of water and 5 ml. of glacial acetic acid and then filtered to yield, after being dried at 110°, 1.30 g. (6.08 mmoles) of 1,4-dihydropyridazino[1,2-*b*]-phthalazine-6,11-dione (III), which possessed an infrared spectrum indistinguishable from that of the analytical sample described below.

The basic filtrate from the initial isolation of III was concentrated to *ca.* 30 ml. and adjusted to *p*H 0 with concd. nitric acid. The buff-colored precipitate that appeared was isolated by filtration and, after being air dried, amounted to 1.26 g. (7.60 mmoles) of phthalic acid, identified by its infrared spectrum and its neutralization equivalent (required, 83; found, 85).

D. With one mole of lead tetraacetate in the presence of butadiene. 1,4-Dihydropyridazino[1,2-b]phthalazine-6,11-dione (III). To a slurry of I (4.05 g., 25.0 mmoles), butadiene (11.0 g.), and acetonitrile (125 ml.) in a flask equipped with a loose-fitting stopper and cooled in an ice bath, was added lead tetraacetate (11.0 g., 24.8 mmoles); the mixture was stirred magnetically. As reaction proceeded, the solution became thick with precipitate, but at no time was there visible a green color. At the end of 1.75 hr., solvent was removed from the reaction mixture under reduced pressure and the residue was stirred vigorously and in succession with 100 ml. of water, 100 ml. of 0.1*N* nitric acid, 100 ml. of 0.1*N* sodium hydroxide, and 100 ml. of water, being isolated by filtration after each operation. The final filtration afforded a tan solid which, after being dried at 110°, amounted to 4.82 g. (90%) of III and which possessed an infrared spectrum indistinguishable from that of the analytical sample. The analytical sample of III was obtained as fine white needles, m.p. 272–275° dec. (sealed capillary), after two recrystallizations from acetic acid–water, and possessed absorption in the infrared (3% in chloroform) at 1627 (carbonyl) and 1604 (carbonyl-conjugated unsaturation) cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71. Found: C, 67.36; H, 4.88.

Hydrogenation of 1,4-dihydropyridazino[1,2-b]phthalazine-6, 11-dione (III). *1,2,3,4-Tetrahydropyridazino[1,2-b]phthalazine-6,11-dione* (IV). A slurry of III (0.149 g.) in glacial acetic acid (45 ml.) was hydrogenated in the presence of 10% palladium-on-charcoal (0.10 g.), the reduction in volume corresponding to 99% of theory for the absorption of 1 mole of hydrogen and being attained in 15 min. The reaction mixture was filtered, the filtrate was evaporated to dryness under reduced pressure, and the residue was crystallized from water to yield 0.124 g. (82%) of IV as white swords, m.p. 146°. The analytical sample was obtained, after two more crystallizations from water, as white swords, m.p. 145.5–146.5°, or as very fine white needles, m.p. 156.0–156.5°. An intimate mixture of the two forms melted at 156.0–156.5°, and occasionally the lower-melting form resolidified to remelt at 156.0–156.5°. In the infrared (1% in chloroform) IV possessed absorption at 1648 (carbonyl) and 1607 (carbonyl-conjugated unsaturation) cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.60. Found: C, 66.75; H, 5.60.

1,2,3,6-Tetrahydropyridazine (V). This material was prepared as previously described,[4] b.p. 88–91°/50 mm., n_D^{25} 1.5126 (lit.[4] b.p. 68.5°/20 mm.). *1,2-Dibenzoyl-1,2,3,6-tetrahydropyridazine* (VI) was prepared from V and benzoyl chloride in pyridine and, after recrystallization from ethanol-water, melted at 162.5–164.0° (lit.[4] m.p. 160.5°) and possessed absorption in the infrared (5% in chloroform) at 1673 and (a shoulder) 1650 (carbonyl) cm^{-1}.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52. Found: C, 74.02; H, 5.89.

1,4-Dihydropyridazino[1,2-b]phthalazine-6,11-dione (III) *from phthalic anhydride and 1,2,3,6-tetrahydropyridazine* (V). A mixture of phthalic anhydride (2.96 g., 20.0 mmoles) and V (1.68 g., 20.0 mmoles) in 50 ml. of water, 7 ml. of concd. hydrochloric acid, and 3 ml. of ethanol (to control foaming) was heated under reflux for 11 hr. At the end of this time the reaction mixture was cooled and filtered and the tan solid collected was washed with 50 ml. of water. This material, after being dried at 110°, amounted to 3.31 g. (77%) of III and possessed an infrared spectrum indistinguishable from that of the analytical sample described above.

Hydrolysis of 1,4-dihydropyridazino[1,2-b]phthalazine-6,11-dione (III). A mixture of III (2.14 g., 10.0 mmoles, as obtained in *D*) and potassium hydroxide (4.0 g., 71 mmoles) in 25 ml. of water was heated under reflux for 20.5 hr. At the end of this time, the homogeneous solution was extracted with ten 50-ml. portions of methylene chloride and the aqueous layer was preserved for further treatment. The combined methylene chloride extracts were dried over potassium carbonate, filtered, and evaporated under reduced pressure to yield 0.56 g. of a pale yellow residue which possessed an amine-like odor. This residue was dissolved in pyridine (25 ml.), benzoyl chloride (3.00 g.) was added, and the mixture was stirred at room temperature for 3.5 hr. At the end of this time, the reaction mixture was poured into 400 ml. of water and stirred vigorously until the odor of benzoyl chloride was no longer noticeable. Filtration yielded a tan solid which, after being dried at 110°, amounted to 0.90 g. (31%) of VI, m.p. 152–160°, identified by mixture melting point and infrared spectral comparison with authentic VI described above.

The aqueous layer preserved after the methylene chloride extractions was acidified to *p*H 0 with concd. hydrochloric acid and the precipitate which appeared was filtered and air dried to yield 0.86 g. (52%) of phthalic acid, identified by its infrared spectrum and its neutralization equivalent (required, 83; found, 84).

CHICAGO 37, ILL.

[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION]

Reactions of Trichloromethyl-Substituted *s*-Triazines in the Presence of Tertiary Amines[1a]

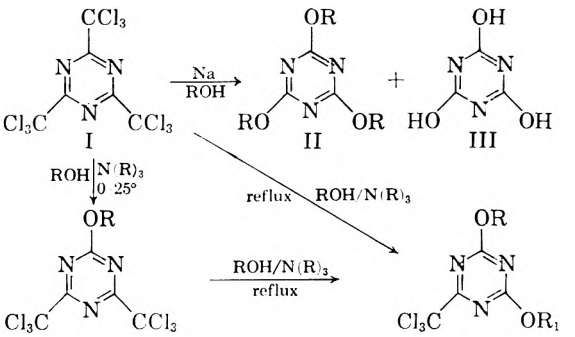
EHRENFRIED KOBER[1b]

Received February 25, 1960

A method has been found which permits the stepwise replacement of one or two trichloromethyl groups attached to a *s*-triazine ring by alkoxy groups. By a variation of this method tertiary amine salts of 2-hydroxy-4,6-bistrichloromethyl-*s*-triazine can be synthesized from 2,4,6-tristrichloromethyl-*s*-triazine.

It is known that trichloromethyl groups attached to *s*-triazine rings can be replaced stepwise by amino or secondary amino groups[2,3]; the reaction involves elimination of trichloromethyl anions[4] which sombine with a proton to form chloroform. Whether one or more trichloromethyl groups are replaced by this reaction depends largely on the reaction temperature. The assumption that the nucleophilic replacement of trichloromethyl groups attached to the *s*-triazine ring would also proceed with other suitable agents, *e.g.*, alcohols was confirmed by the reaction of 2,4,6-tristrichloromethyl-*s*-triazine (I) with ethanol in the presence of three moles of sodium ethoxide or sodium hydroxide which gave 2,4,6-trisethoxy-*s*-triazine (II) and cyanuric acid (III). Stepwise replacement of the trichloromethyl groups, however, could not be achieved by variation of the reaction temperatures. Even when the amount of base was varied from catalytic amounts to two equivalents, the intermediates, 2-ethoxy-4,6-bistrichloromethyl-*s*-triazine (V) and 2,4-bisethoxy-6-trichloromethyl-*s*-triazine (VIII), could not be isolated. If at a given temperature reaction took place at all, the sole reaction products were II and III, indicating that—under the described conditions—the process cannot be stopped after the exchange of one or two trichloromethyl groups.

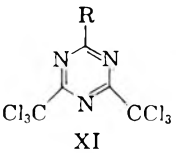
The desired stepwise replacement of trichloromethyl groups by alkoxy groups was accomplished in the presence of aliphatic tertiary amines such as triethylamine. When the reaction of I with alcohols in the presence of triethylamine was carried out between 0° and room temperature, only one trichloromethyl group was replaced by an alkoxy group resulting in 2-alkoxy-4,6-bistrichloromethyl-*s*-triazines (IV-VII), while at reflux temperatures the reaction proceeded to give exclusively 2,4-bisalkoxy-6-trichloromethyl-*s*-triazines (VIII, IX).[5] It was also possible to convert 2-alkoxy-4,6-bistrichloromethyl-*s*-triazines to the 2,4-bisalkoxy-6-trichloromethyl-*s*-triazines by refluxing with the corresponding alcohol in the presence of triethylamine as demonstrated by the conversion of V to VIII and of VII to IX.



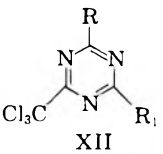
IV. R = CH_3
V. R = C_2H_5
VI. R = $CH(CH_3)_2$
VII. R = n-C_4H_9
VIII. R = C_2H_5; R_1 = C_2H_5
IX. R = n-C_4H_9; R_1 = n-C_4H_9
X. R = CH_3; R_1 = C_2H_5
XXII. R = CH_2CF_3

An attempt to synthesize a 2,4-bisalkoxy-6-trichloromethyl-*s*-triazine bearing two different alkoxy groups was not successful; 2-methoxy-4,6-bistrichloromethyl-*s*-triazine (IV)—upon refluxing with ethanol in the presence of triethylamine—did not give 2-ethoxy-4-methoxy-6-trichloromethyl-*s*-triazine (X) but instead 2,4-bisethoxy-6-trichloromethyl-*s*-triazine (VIII), indicating complete transesterification of the methoxy group by ethanol.

The described method could also be successfully applied for the preparation of *s*-triazine derivatives of type XII from compounds of type XI.



XI



XII

XIII. R = CH_3
XIV. R = C_6H_5
XV. R = CH_3; R_1 = OC_2H_5
XVI. R = CH_3; R_1, = O-n-C_4H_9
XVII. R = C_6H_5; R_1 = OC_2H_5

(1) (a) This article is based on work performed under Project 116-B of The Ohio State University Research Foundation sponsored by the Olin Mathieson Chemical Corp., New York, N.Y. (b) Olin Mathieson Chemical Corp., New Haven, Conn.

(2) A. Weddige, *J. prakt. Chem.*, [2] **33**, 81 (1886).

(3) A. Kreutzberger, *J. Am. Chem. Soc.*, **79**, 2629 (1956).

(4) F. Arndt and B. Eistert, *Ber.*, **68**, 196 (1935).

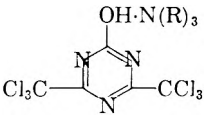
(5) The synthesis of compounds IV–VIII from 2-chloro-4,6-bistrichloromethyl-*s*-triazine by a different procedure has been described recently; H. Schroeder, *J. Am. Chem. Soc.*, **81**, 5658 (1959).

To obtain compounds XV, XVI, and XVII, the starting materials XIII or XIV, respectively, had to be refluxed in the appropriate alcohol in the presence of triethylamine.

The extension of the described method to other tertiary amines as well as to tertiary alcohols or phenols was investigated. From the results obtained we conclude that other aliphatic amines, such as tributylamine, and tertiary heterocyclic *N*-alkylamines, such as *N*-ethylpiperidine and *N*-methylmorpholine, can also be successfully employed for the described method. Reaction, however, could not be achieved in the presence of pyridine or *N*,*N*-dimethylaniline.

Trichloromethyl groups attached to the *s*-triazine ring could not be replaced by tertiary alkoxy or phenoxy groups. When compounds I or XIII were refluxed with tertiary butyl alcohol or phenol, only starting materials were recovered besides small amounts of unidentified products.

Although the conversion of 2,4,6-tristrichloromethyl-*s*-triazine to the desired mono- or dialkoxy substituted trichloromethyl-*s*-triazines occurred in excellent yields, small amounts of solid by-products were isolated. These by-products, only slightly soluble in and not attacked by boiling water and ethanol, had the correct analysis in each case for the tertiary amine salts of 2-hydroxy-4,6-bistrichloromethyl-*s*-triazine (XVIII–XXI), depending on the tertiary amine used for the reaction.



XVIII. $N(R)_3$, triethylamine
XIX. $N(R)_3$, tributylamine
XX. $N(R)_3$, *N*-ethylpiperidine
XXI. $N(R)_3$, *N*-methylmorpholine

The only explanation for the formation of these tertiary amine salts was that traces of water present in the reactants caused a side reaction, which indicated that the tertiary amine salts XVIII–XXI could be prepared exclusively, if water instead of an alcohol were employed in the reaction. This was confirmed by the formation of these salts (XVIII–XXI) when 2,4,6-tristrichloromethyl-*s*-triazine (I) was refluxed in water in the presence of the corresponding tertiary amines. The desired reaction could not be achieved in the presence of *N*,*N*-dimethylaniline or pyridine, although in the latter reaction small amounts of cyanuric acid (III) could be isolated besides unchanged I.

Surprisingly, the tertiary amine salt XVIII was also formed, when 2,4,6-tristrichloromethyl-*s*-triazine (I) was treated with trifluoroethanol in the presence of triethylamine; not even traces of the desired 2-trifluoroethoxy-4,6-bistrichloromethyl-*s*-triazine (XXII) were obtained. Apparently, trifluoroethanol is too acidic and, therefore, the reaction leads to the quantitative formation of XVIII rather than to XXII.

The configuration of the tertiary amine salts XVIII–XXI was confirmed by their reaction with phosphorus oxychloride to give nearly quantitative yields of 2-chloro-4,6-bistrichloromethyl-*s*-triazine (XXIII)[6] and by their hydrogenolysis to give 2-hydroxy-4,6-dimethyl-*s*-triazine (XXIV)[6] directly and not the corresponding tertiary amine salt. This is in contrast to the reported hydrogenolysis of 2-hydroxy-4,6-bis(mono-, di-, or trichloromethyl)-*s*-triazine mono-, di-, or trichloroacetamidine salts which gave in each case the 2-hydroxy-4,6-dimethyl-*s*-triazine acetamidine salt.[6] Apparently, 2-hydroxy-4,6-dimethyl-*s*-triazine (XXIV) is not acidic enough to form salts with tertiary amines. This was confirmed by an experiment in which an ethanolic solution of XXIV and excess triethylamine were allowed to evaporate resulting in the quantitative recovery of XXIV.

Finally, the reaction of trichloromethyl substituted *s*-triazines with mercaptans or hydrogen sulfide in the presence of tertiary amines was investigated. The results of these experiments differ entirely from those obtained with alcohols or water and for this reason will be the subject of further investigations.

EXPERIMENTAL[7]

Reaction of 2,4,6-tristrichloromethyl-s-triazine (I) *with ethanol in the presence of sodium ethoxide or sodium hydroxide.* The reactants were refluxed in ethanol for 30 min. and, after cooling, the solvent removed *in vacuo*. The products obtained from the resulting residue by treatment with ethanol or petroleum ether (b.p. 90–97°) are listed in Table I.

TABLE I

REACTION OF I WITH ETHANOL IN BASE

Base	Mole Equivalents	Compounds Obtained, % I	II[a]	III[b]	Unidentified
C_2H_5ONa	0.1	90	5	5	—
C_2H_5ONa	1	—	62	29	—
C_2H_5ONa	2	—	84	11	—
C_2H_5ONa	3	—	87	9	—
NaOH	1	—	9	35	56

[a] 2,4,6-Trisethoxy-*s*-triazine. [b] Cyanuric acid.

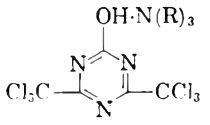
General procedure for the preparation of 2-alkoxy-4,6-bistrichloromethyl-s-triazines. 2-n-Butoxy-4,6-bistrichloromethyl-s-triazine (VII). A 30-g. sample of triethylamine was added at 0°, with stirring, to the solution of 33 g. of 2,4,6-tristrichloromethyl-s-triazine (I) in 200 ml. of *n*-butyl alcohol. The reaction mixture was kept overnight between 0° and room temperature. Triethylamine, excess butyl alcohol, and the chloroform formed were removed *in vacuo* at a maximum bath temperature of 20°. The oily residue was dissolved in 250 ml. of petroleum ether (b.p. 30–40°) whereupon a small amount of a solid by-product precipitated.

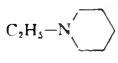
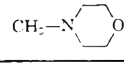
(6) H. Schroeder, *J. Am. Chem. Soc.*, **78**, 2447 (1956).

(7) All melting points were determined with the Fisher-Johns apparatus; microanalyses were by Spang, Microanalytical Laboratory, Ann Arbor, Mich.

TABLE II

TERTIARY AMINE SALTS OF 2-HYDROXY-4,6-BISTRICHLOROMETHYL-*s*-TRIAZINE



Compound	N(R)$_3$	M.P.	Yield, %	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	Cl, % Calcd.	Cl, % Found	N, % Calcd.	N, % Found
XVIII	N C_2H_5	178–180	81.5	$C_{11}H_{16}Cl_6N_4O$	30.51	30.59	3.75	3.77	49.11	47.86	12.94	12.89
XIX	N n-C_4H_9	106–108	76.5	$C_{17}H_{28}Cl_6N_4O$	39.48	39.63	5.46	5.49	41.14	41.11	10.83	10.73
XX		215–216.5	90.0	$C_{12}H_{16}Cl_6N_4O$	32.38	32.20	3.62	3.94	47.81	47.81	12.59	12.60
XXI		202–204	100	$C_{10}H_{12}Cl_6N_4O_2$	27.74	27.67	2.79	2.92	49.11	49.04	12.94	12.83

The petroleum ether was removed from the filtrate and the remainder distilled *in vacuo*, yielding 20.1 g. (72.5%) of 2-*n*-butoxy-4,6-bistrichloromethyl-*s*-triazine (VII); colorless liquid; b.p. 152–154° (0.7 mm.) (lit.[5] b.p. 146 (0.3 mm.)), n_D^{25} 1.5282 (lit.[5] n_D^{27} 1.5289).

Anal. Calcd. for $C_9H_9Cl_6N_3O$: C, 27.86; H, 2.34; N, 10.83; Cl, 54.84. Found: C, 27.99; H, 2.26; N, 10.89; Cl, 54.69.

The same product was obtained with *N*-ethylpiperidine instead of triethylamine; yield: 66%.

Other 2-alkoxy-4,6-bistrichloromethyl-*s*-triazines prepared by this procedure were 2-methoxy-4,6-bistrichloromethyl-*s*-triazine (IV, yield: 92%), 2-ethoxy-4,6-bistrichloromethyl-*s*-triazine (V, yield: 82.3%), and 2-isopropoxy-4,6-bistrichloromethyl-*s*-triazine (VI, yield: 82.7%). Boiling points and refractive indices of these compounds corresponded closely with those reported in the literature.[5]

General procedures for the preparation of 2,4-bisalkoxy-6-trichloromethyl-s-triazines. 2,4-Bisethoxy-6-trichloromethyl-s-triazine (VIII). (a) The solution of 21.7 g. of tristrichloromethyl-*s*-triazine and 20 g. of triethylamine in 400 ml. of ethanol was refluxed for 8 hr. Then the triethylamine, the excess ethanol, and the chloroform formed were removed by distillation and the oily residue was dissolved in 150 ml. of petroleum ether (b.p. 30–40°) whereupon a small amount of an insoluble by-product precipitated. The petroleum ether was distilled from the filtrate and the remainder distilled *in vacuo*, yielding 11.6 g. (81.3%) of 2,4-bisethoxy-6-trichloromethyl-*s*-triazine (VIII); b.p. 134–135.5° (1.9 mm.) (lit.[6] b.p. 124° (0.1 mm.)), n_D^{25} 1.5111 (lit.[5] n_D^{30} 1.5112). (b) This compound was also obtained by refluxing a solution of 2-ethoxy-4,6-bistrichloromethyl-*s*-triazine (27 g). and triethylamine (31.3 g.) in 150 ml. of ethanol for 7 hr. 2,4-Bisethoxy-6-trichloromethyl-*s*-triazine (VIII) was isolated from the reaction mixture as described above; yield: 88.2%; b.p. 133.5–135.5° (1.9 mm.); n_D^{26} 1.5108.

2,4-Bis-n-butoxy-6-trichloromethyl-s-triazine (IX) was prepared from 2-*n*-butoxy-4,6-bistrichloromethyl-*s*-triazine and *n*-butyl alcohol in the presence of triethylamine by procedure (b) as a colorless oil, b.p. 135–138.5° (0.1 mm.), n_D^{24} 1.5005; yield: 88.5%.

Anal. Calcd. for $C_{12}H_{18}Cl_3N_3O_2$: C, 42.06; H, 5.29; N 12.27. Found: C, 42.24; H, 5.34; N, 12.76.

General procedure for the preparation of 2-alkoxy-4-methyl-6-trichloromethyl-s-triazines. Compounds XV and XVI were obtained by refluxing 2-methyl-4,6-bistrichloromethyl-*s*-triazine (XIII) in the appropriate alcohol in the presence of a tertiary amine for 6–8 hr. The reaction products were isolated in the same manner as described for the 2,4-bisalkoxy-6-trichloromethyl-*s*-triazines.

2-Ethoxy-4-methyl-6-trichloromethyl-s-triazine (XV) was obtained from XIII (33 g.), ethanol (150 ml.), and *N*-ethylpiperidine (30 g.) as a colorless oil, b.p. 94–95° (0.55 mm.); n_D^{23} 1.5177; yield: 56%.

Anal. Calcd. for $C_7H_8Cl_3N_3O$: C, 32.77; H, 3.14; Cl, 41.46; N, 16.38. Found: C, 32.60; H, 3.24; Cl, 41.46; N, 16.36.

2-Butoxy-4-methyl-6-trichloromethyl-s-triazine (XVI) was obtained from XIII (32.6 g.), *n*-butyl alcohol (200 ml.), and *N*-ethylpiperidine (30 g.) as a yellowish oil, b.p. 128–130° (0.6 mm.); n_D^{23} 1.5088; yield: 33.5%.

Anal. Calcd. for $C_9H_{12}Cl_3N_3O$: C, 37.98; H, 4.25; N, 14.77. Found: C, 37.99; H, 4.21; N, 14.81.

General procedure for the preparation of 2-alkoxy-4-phenyl-6-trichloromethyl-s-triazines. 2-Ethoxy-4-phenyl-6-trichloromethyl-s-triazine (XVII). 2-Phenyl-4,6-bistrichloromethyl-*s*-triazine (20 g.) (XIV), ethanol (200 ml.), and triethylamine (39 g.) were refluxed for 8 hr. Triethylamine, excess ethanol, and chloroform were removed by distillation. The remainder solidified at room temperature and was recrystallized from petroleum ether (b.p. 90–97°), resulting in crystals which proved to be 2-ethoxy-4-phenyl-6-trichloromethyl-*s*-triazine (XVII); yield: 14.2 g. or 89%; m.p. 78–79.5°.

Anal. Calcd. for $C_{12}H_{10}Cl_3N_3O$: C, 45.24; H, 3.16; Cl, 33.39; N, 13.19. Found: C, 45.29; H, 3.27; Cl, 32.76; N, 13.14.

General procedure for the preparation of tertiary amine salts of 2-hydroxy-4,6-bistrichloromethyl-s-triazine. Triethylamine salt of 2-hydroxy-4,6-bistrichloromethyl-2-triazine (XVIII). A mixture of 2,4,6-tristrichloromethyl-*s*-triazine, (I, 43.35 g.), triethylamine (42.8 g.), and water (250 ml.) was refluxed, with stirring, for 3 hr. After cooling, the precipitated triethylamine salt of the 2-hydroxy-4,6-bistrichloromethyl-*s*-triazine was filtered, yielding 35.3 g. or 81.5% of product, m.p. 173–177°. After one crystallization from dioxane the salt melted at 178–180°.

According to this procedure other tertiary amine salts were synthesized which are listed in Table II. The tributylamine salt separated from the reaction mixture as an oil. Addition of petroleum ether (b.p. 63–68°) and subsequent evaporation of the solvent resulted in crystallization of the salt. The triethylamine salt XVIII was also obtained, when 2,4,6-tristrichloromethyl-*s*-triazine (35 g.), trifluoroethanol (80 g.), and triethylamine (35 g.) were stirred at 0° for 6 hr. Upon removing the low boiling material between 0° and 20°, 32 g. (92%) of XVIII separated; m.p. 174–178°. A mixed melting point with an authentic sample showed no depression.

2-Chloro-4,6-bistrichloromethyl-s-triazine (XXIII). The triethylamine salt XVIII (30 g.) was stirred and refluxed with phosphorus oxychloride (150 ml.) for 3 hr. The excess phosphorus oxychloride was removed *in vacuo* and the resulting oil slowly added to a mixture of ice and water. The separated 2-chloro-4,6-bistrichloromethyl-*s*-triazine (XXIII)

was taken up with petroleum ether (b.p. 30–40°). After the solution had been concentrated to about 50 ml. and kept at −20° for 5 hr., 11 g. of crystals precipitated.

A further crop of crystals (11.1 g.) was obtained, when the mother liquor was concentrated to about 25 ml. and cooled again to −20°, thus improving the yield of XXIII to 91.4%. The melting point of this compound was 56–57° and showed no depression with an authentic sample.

The tertiary amine salts XX and XXI, respectively, were converted into XXIII by the same procedure; yield: 94.2% and 87%, resp.

2-Hydroxy-4,6-dimethyl-s-triazine (XXIV). A mixture of the triethylamine salt XVIII (8.6 g., 0.02 mole), triethylamine (12.32 g., 0.12 mole), 2% palladium on carbon (12 g.), and methanol (150 ml.) was shaken at room temperature with hydrogen. After the absorption of hydrogen was complete, the catalyst was filtered and a solution of sodium hydroxide (4.8 g., 0.12 mole) in methanol (50 ml.) was added to the filtrate, whereby the triethylamine hydrochloride was converted into triethylamine and sodium chloride. After the precipitated sodium chloride was removed by filtration, the filtrate was evaporated to dryness at reduced pressure. The residue was taken up with absolute ethanol, a further crop of insoluble sodium chloride removed by filtration, and the 2-hydroxy-4,6-dimethyl-s-triazine (XXIV) precipitated with ether. The precipitate was sublimed *in vacuo* (bath temperature 160–178° at 0.05–0.02 mm), yielding 2 g. (80%) of pure XXIV; m.p. 236–237° (lit.[6] m.p. 230–231°). A mixed melting point with an authentic sample showed no depression.

By the same procedure, XXIV was obtained from the *N*-ethylpiperidine salt (XX), yield 84%.

Acknowledgment. The author is indebted to the Olin Mathieson Chemical Corporation for their generous support of this work. He also wishes to thank Dr. C. J. Grundmann for stimulating discussions.

COLUMBUS 10, OHIO

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

Synthesis and Reactions of 5-Bromomethyl- and 5-Chloromethyluracil

JOHN A. CARBON

Received March 25, 1960

The chlorination of 6-methyl-2-methylmercapto-4-pyrimidinol (I) with *N*-chlorosuccinimide in the presence of benzoyl peroxide gives only the nuclear halogenated product, 5-chloro-6-methyl-2-methylmercapto-4-pyrimidinol (III), and not the isomeric 6-chloromethyl derivative (II) as was previously assumed.[4] 5-Chloromethyluracil (VI) was prepared by the reaction of 5-hydroxymethyluracil (V) with thionyl chloride in the presence of pyridine. Similarly, the treatment of V with hydrogen bromide in glacial acetic acid results in the formation of 5-bromomethyluracil (VII). A few displacement reactions of these compounds are presented, including the preparation of the thiamine analog, 3-(2′,4′-dihydroxy-5′-pyrimidylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium bromide (XI).

The halogenated thymine derivatives, 5-bromomethyluracil (VII) and the corresponding chloro compound (VI), have long been desired as reactive intermediates for the introduction of the thyminyl residue into other molecules.[1] Although Johnson and his coworkers were successful in preparing 5-chloromethyl-6-methyluracil from the reaction of 6-methyluracil with chloromethyl methyl ether, the synthesis of 5-chloromethyluracil by this method was not possible.[1c] These workers apparently did not attempt the direct conversion of 5-hydroxymethyluracil (V) to the corresponding 5-halomethyl derivatives, as the former compound (V) was erroneously thought to be quite unstable, decomposing readily to formaldehyde and uracil.[2] Recent work, however, has shown that 5-hydroxymethyluracil (V) is a reasonably stable compound and may be prepared in good yield from uracil and formaldehyde in alkaline solution.[3]

A compound, obtained by the interaction of *N*-chlorosuccinimide with thymine in chloroform containing benzoyl peroxide, was assigned the 5-chloromethyluracil (VI) structure in 1954.[4] However, this structural assignment seemed to us fairly unlikely, as (1) the chlorine in their compound was stable to boiling ethanol or water, whereas halomethylpyrimidines are notoriously labile compounds,[1c,5] and (2) *N*-chlorosuccinimide is known to be ineffective in producing allylic substitution.[6] We have discovered that the compound of West and Barrett[4] is, in reality, 5-chloro-6-ethoxy-5-methylhydrouracil, a compound previously obtained by Johnson and Sprague[7] from another route. These findings are corroborated by a recent paper,[8] which has appeared since our work was completed.

Because of the above facts, it was desirable to investigate a second allylic chlorination reported in the West and Barrett paper.[4] These workers ob-

(1) (a) D. Riehl and T. B. Johnson, *Rec. trav. chim.*, 59, 87 (1940); (b) M. M. Endicott and T. B. Johnson, *J. Am. Chem. Soc.*, 63, 1286 (1941); (c) M. M. Endicott and T. B. Johnson, *J. Am. Chem. Soc.*, 63, 2063 (1941).

(2) T. B. Johnson and A. Litzinger, *J. Am. Chem. Soc.*, 58, 1940 (1936).

(3) R. E. Cline, R. M. Fink, and K. Fink, *J. Am. Chem. Soc.*, 81, 2521 (1959).

(4) R. A. West and H. W. Barrett, *J. Am. Chem. Soc.*, 76, 3146 (1954).

(5) T. Okuda and C. C. Price, *J. Org. Chem.*, 24, 14 (1959).

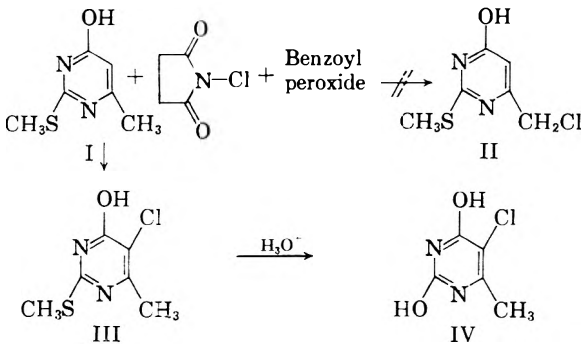
(6) C. Djerassi, *Chem. Revs.*, 43, 271 (1948).

(7) T. B. Johnson and J. M. Sprague, *J. Am. Chem. Soc.*, 59, 2436 (1937).

(8) J. H. Burckhalter, R. J. Seiwald, and H. C. Scarborough, *J. Am. Chem. Soc.*, 82, 991 (1960).

tained a compound, m.p. 230–235°, from the *N*-chlorosuccinimide reaction with 6-methyl-2-methylmercapto-4-hydroxypyrimidine (I) in chloroform containing benzoyl peroxide. Although correct analyses could not be obtained, these authors assigned the compound the structure, 6-chloromethyl-2-methylmercapto-4-hydroxypyrimidine (II), as it was converted by hot aqueous hydrochloric acid to 6-chloromethyluracil, a compound previously prepared by Johnson, *et al.*[9] Neither analyses nor infrared spectra were reported for the latter compound, however.

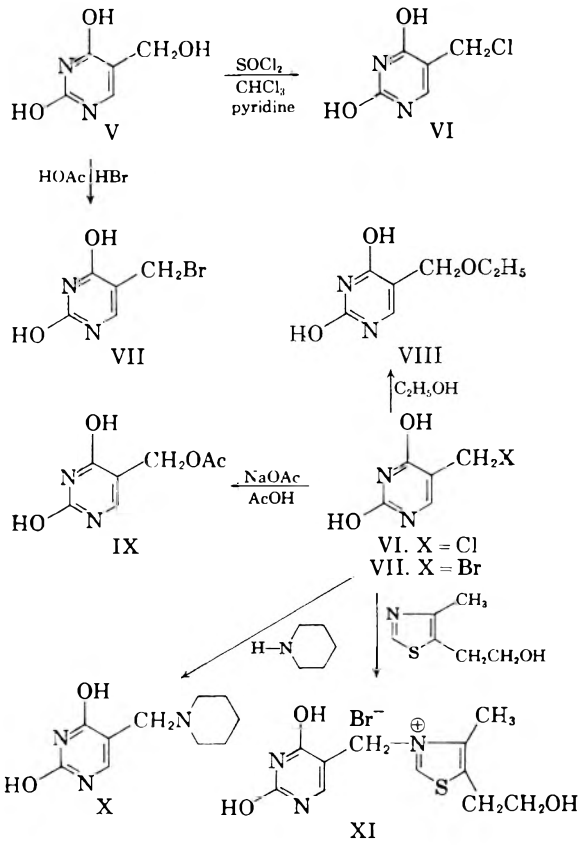
Several repetitions of the *N*-chlorosuccinimide reaction with I did not give the 230–235° material. The only product, regardless of whether the reaction was carried out in dry chloroform or carbon tetrachloride, was a crystalline material, m.p. 269–270°, and empirical formula $C_6H_7ClN_2OS$. This substance was identified as the isomeric compound 5-chloro-6-methyl-2-methylmercapto-4-hydroxypyrimidine (III) by hydrolysis to the known 5-chloro-6-methyluracil (IV).[10] In no case could we obtain the isomeric 6-chloromethyl derivative (II).



The synthesis of 5-chloromethyluracil[11,12](VI) was accomplished simply by treating 5-hydroxymethyluracil (V) with thionyl chloride in dry chloroform containing a little dry pyridine. The analogous 5-bromomethyl compound (VII) was readily obtained by treatment of V with hydrogen bromide in glacial acetic acid. As might be expected from theoretical considerations, the halogen atom in these molecules is extremely reactive; *e.g.*, treatment with warm water or ethanol for only one to two minutes is sufficient to remove all the halogen. A virtually quantitative yield of 5-ethoxymethyluracil (VIII) can be obtained merely by recrystallization of either material from ethanol.

Although 5-bromomethyluracil (VII) could be obtained analytically pure by recrystallization from glacial acetic acid, we were unable to completely purify 5-chloromethyluracil (VI) because of its extreme insolubility in all solvents tried (*e.g.*, glacial acetic acid, *N*,*N*-dimethylformamide, diethylene glycol dimethyl ether, etc.). The structure of VI was proven, however, by (1) conversion to 5-ethoxymethyluracil (VIII) in warm ethahol, (2) conversion to 5-piperidinomethyluracil (X) by treatment with piperidine in dioxane solution, and (3) conversion to 5-acetoxymethyluracil (IX) in glacial acetic acid containing sodium acetate. The identical products could be obtained in a like manner from 5-bromomethyluracil (VII).

The availability of the 5-halomethyluracils has now made possible the ready preparation of 5-substituted aminomethyluracils, such as X, by simple substitution reactions. These compounds were previously obtained by roundabout methods, *e.g.*, 5-aminomethyluracil (thyminyl amine) was obtained by the Curtius degradation of uracil-5-acetic acid.[13]



Treatment of 5-bromomethyluracil (VII) in anhydrous diglyme or dioxane with 5-(2′-hydroxy-

(9) T. B. Johnson and L. H. Chernoff, *J. Am. Chem. Soc.*, 36, 1742 (1914).

(10) R. Behrend, *Ann.* **236**, 57 (1886); T. B. Johnson and J. M. Sprague, *J. Am. Chem. Soc.*, **60**, 1622 (1938).

(11) This compound has also been prepared by the chloromethylation of uracil in aqueous hydrochloric acid (see ref. 8 and 12). Although Skinner, *et al.* (ref. 12) state that attempts to convert 5-hydroxymethyluracil (V) to 5-chloromethyluracil (VI) using thionyl chloride in pyridine gave only the quaternary salt formed from VI and pyridine, we have found that the reaction proceeds quite satisfactorily using slightly more than the theoretical quantity of pyridine in chloroform.

(12) W. A. Skinner, M. G. M. Schelstraete, and B. R. Baker, *J. Org. Chem.*, **25**, 149 (1960).

(13) T. B. Johnson and A. Litzinger, *J. Am. Chem. Soc.*, **57**, 1139 (1935); A. Litzinger and T. B. Johnson, *J. Am. Chem. Soc.*, **58**, 1936, 1940 (1936).

ethyl)-4-methylthiazole gave an excellent yield of the thiamine analog, 3-(2′,4′-dihydroxy-5′-pyrimidylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium bromide (XI). The use of diethylene glycol dimethyl ether rather than dioxane as solvent in this reaction is preferable, as the product is more readily crystallized and purified.

Biological testing of many of these compounds is now in progress and will be reported elsewhere.

EXPERIMENTAL[14]

5-Chloro-6-methyl-2-methylmercapto-4-hydroxypyrimidine (IV). A mixture of 15.6 g. (0.10 mole) of 6-methyl-2-methylmercapto-4-hydroxypyrimidine,[15] 14.7 g. (0.11 mole) of *N*-chlorosuccinimide, 3.63 g. (0.015 mole) of benzoyl peroxide, and 250 ml. of purified chloroform was heated under reflux for 16 hr. (drying tube). The mixture was cooled and the crystalline material filtered with suction and air-dried to give 10.5 g. of crude product, m.p. 267.5–269°. An additional 0.6 g. was obtained by concentration of the chloroform mother liquor and washing with water to remove succinimide. Recrystallization of the combined solids from methyl Cellosolve gave 9.7 g. (51%) of colorless prismatic needles, m.p. 269–270° with sublimation; reported[4] m.p. 270° dec.

Anal. Calcd. for $C_6H_7ClN_2OS$: C, 37.79; H, 3.70; Cl, 18.59; N, 14.69. Found: C, 37.99; H, 3.65; Cl, 18.40; N, 14.85.

A repetition of this reaction using purified carbon tetrachloride as solvent gave a 69.5% yield of product, which was identical in all respects with that obtained above. In no case could we isolate any of the isomeric compound, 6-chloromethyl-2-methylmercapto-4-hydroxypyrimidine (II).

Hydrolysis of 1.9 g. (0.01 mole) of compound V with 25 ml. of aqueous hydrochloric acid (1:1) at 100° for 5 hr. gave 1.6 g. (100%) of *5-chloro-6-methyluracil* (IV), m.p. >300°. The infrared spectrum of this compound was identical with that of an authentic sample of IV, prepared by the method of Behrend.[10]

Anal. Calcd. for $C_5H_5ClN_2O_2$: C, 37.39; H, 3.14; Cl, 22.08; N, 17.44. Found: C, 37.71; H, 3.25; Cl, 22.11; N, 17.64.

5-Bromomethyluracil (VII). Five grams (0.0352 mole) of 5-hydroxymethyluracil (V)[3] was added to 100 ml. of 32% hydrogen bromide in glacial acetic acid, and carefully warmed on the steam bath for 8 hr. (drying tube). The mixture was cooled, filtered with suction, and the colorless powder washed thoroughly with dry ether. There was thus obtained 5.7 g. (79.0%) of product, m.p. >330° (capillary) with slow decomposition. A small sample was recrystallized from glacial acetic acid to obtain colorless tiny needles, m.p. >330° dec. This sample was dried overnight at 100° *in vacuo* for analysis.

Anal. Calcd. for $C_5H_5BrN_2O_2$: C, 29.29; H, 2.46; Br, 38.98. Found: C, 29.32; H, 2.72; Br, 38.47, 38.55.

This material (VII) was extremely reactive toward water or ethanol, and was routinely stored in a vacuum dessicator over potassium hydroxide pellets.

5-Chloromethyluracil (VI). Five grams (0.0352 mole) of 5-hydroxymethyluracil (V)[3] was added to 50 ml. of purified chloroform containing 3.0 ml. dry pyridine, and, with mechanical stirring, 5.5 g. (0.042 mole) of thionyl chloride in 10 ml. of chloroform slowly added. The mixture was refluxed for 0.5 hr. (drying tube), and the colorless solid filtered with suction and washed with dry ether. This crude product weighed 5.75 g. (100%), sintered at 268–270° and decomposed at 315–320°. This compound could not be obtained analytically pure because of its high reactivity toward hydroxylic solvents, coupled with its high insolubility in more inert solvents. An analysis for chlorine of the crude material was low.

Anal. Calcd. for $C_5H_5ClN_2O_2$: Cl, 22.08. Found: 17.89, 18.10.

The infrared spectrum of VI indicated a complete loss of the peak at 2.9 μ, usually assigned to the aliphatic hydroxyl group. The spectrum of the starting material (V) contains a strong peak at this frequency.

Identical products were obtained from substitution reactions using either this compound (VI) or 5-bromomethyluracil (VII).

5-Ethoxymethyluracil (VIII). 5-Bromomethyluracil (VII) (0.50 g.; 0.0024 mole) was boiled with 20 ml. of ethanol until a clear solution was obtained (about 3 min. required). Upon cooling, a colorless solid separated (0.30 g.;72 %), m.p. 212–214° dec. An analytical sample, prepared by recrystallization from ethanol, consisted of a colorless microcrystalline powder, m.p. 217–218° dec.

Anal. Calcd. for $C_7H_{10}N_2O_3$: C, 49.39; H, 5.92; N, 16.46; O, 28.23. Found: C, 49.57; H, 5.88; N, 16.61; O, 28.29.

This compound has been previously prepared by another route, reported[3] m.p. 212°.

5-Piperidinomethyluracil (X).[8] One gram (0.0049 mole) of 5-bromomethyluracil (VII) was added portionwise to 15 ml. of dry dioxane containing 2 ml. of piperidine. After refluxing gently for 75 min., the mixture was cooled to 5° and the colorless solid filtered with suction. This material was extracted with 15 ml. of boiling dioxane, filtered while hot to remove piperidine hydrochloride, and cooled to 5°. The resulting product was recrystallized from ethanol to give 0.45 g. (44%) of colorless leaflets, m.p. > 300°. For analysis, a small sample was recrystallized from ethanol and dried *in vacuo* at 75°.

Anal. Calcd. for $C_{10}H_{15}N_3O_2$: C, 57.41; H, 7.22; N, 20.09. Found: C, 57.49; H, 7.34; N, 20.23.

This material is quite soluble in water, but only slightly soluble in cold ethanol or dioxane.

5-Acetoxymethyluracil (IX). 5-Bromomethyluracil (VII) (1.0 g.; 0.005 mole) was mixed with 10 ml. of glacial acetic acid containing 0.80 g. (0.01 mole) of anhydrous sodium acetate. The mixture was heated to reflux for 5 min., cooled to room temperature, and filtered with suction. Additional product was obtained by dilution of the acetic acid mother liquor with ether. The combined solids were recrystallized from water to obtain 0.58 g. (63%) of colorless leaflets, m.p. 217–223° dec., when placed on the block at about 160° and heated fairly rapidly. When heated slowly from room temperature, the compound did not melt under 300°.

Anal. Calcd. for $C_7H_8N_2O_4$: C, 45.65; H, 4.38; N, 15.22. Found: C, 45.26; H, 4.89; N, 15.93.

This compound has been previously obtained by another route, but was presented without analytical data as m.p. >300°.[3]

3-(2′,4′-Dihydroxy-5′-pyrimidylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium bromide (XI). One gram (0.0050 mole) of 5-bromomethyluracil (VII) was added to 15 ml. of dry, redistilled diethylene glycol dimethyl ether containing 0.82 g. (0.0057 mole) of 5-(2′-hydroxyethyl)-4-methylthiazole (Merck), and heated on the steam bath for 1 hr. (drying tube). The mixture was cooled and filtered with suction. The crude product (m.p. 221–222°) was recrystallized by dissolving in a minimum of hot methanol, filtering, and adding 2 volumes of dry diethylene glycol dimethyl ether. The colorless prisms thus obtained weighed 1.1 g. (63%), m.p. 219–221° dec. when placed on the block at 180°. It melted at 215–217° dec. when heated slowly from room temperature.

(14) All melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus.

(15) R. List, *Ann.*, **236**, 1 (1886); H. L. Wheeler and H. F. Merriam, *Am. Chem. J.*, **29**, 478 (1903).

Anal. Calcd. for $C_{11}H_{14}BrN_3O_3S$: C, 37.94; H, 4.06; Br, 22.95; N, 12.07. Found: C, 38.04; H, 4.36; Br, 22.93; N, 12.08.

The yield in a second run using three times the above quantities was 74%. The reaction could also be run in dioxane solution, but the gummy product was difficult to crystallize and purify.

Acknowledgment. The author would like to thank Mr. E. F. Shelberg and his staff for the microanalyses and Mr. W. Washburn and his staff for the infrared absorption spectra.

NORTH CHICAGO, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICAL SCIENCES, UNIVERSITY OF IDAHO]

Preparation of Some Alkyl-Substituted Monohydroxamic Acids, *N*-Acyl-*O*-alkylhydroxylamines. I

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In order to initiate a study of the reactions of the alkyl hydroxamates, the preparation of representative benzo-, aniso-, toluo-, aceto-, and propionhydroxamic esters has been carried out by the reaction of sodium and potassium salts of hydroxamic acid with alkyl halides. Several dialkyl hydroxamates were also obtained as by-products in these reactions. The infrared spectra of these compounds were studied and the bands attributed to N—H stretching, C=O stretching, amide II, and C—O stretching were observed.

The preparation of a number of hydroxamic acid esters has been carried out in order subsequently to study their reactions. The reaction of a hydroxamic acid salt with an alkyl halide was used to prepare the hydroxamic acid esters.[2,3]

Esters of aromatic hydroxamic acids were made using a procedure similar to that of Fuller and King,[4] who prepared *n*-butyl benzohydroxamate. Potassium salts of the hydroxamic acids were prepared by the reaction of ethyl esters with hydroxylamine and potassium hydroxide.[5] In this preparation the potassium salt precipitates from methanolic solution. Barium toluhydroxamate was also prepared by the reaction of the mother liquor from the potassium toluhydroxamate preparation with barium chloride. When the potassium or barium salt, sodium carbonate, and a primary alkyl halide in alcohol-water solution were stirred together and warmed, the alkyl hydroxamates were obtained in good yields. A ferric chloride spot test was used to follow the reaction. This color test changed from an initial dark purple to a final pale red during an interval that varied from two days, when the solutions were refluxed, to three weeks, when the solutions were stirred at room temperature.

The aceto- and propionhydroxamic acid esters were prepared in essentially the same manner. Ethyl acetate and ethyl propionate, respectively, were allowed to react with hydroxylamine and sodium methoxide in absolute methanol, and without isolation of the hydroxamic acid salt an alkyl halide, sodium carbonate, and water were added to prepare the hydroxamic ester.

Both the aromatic and aliphatic acid esters were worked up in the same way. The alcohol was removed by distillation from the reaction mixture, and the product was taken up in chloroform. Extraction of the chloroform with sodium bicarbonate removed all unchanged carboxylic acid formed by saponification of the starting material. The hydroxamic ester was extracted from the chloroform with sodium hydroxide. This alkaline solution was acidified and the hydroxamic ester was taken up in chloroform.

Dialkylhydroxamate esters were found in a number of the preparations in the chloroform solutions after they had been extracted with sodium hydroxide. In a few cases these were purified, and in some cases they were found to be intractable oils. We are uncertain of the structures of the dialkylhydroxamates. The several possible isomeric structures are *N*,*O*-dialkylhydroxamates(I) and syn- and anti- forms of the *O*,*O'*-dialkylhydroxamates (II). All of the dialkyl benzohydroxamates

I II

that have been reported in the literature have been assigned structure II.[2,4,6,7] On the other

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(2) H. L. Yale, *Chem. Revs.*, **33**, 209 (1944).

(3) F. Mathis, *Bull. soc. chim. France*, 5, D9 (1953).

(4) A. T. Fuller and H. King, *J. Chem. Soc.*, 963 (1947).

(5) C. R. Hauser and W. B. Renfrow, Jr., *Org. Syntheses*, Coll. Vol. II, 67 (1953); W. B. Renfrow and C. R. Hauser, *J. Am. Chem. Soc.*, 59, 2312 (1937).

TABLE I

HYDROXAMIC ACID ESTERS PREPARED BY THE SAME PROCEDURE USED TO PREPARE ALLYL BENZOHYDROXAMATE

Name	M.P.[a]	Yield,[b] %	Analyses[c]		
Benzyl benzohydroxamate	103–105°	65	Previously reported,[d] m.p. 103°		
Methyl benzohydroxamate	63.5–64.5°	43	Previously reported,[e] m.p. 62°		
			C	H	N
Benzyl *p*-toluhydroxamate	127.5–129.5°	70	74.67	6.27	5.80
			74.86	6.40	5.77
n-Propyl *p*-toluhydroxamate[f]	47–48°	53	68.37	7.82	7.25
			68.53	7.82	7.23
n-Butyl *p*-toluhydroxamate[g]	50.5–51.5°	77	69.54	8.27	6.76
			69.41	8.52	6.96
Allyl anisohydroxamate	52.8–54°	82	63.75	6.32	6.76
			63.86	6.17	6.83
n-Propyl anisohydroxamate	83.5–84°	54	63.14	7.27	6.70
			63.02	6.98	6.95
Propargyl anisohydroxamate	116–116.7°	47	64.37	5.40	6.82
			64.48	5.62	6.60
n-Butyl anisohydroxamate[g]	67–67.8°	64	64.55	7.67	6.27
			64.71	7.72	6.19
Benzyl anisohydroxamate	113–114.5°	45	Previously reported,[h] m.p. 113°		

[a] All melting points are corrected and represent analytical samples. [b] The yields are based on the potassium salts of the hydroxamic acids. [c] The first line values represent calculated values, and the second line the analytical results. [d] See ref. 6. [e] W. Lossen, *Ann.*, 252, 226 (1889). [f] Also isolated as a crystalline sodium salt during the extraction procedure. [g] These products were purified by vacuum sublimation. [h] W. Lossen, *Ann.*, 281, 169 (1894).

hand the *N*-alkylation of ethyl ethoxycarbamate has been reported.[8–10]

The unsaturated hydroxamic acid esters, allyl benzohydroxamate and allyl anisohydroxamate, were hydrogenated using a platinum catalyst and low pressure. The resulting *n*-propyl benzohydroxamate and *n*-propyl anisohydroxamate were isolated directly in nearly quantitative yields. Similar results have been reported for the hydrogenation of *cis*-6-cyclopentena(e)tetrahydro-1,2-oxazin-3-one.[11]

EXPERIMENTAL

Allyl benzohydroxamate,[12] *(N-benzoyl-O-allylhydroxylamine), and diallyl benzohydroxamate.* A solution of 87.5 g. (0.50 mole) of potassium benzohydroxamate,[5] 72.5 g. (0.60 mole) of allyl bromide, 25 g. of anhydrous sodium carbonate in 375 ml. of methanol, and 250 ml. of water was stirred for 24 hr. The methanol was removed by distillation and the residue was acidified with 12*N* hydrochloric acid. The crude product was taken up in four 100-ml. portions of chloroform and was washed with 10% sodium bicarbonate. The allyl benzohydroxamate was extracted from the chloroform with six 50-ml. portions of 6*N* sodium hydroxide. Diallyl benzohydroxamate remained in the chloroform. The combined sodium hydroxide extracts were acidified with 12*N* hydrochloric acid and the aqueous solution was extracted with four 50-ml. portions of chloroform. The chloroform was removed by distillation and the residue which slowly solidified upon cooling to room temperature was recrystallized from ether and petroleum ether (b.p. 30–60°) mixture. The yield was 63.2 g. (68%), m.p. 62–63.5°. Two more recrystallizations gave 55.1 g. (59%) of pure allyl benzohydroxamate m.p. 62.5–63.5°,[13] reported[12] m.p. 58°. ν_{N-H} 3160 in Nujol, 3370, 3200 in chloroform, 3400, 3200 in potassium bromide; $\nu_{C=O}$ 1640 in Nujol, 1660 in chloroform, 1640 in potassium bromide; $\nu_{Amide\ II}$ 1500; ν_{C-O} 1300 cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.81; H, 6.26; N, 7.91. Found: C, 67.82; H, 6.22; N, 7.68.

A yield of 5 g. (5%) of diallyl benzohydroxamate, b.p. 101.5–102° at 0.6 mm., n_D^{20} 1.5312 was also obtained. ν_{C-H} 3120, 3040, 3010, 2950; $\nu_{C=O}$ 1660, ν_{C-O} 1270 $cm.^{-1}$ on pure liquid.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.72; H, 6.85; N, 6.34.

Propargyl p-toluhydroxamate (N-p-methylbenzoyl-O-propargylhydroxylamine). When 110 g. (0.25 mole) of barium *p*-toluhydroxamate, 30 g. of sodium carbonate, 375 ml. of methanol, 250 ml. of water, and 68 ml. (104 g., 0.87 mole) of propargyl bromide were stirred together, 6 days were required for a ferric chloride test for hydroxamic acid to become very weak. The methanol was removed under reduced pressure, and the remaining mixture was acidified with 12*N* hydrochloric acid. A solid precipitated and was removed by filtration. Extraction of the organic material from this precipitate with acetone, and distillation of the acetone gave 69.0 g. of solid product. An additional 2 g. of product was obtained by extraction of the water solution with chloroform. The overall yield was 71 g. (75%). Two recrystallizations of 10 g. of this crude product from benzene gave 7.2 g. (55%) of pure ester, which was vacuum sublimed, m.p. 101.5–102.5°. ν_{N-H} 3450, 3350; ν_{C-H} 3300; $\nu_{C=O}$ 1675; $\nu_{Amide\ II}$ 1510; ν_{C-O} 1300 $cm.^{-1}$ in chloroform.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 70.05; H, 6.07; N, 7.35.

Allyl *p*-toluhydroxamate (*N-p*-methylbenzoyl-*O*-allylhydroxylamine) was prepared from barium toluhydroxamate in 74% yield, b.p. 138° at 0.2 mm., $n_D^{21.5}$ 1.5531. ν_{N-H}

(6) E. Beckman, *Ber.*, 26, 2633 (1893).
(7) W. Lossen, *Ann.*, 252, 170 (1889).
(8) L. W. Jones, *Am. Chem. J.*, 38, 253 (1907).
(9) C. H. Hecker, *Am. Chem. J.*, 50, 444 (1913).
(10) L. W. Jones and L. Neuffer, *J. Am. Chem. Soc.*, 36, 2202 (1914).
(11) W. E. Noland, J. H. Cooley, and P. A. McVeigh, *J. Am. Chem. Soc.*, 81, 1209 (1959).
(12) O. L. Brady and F. H. Peakin, *J. Chem. Soc.*, 226 (1930).
(13) All melting points were determined in capillaries in an electrically heated aluminum block with a calibrated thermometer.

TABLE II

HYDROXAMIC ESTERS PREPARED BY THE SAME PROCEDURE USED TO PREPARE BENZYL ACETOHYDROXAMATE

Name	M.P., B.P.	n^t_D	Yield,[a] %	Analyses[b] C	H	N
Allyl acetohydroxamate	19–21°[c] 80/1 mm.	1.4619 (23°)	24	52.15	7.88	12.17
				51.49	7.70	12.05
Diallyl acetohydroxamate	93°/14 mm.	1.4586 (23°)	10	61.91	8.44	9.03
				61.66	8.39	8.97
n-Propyl acetohydroxamate	72°/0.5 mm.	1.4403 (24°)	34	51.26	9.47	11.96
				51.24	9.35	12.05
p-Nitrobenzyl acetohydroxamate	133.5–134°[d]		31	51.43	4.80	13.33
				51.88	4.93	13.41
Allyl propionhydroxamate[e]	11°[c] 74.5–76°/ 1 mm.	1.4618 (17.5°)	36	55.79	8.59	10.85
				55.54	8.37	10.95
Ethyl benzohydroxamate	63–64.2°		28.5	Previously reported,[f] m.p. 64–65°		

[a] The yields are based on hydroxylamine and the products were distilled once. [b] The first line values represent calculated values and the second line the analytical results. [c] These melting points are not exact. [d] This melting point is correct and represents an analytical sample. [e] A crude yield of diallyl propionhydroxamate of 11% was also obtained in this preparation. [f] W. Lossen, *Ber.*, **24**, 4059 (1891).

3220, $\nu_{C=O}$ 1650, $\nu_{Amide\ II}$ 1500, ν_{C-O} 1310 cm.$^{-1}$ on the pure liquid.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.28; H, 7.09; N, 7.12.

Benzyl acetohydroxamate (*N-acetyl-O-benzylhydroxylamine*) *and dibenzyl acetohydroxamate.* Sodium (23 g., 1 g.-atom) was dissolved in 600 ml. of absolute methanol, and a solution of 34.75 g. (0.50 mole) of hydroxylamine hydrochloride in 500 ml. of absolute methanol was added to the sodium methoxide solution during a half hour period. The mixture was stirred during the addition and then chilled for 15 min. in an ice bath. Ethyl acetate (44 g., 0.50 mole) was added and the sodium chloride was removed by pumping the solution under 2 p.s.i. of nitrogen through a sintered glass funnel. Three days later 750 ml. of methanol was removed by distillation, and 100 ml. of water, 20 g. of anhydrous sodium carbonate, and 75.5 g. (0.60 mole) of benzyl chloride were added. To obtain a negative ferric chloride test it was necessary to stir this mixture for 2 days, and then reflux it briefly. The remaining methanol was removed by distillation, and the residue was acidified with 12*N* hydrochloric acid. The aqueous solution was extracted with four 100-ml. portions of chloroform. The combined chloroform extracts were washed with two 100-ml. portions of 5% sodium bicarbonate. The weakly acidic hydroxamic acid ester was extracted into two 100-ml. portions of 20% sodium hydroxide while the neutral dialkyl hydroxamic acid ester remained in the chloroform solution. Removal of the chloroform and distillation of the product gave 10 g. (9%) of dibenzyl acetohydroxamate, b.p. 135–138° at 0.04 mm., m.p. 53–56°, which was recrystallized from ether-petroleum ether (b.p. 30–60°), m.p. 56–57°. $\nu_{C=O}$ 1670, ν_{C-O} 1260 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.26; H, 6.71; N, 5.49. Found: C, 74.92; H, 6.56; N, 5.72.

The combined sodium hydroxide extracts were acidified with 12*N* hydrochloric acid, and the monoalkyl hydroxamate was taken up in two 100-ml. portions of chloroform. Removal of the chloroform and distillation of the resulting oil gave 58.7 g. (71%) of benzyl acetohydroxamate b.p. 124° at 0.07 mm., m.p. 46–48°, n^{28}_D 1.5343 on the supercooled liquid. ν_{N-H} 3200, $\nu_{C=O}$ 1670, $\nu_{Amide\ II}$ 1500, ν_{C-O} 1290 cm.$^{-1}$ on the supercooled liquid.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.43; H, 6.71; N, 8.48. Found: C, 65.59; H, 6.75; N, 8.19.

n-Propyl benzohydroxamate (*N-benzoyl-O-n-propylhydroxylamine*). Platinum oxide (0.1 g.) was added to 7.4 g. (0.041 mole) of allyl benzohydroxamate dissolved in 10 ml. of 95% ethanol and the mixture was shaken with 2 atm. of hydrogen in a Parr apparatus. Approximately 3.25 p.s.i. (0.038 mole) of hydrogen was taken up over a 6-hr. period. The catalyst was removed by filtration, and the ethanol was removed by distillation leaving 7.0 g. (93%) of a white solid. Recrystallization of this solid from ether–petroleum ether (b.p. 30–60°) gave a pure product m.p. 58–59°, mixed melting point with allyl benzohydroxamate 45–50°. Vacuum sublimation did not change the melting point. ν_{N-H} 3200, $\nu_{C=O}$ 1645, $\nu_{Amide\ II}$ 1520, ν_{C-O} 1300 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.01; H, 7.31; N, 7.82. Found: C, 67.11; H, 7.26; N, 7.65.

n-Propyl anisohydroxamate was also prepared by hydrogenation of allyl anisohydroxamate under these same conditions in 91% yield.

Infrared spectra. The following characteristic absorption peaks were observed in the infrared spectra of the *N*-acyl-*O*-alkylhydroxylamines reported here: In chloroform solution ν_{N-H} 3450–3400 and 3300–3230, $\nu_{C=O}$ 1675–1660 and with the solid in Nujol or KBr ν_{N-H} 3220–3160, $\nu_{C=O}$ 1655–1630 cm.$^{-1}$ were observed. A weak band at 1530–1500 cm.$^{-1}$ appeared in all spectra and was considered to be similar to the amide II band appearing in monosubstituted amides. The exact location of this absorption in the spectra of compounds which also contained an aromatic ring is uncertain. Four bands appeared in these spectra between 1600 and 1480 cm^{-1}. Three of these bands can be attributed to the aromatic ring and the other to Amide II. The band chosen as the amide II band most nearly resembled in shape, location, and intensity the single band which appeared in this region with the aliphatic analogues. A comparison of the alkyl hydroxamates reported here with *cis*-6-cyclopentena(e)-tetrahydro-1,2-oxazin-3-one[11] is interesting. The amide II absorption is absent from the latter compound and thus affords a parallel to the monosubstituted amide lactam case. A weak band at 1270–1310 cm.$^{-1}$ attributed to C—O stretching also appeared. In the spectra of the dialkyl hydroxamates as pure liquids $\nu_{C=O}$ 1660–1670 and ν_{C-O} 1270–1250 cm.$^{-1}$ both strong bands were observed.

MOSCOW, IDAHO

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Resolution of 5-Allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric Acid

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Condensation of diethyl allyl(1-methyl-2-pentynyl)malonate with methylurea gave a mixture of the α- and β-forms of 5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid. The α-form was conveniently prepared by condensation of ethyl allyl(1-methyl-2-pentynyl)cyanoacetate with methylurea, followed by acid hydrolysis of the imino derivative (I). The β-form was prepared by acid hydrolysis of 5-allyl-4-imino-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid, which was prepared by N^1-methylation of 5-allyl-4-imino-5-(1-methyl-2-pentynyl)barbituric acid. The α-racemate was resolved at the imino stage, while the β-stereoisomers were obtained by allylation of *d*- and *l*-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid. A study was made of the anesthetic activity of the enantiomorphs in relation to their chemical structure.

In the synthesis of a group of barbituric acids substituted at the 5-carbon with an acetylene containing side-chain, one was chosen for more extensive study.[1] This compound has undergone broad clinical investigation, and for this reason its chemistry is being reported.

The present work describes the preparation of 5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid, and the resolution of its α- and β-forms into their enantiomorphs. Specific methods have been found for the preparation of the higher melting form, designated the α-form, and for the lower melting form, called the β-form.

Condensation of diethyl allyl(1-methyl-2-pentynyl)malonate with methylurea or the allylation of *dl*-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (VIII) gave an oily mixture consisting of the two racemic forms. However, condensation of ethyl allyl(1-methyl-2-pentynyl)cyanoacetate with methylurea formed a relatively pure imino derivative (I), which is designated as α-*dl*-5-allyl-6-imino-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (see Chart 1). The yield of I after one recrystallization from dilute ethanol was 75%, melting at 86–88°, whereas the pure material melts at 92–94°. From I there was obtained by hydrolysis with dilute acid compound II, which has been designated as α-*dl*-5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid; when pure, II melts at 96°.

The exclusive formation of the α-*dl*-imino derivative (I) and the resulting α-*dl*-barbituric acid (II) results because the reaction of disubstituted cyanoacetic acid esters with alkylureas gives iminobarbituric acids in which the imino group is attached to a carbon atom of the ring which is adjacent to the alkylated nitrogen atom.[2]

Also, in the reaction of the sodium derivative of ethyl(1-methyl-2-pentynyl)cyanoacetate with allyl bromide, the composition of the resulting ester must be predominantly of one form.

However, the reaction of 5,5-disubstituted 4-iminobarbituric acids with methyl iodide in a solution of sodium in ethanol gives 5,5-disubstituted 4-imino-1-methyl barbituric acids.[2]

α-Forms. When α-*dl*-5-allyl-6-imino-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (I) was treated with *d*-10-camphorsulfonic acid, the less soluble α-*d*-iminobarbituric acid-*d*-10-camphorsulfonic acid salt (III) was obtained. Treatment with sodium bicarbonate solution gave the α-*d*-iminobarbituric acid (IV) (m.p. 96–100°, $[\alpha]_D^{25}$ +113.5°) which was hydrolyzed to the α-*d*-barbituric acid (V) (m.p. 104–106.5°, $[\alpha]_D^{31}$ +40.6°).

Filtrates from the recrystallization of the less soluble salt III were allowed to evaporate on the steam bath. Instead of obtaining the expected α-*l*-imino base-*d*-10-camphorsulfonic acid salt, the α-*l*-barbituric acid (Va) was isolated (m.p. 104–107°, $[\alpha]_D^{28}$ −40.0°). This obviously resulted from the hydrolysis of the imino compound and demonstrates its lability in strongly acid solution.

However, the α-*l*-imino base (IVa) was obtained by treating the α-*dl*-iminobarbituric acid (I) with half a molecular equivalent of *d*-10-camphorsulfonic acid thereby separating the less soluble α-*d*-imino salt (III). The filtrate was treated with *dl*-10-camphorsulfonic acid and the resulting α-*l*-imino base-*l*-10-camphorsulfonic acid salt (VI) was isolated. The α-*l*-imino base (IVa) could also be purified by preparation of its hydrochloride salt (VIIa).

The β-enantiomorphs were obtained by resolution of *dl*-1-methyl-5-[1-methyl-2-pentynyl)-barbituric acid (VIII) by treatment with brucine, followed by reaction of the *d*- and *l*-isomers with allyl bromide (see Chart 2). The β-*d*- and β-*l*-acids prepared in this manner were slightly contaminated with α-*d*- and α-*l*-isomers respectively, and recrystallization of the reaction products gave the pure β-*d*- and β-*l*-acids.

Neither β-*dl*-5-allyl-4-imino-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (XII) nor *dl*-5-allyl-4-imino-5-(1-methyl-2-pentynyl)barbituric acid (XIII), from which XII was prepared, formed a crystalline salt with *d*-10-camphorsulfonic acid.

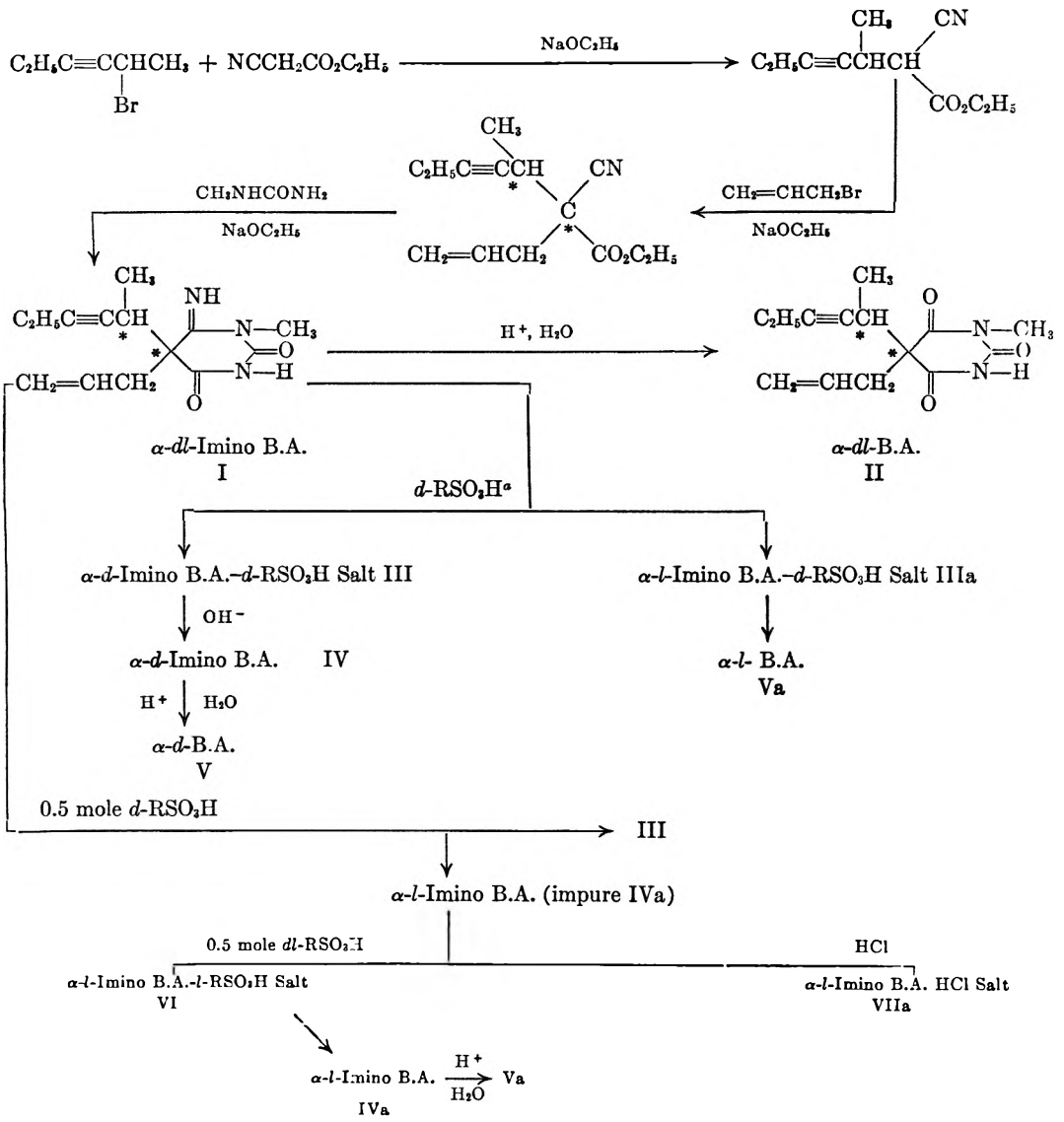
Although the resolution of barbituric acids con-

(1) W. R. Gibson, W. J. Doran, W. C. Wood, and E. E. Swanson, *J. Pharmacol. Exp. Therap.*, **125**, 23 (1959).

(2) M. Conrad and A. Zart, *Ann.*, **340**, 326 (1905).

CHART 1

SYNTHESIS OF α-ISOMERS



[a] RSO_3H is 10-camphorsulfonic acid.

taining on asymmetric carbon has been reported,[3,4] the pharmacological data show only minor differences in the anesthetic potency of the enantiomorphs. However, in the compounds reported in this publication considerable differences were found in their anesthetic potencies (see Table I).

As mentioned above, the allylation of *d*-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (Xa) gave a mixture of β-*l*- and α-*l*-acids, while *l*-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (X) gave a mixture of β-*d*- and α-*d*-acids. This then shows that the configuration of the (1-methyl-2-pentynyl) side-chain is the same in the β-*l*- and α-*l*-acids (and in the β-*d*- and α-*d*-acids), and the difference between these two compounds must be at the 5-carbon atom of the ring.

TABLE I

ANESTHETIC POTENCIES OF THE ISOMERS OF 5-ALLYL-1-METHYL-5-(1-METHYL-2-PENTYNYL)BARBITURIC ACID (SODIUM SALT) IV IN RATS

Compound No.	Isomer	AD_{50}, Mg./Kg.	LD_{50}, Mg./Kg.	Duration, Min
V	α-*d*-B.A.	11	18	13
Va	α-*l*-B.A.	35	47	14
II	α-*dl*-B.A.	15	28	14
XI	β-*d*-B.A.	17	23	12
XIa	β-*l*-B.A.	7	15	13[a]
IIa	β-*dl*-B.A.	10	19	14

[a] Postanesthetic stimulant activity.

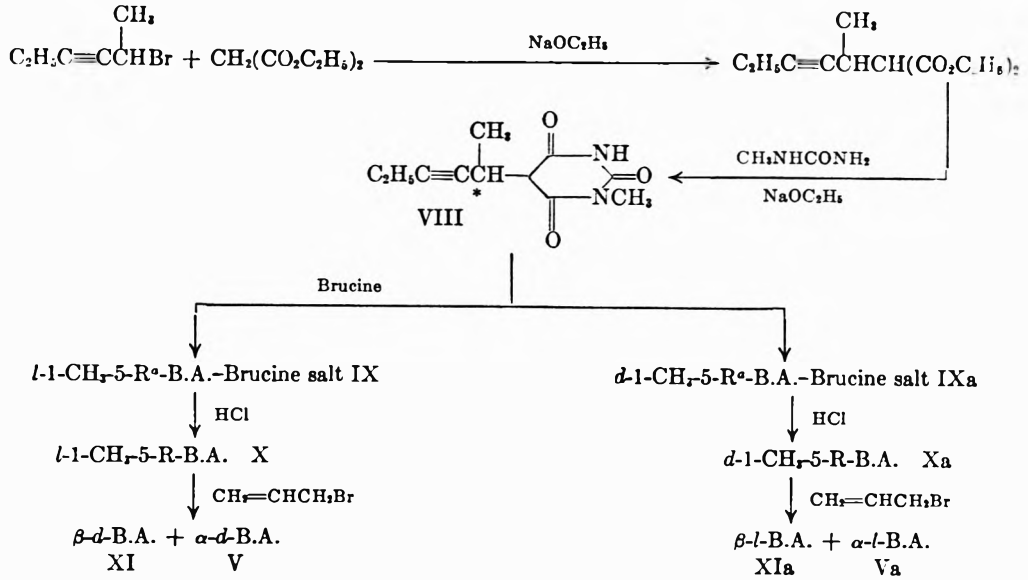
(3) C.-M. Hsueh and C. S. Marvel, *J. Am. Chem. Soc.*, 50, 855 (1928).

(4) E. C. Kleiderer and H. A. Shonle, *J. Am. Chem. Soc.*, 56, 1772 (1934).

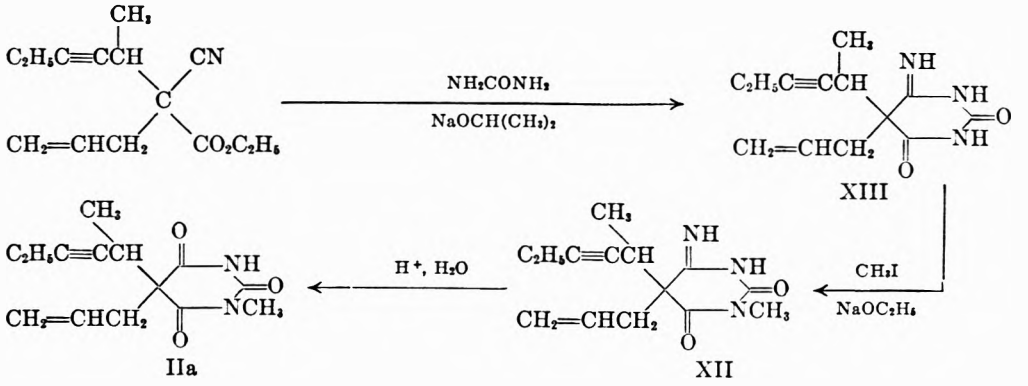
CHART 2

SYNTHESIS OF β-ISOMERS

(A) *Synthesis of β-Enantiomorphs*



(B) *Synthesis of β-dl-Acid* (IIa)



ᵃ R is $C_2H_5C{\equiv}CCH(CH_3)$.

A striking difference in potency is seen between the β-*l*-acid (XIa) and the α-*l*-acid (Va), in which the configuration of the (1-methyl-2-pentynyl) side chains is identical and that at the 5-carbon of the rings differ. This change in configuration at the 5-carbon results in a five-fold increase in potency of the β-*l*-form. Although the β-*l*-form is the most potent, its depressant action is accompanied by stimulating action making it less suitable for use as an anesthetic. Even though the α-*l*-form is more potent than the α-*dl*-form, the difference in potency is not sufficient to make the resolution commercially feasible. The α-*dl*-barbituric acid has had extensive clinical use as an anesthetic.[5]

EXPERIMENTAL

The physical properties of the barbituric acid derivatives (with the exception of the starting materials) are listed in Tables II and III. All of the melting points were taken by the capillary method, and temperatures are uncorrected.

3-Hexyne-2-ol[6] was prepared by the reaction of ethylacetylenemagnesium bromide with acetaldehyde in 72% yield, b.p. 78–80° at 60 mm., n_D^{25} 1.4445.

Anal. Calcd. for $C_6H_{10}O$: C, 73.42; H, 10.27. Found: C, 73.15; H, 10.33.

2-Bromo-3-hexyne. An ether solution of 3-hexyne-2-ol containing a catalytic amount of pyridine was treated with phosphorus tribromide. The bromide was obtained in 70% yield, b.p. 74–76° at 50 mm., n_D^{25} 1.4853–1.4858.

Anal. Calcd. for C_6H_9Br: C, 44.72; H, 5.63. Found: C, 44.97; H, 5.78.

Ethyl(1-methyl-2-pentynyl)cyanoacetate. An ethanol solution of the sodium derivative of ethyl cyanoacetate was treated with 2-bromo-3-hexyne. The yield was 35%, b.p. 104–107° at 5 mm., n_D^{25} 1.4483–1.4495.

Anal. Calcd. for $C_{11}H_{15}NO_2$: N, 7.25. Found: N, 7.06.

Ethyl allyl(1-methyl-2-pentynyl)cyanoacetate. An ethanol solution of the sodium derivative of ethyl(1-methyl-2-pentynyl)cyanoacetate was treated with allyl bromide. The

(5) V. K. Stoelting, *Current Researches Anesthesia & Analgesia*, **36**, 49 (1957).

(6) 3-Hexyne-2-ol is listed with the "Special Acetylenic Chemicals" in the Farchan Laboratories price list A-4, April 1952.

TABLE II

PHYSICAL PROPERTIES OF THE α-ISOMERS

Compound No.	Compound	M.P.	$[\alpha]^{t}_{D}$[a]	t	Empirical Formula	Nitrogen, % Calcd.	Nitrogen, % Found
III	α-*d*-Imino B.A.[b]-*d*-RSO_3H[c] salt	215–217	+30.0	25	$C_{24}H_{35}N_3O_6S$	8.51	8.30
VI	α-*l*-Imino B.A.-*l*-RSO_3H salt	210–213	−28.2	25	$C_{24}H_{35}N_3O_6S$	8.51	8.61
IV	α-*d*-Imino B.A.	96–100	+113.5	25	$C_{14}H_{19}N_3O_2$	16.08	16.31
IVa	α-*l*-Imino B.A.	96–99	−113.6	30	$C_{14}H_{19}N_3O_2$	16.08	15.91
I	α-*dl*-Imino B.A.	92–94			$C_{14}H_{19}N_3O_2$	16.08	15.80
VII	α-*d*-Imino B.A. HCl	214–216	+9.2	27	$C_{14}H_{20}ClN_3O_2$	14.11	13.88
VIIa	α-*l*-Imino B.A. HCl	218	−8.2	28	$C_{14}H_{20}ClN_3O_2$	14.11	13.24
	α-*dl*-Imino B.A. HCl	203			$C_{14}H_{20}ClN_3O_2$	14.11	13.84
V	α-*d*-B.A.	104–106.5	+40.6	31	$C_{14}H_{18}N_2O_3$	10.68	10.48
Va	α-*l*-B.A.	104–107	−40.0	28	$C_{14}H_{18}N_2O_3$	10.68	10.44
II	α-*dl*-B.A.	96			$C_{14}H_{18}N_2O_3$	10.68	10.83

[a] Concn. 5% in ethanol. [b] B.A. is 5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid. [c] 10-Camphorsulfonic acid.

TABLE III

PHYSICAL PROPERTIES OF THE β-ISOMERS

Compound No.	Compound	M.P.	$[\alpha]^{t}_{D}$[a]	t	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
IXa	*d*-1-CH_3-5-R[b]-B.A.-brucine salt	135–150	−50.4[c,d]	32	$C_{34}H_{40}N_4O_7$	9.08	8.86
IX	*l*-1-CH_3-5-R-B.A.-brucine salt	103–110	−60.7[c]	29	$C_{34}H_{40}N_4O_7$	9.08	9.68
Xa	*d*-1-CH_3-5-R-B.A.	112–116	+5.0	30	$C_{11}H_{14}N_2O_3$	12.61	12.90
X	*l*-1-CH_3-5-R-B.A.	114–118	−5.2	28	$C_{11}H_{14}N_2O_3$	12.61	12.36
VIII	*dl*-1-CH_3-5-R-B.A.	89–92			$C_{11}H_{14}N_2O_3$	12.61	12.88
XII	β-*dl*-imino B.A.[e]	142–143			$C_{14}H_{19}N_3O_2$	16.08	15.88
XI	β-*d*-B.A.	66–70	+55.8	31	$C_{14}H_{18}N_2O_3$	10.68	10.45
XIa	β-*l*-B.A.	68–70	−56.3	28	$C_{14}H_{18}N_2O_3$	10.68	10.72
IIa	β-*dl*-B.A.	65–66			$C_{14}H_{18}N_2O_3$	10.68	10.68
XIII	5-Allyl-4-NH=5-R-B.A.	233			$C_{13}H_{17}N_3O_2$	16.99	16.96

[a] Concn. 5% in ethanol. [b] R is $C_2H_3C{\equiv}CCH(CH_3)$—. [c] $[\alpha]_D$ concn. 5% in chloroform. [d] $[\alpha]^{32}_{D}$ −26.6° concn. 5% in ethanol. [e] B.A. is 5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid.

yield of ester was 92%, b.p. 105–115° at 1 mm., n^{25}_{D} 1.4582–1.4592.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.80; H, 8.42; N, 6.21.

Synthesis of α-isomers. α-dl-5-Allyl-6-imino-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (I). Ethyl allyl(1-methyl-2-pentynyl)cyanoacetate was condensed with methylurea by refluxing in a solution of two molecular equivalents of sodium in ethanol for 4 hr. Most of the ethanol was distilled under vacuum, and the residue was dissolved in water. The aqueous solution was extracted with ether and acidified with acetic acid. The oil which separated crystallized on standing and was filtered. The α-*dl*-iminobarbituric acid (I) was recrystallized three times from dilute ethanol.

The hydrochloride of I was prepared in ether and recrystallized from acetone.

α-dl-5-Allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (II). A mixture of 38 g. (0.15 mole) of the α-*dl*-imino base (I), 20 ml. of concd. hydrochloric acid, and 380 ml. of water was refluxed with stirring for 1 hr. The α-*dl*-barbituric acid (II) separated as an oil that crystallized on cooling. It was filtered and recrystallized twice from dilute ethanol.

Reaction of α-dl-5-allyl-6-imino-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid with d-10-camphorsulfonic acid. A solution of 50 g. (0.19 mole) of I in 100 ml. of acetone was added to a solution of 45 g. (0.19 mole) of *d*-10-camphorsulfonic acid in 300 ml. of acetone. The less soluble α-*d*-imino base-*d*-10-camphorsulfonic acid salt (III) was filtered and recrystallized twice from ethanol.

α-d-5-Allyl-6-imino-5-(1-methyl-2-pentynyl)barbituric acid (IV). A suspension of 21 g. of III in water was neutralized with a solution of sodium bicarbonate and the oil which formed crystallized. The solid was recrystallized twice from ethanol.

The hydrochloride (VII) of IV was prepared in ether and recrystallized from isopropanol.

α-d-5-Allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (V). The α-*d*-imino base (IV) was hydrolyzed in the same manner as the α-*dl*-imino base (I). Recrystallization from dilute ethanol gave pure V.

α-l-5-Allyl-6-imino-5-(1-methyl-2-pentynyl)barbituric acid (IVa). *Method 1.* An acetone solution of the α-*dl*-imino base (I) was treated with half a molecular equivalent of *d*-10-camphorsulfonic acid. The less soluble salt III which formed was filtered. The filtrate containing the impure α-*l*-imino base (IVa) was concentrated under vacuum to an oily residue. The hydrochloride (VIIa) of IVa was prepared and recrystallized twice from isopropanol.

Method 2. The impure α-*l*-imino base (IVa), as obtained above from the filtrate of the salt III, was purified by treating it with half a molecular equivalent of *dl*-10-camphorsulfonic acid in acetone solution. The α-*l*-imino base-*l*-10-camphorsulfonic acid salt (VI) precipitated and was filtered and recrystallized three times from ethanol.

The α-*l*-imino salt obtained by either method 1 or 2 was neutralized with sodium bicarbonate solution and the base IVa recrystallized twice from dilute ethanol.

α-l-5-Allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (Va). *Method 1.* Evaporation to dryness on the steam bath of the acetone filtrate containing the more soluble α-*l*-imino base-*d*-10-camphorsulfonic acid (IIIa) resulted in hydrolysis of the imino group giving the α-*l*-barbituric acid

(Va). The latter was recrystallized once from petroleum ether (b.p. 35–60°), once from methanol, and once from ethanol.

Method 2. The *α-l*-imino base (IVa), obtained by method 1 or 2 above, was hydrolyzed to Va as described for the *α-dl*-barbituric acid (II).

Synthesis of β-isomers. Diethyl(1-methyl-2-pentynyl)malonate. The sodium derivative of diethyl malonate was alkylated with 2-bromo-3-hexyne in alcohol solution. The ester was obtained in 77% yield, b.p. 123° at 7 mm., n_D^{25} 1.4418–1.4423.

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.79; H, 8.47.

dl-1-Methyl-5-(1-methyl-2-pentynyl)barbituric acid (VIII). Diethyl(1-methyl-2-pentynyl)malonate was condensed with methylurea by refluxing in ethanol solution containing 2 equivalents of sodium ethylate for 0.5 hr. The alcohol was distilled under vacuum, and the residue was dissolved in water and acidified with hydrochloric acid. The oil which separated crystallized on standing, and was filtered and the solid recrystallized twice from dilute ethanol.

Reaction of dl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (VIII) *with brucine.* A solution of VIII in absolute ethanol was added to a hot solution of an equimolecular amount of brucine in ethanol. After standing overnight, the less soluble *l*-barbituric acid-brucine salt (IX) was filtered and recrystallized twice from absolute ethanol.

The filtrates from the less soluble salt (IX) were combined and concentrated, and the precipitate that formed was filtered and recrystallized once from methanol and once from ethanol giving the more soluble *d*-barbituric acid-brucine salt (IXa).

l-1-Methyl-5-(1-methyl-2-pentynyl)barbituric acid (X). A suspension of IX in water was acidified with hydrochloric acid. The precipitate which formed was filtered and recrystallized twice from dilute ethanol.

β-d-5-Allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (XI). A mixture of an aqueous solution of the sodium salt of X and an equimolecular amount of allyl bromide was stirred for 17 hr. at 40–50°. The oily product was separated from the mixture by ether extraction. The ether solution was extracted once with sodium bicarbonate solution and then with dilute sodium hydroxide solution. The solution of the sodium salt was acidified with acetic acid, and the oil which separated crystallized on standing. The *β-d*-barbituric acid (XI) was filtered and recrystallized three times from dilute ethanol.

Filtrates from the recrystallization of XI were allowed to evaporate and the precipitate that was obtained was recrystallized twice from dilute ethanol, m.p. 104–105°. It was shown to be *α-d*-acid (V) when a sample mixed with authentic *α-d*-stereoisomer (V) showed no depression, m.p. 104–106°; a sample mixed with the *α-l*-stereoisomer (Va) showed a depression, m.p. 88–90°.

d-1-Methyl-5-(1-methyl-2-pentynyl)barbituric acid (Xa). The *d*-acid was obtained from the more soluble brucine salt and was purified in a manner similar to that used for the *l*-acid (X).

β-l-5-Allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (XIa). The *d*-acid (Xa) was allylated in the same manner as the *l*-acid (X). The product was recrystallized twice from dilute ethanol.

Filtrates from the recrystallization of XIa gave some of the *α-l*-acid (Va), which was identified by mixed melting point with authentic Va.

Alternate synthesis of β-dl-5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (IIa). *5-Allyl-4-imino-5-(1-methyl-2-pentynyl)barbituric acid* (XIII). To a solution of 23 g. (1 mole) of sodium in 460 ml. of isopropyl alcohol was added 45 g. (0.75 mole) of urea. The solution was cooled to 50° and 117 g. (0.5 mole) of ethyl allyl(1-methyl-2-pentynyl)-cyanoacetate was added. The solution was warmed at 60° for 4 hr. and then allowed to stand 92 hr. at room temperature. The isopropyl alcohol was distilled under vacuum, the residue was dissolved in water and the solution made neutral (*p*H 7.0–7.5) with dilute hydrochloric acid. The precipitate which formed was filtered and recrystallized twice from dilute ethanol.

β-dl-5-Allyl-4-imino-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (XII). To a solution of 0.56 g. (0.024 mole) of sodium in 20 ml. of ethanol were added 6 g. (0.024 mole) of XIII and 3.8 g. (0.024 mole) of methyl iodide. The solution was allowed to reflux for 3 hr. The ethanol was distilled under vacuum and the residue was treated with water, giving an oily mixture. The mixture was neutralized with acetic acid and ether extracted three times. The ether solution of Ia was dried with anhydrous sodium sulfate and treated with hydrogen chloride in ether. The hydrochloride oiled out, but soon crystallized. It was filtered, dissolved in water, and neutralized with sodium bicarbonate solution. The *β-dl*-iminobarbituric acid (XII) was recrystallized twice from dilute ethanol.

β-dl-5-Allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (IIa). The hydrolysis of XII was carried out in a manner similar to that used for the *α-dl*-imino base (I). The *β-dl*-barbituric acid (IIa) was recrystallized twice from dilute methanol and once from dilute ethanol, m.p. 47–48°. The acid IIa was polymorphous for, on recrystallization from petroleum ether (b.p. 35–60°), it melted at 65–66°.

Acknowledgment. We are indebted to Dr. N. R. Easton for suggesting the *d*-10-camphorsulfonic acid resolution of the imino derivative, and for many other valuable suggestions in this work. The pharmacological results were kindly furnished by Messrs. W. R. Gibson and W. C. Woods of the Lilly Pharmacological Division. Several of the intermediates used in the resolutions were supplied by C. F. Christie of the Lilly Organic Development Department. We wish to thank Miss Gloria Beckmann, Messrs. H. L. Hunter, G. M. Maciak, and R. M. Hughes for the microchemical analyses.

INDIANAPOLIS, IND.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF SOCONY MOBIL OIL CO.]

Synthesis and Reactions of 4-Neopentyl-5-*t*-butyl-1,2-dithiole-3-thione

PHILLIP S. LANDIS AND LYLE A. HAMILTON

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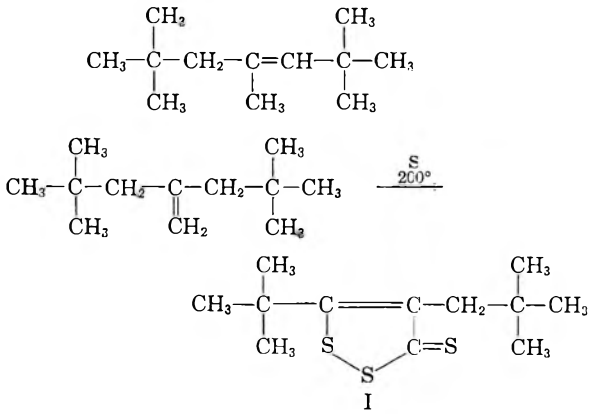
The reaction of sulfur with triisobutylene at 200° yields exclusively 4-neopentyl-5-*t*-butyl-1,2-dithiole-3-thione. This compound has been characterized by physical and chemical analysis, including basic hydrolysis to 2,2-dimethylpropionic and 2,2-dimethylvaleric acids. Chlorination of the thione followed by hydrolysis gives the ketone analog.

Olefins having methyl substituents or olefins which are easily converted to the methyl substituted compound are known to react with sulfur and/or phosphorus pentasulfide at elevated temperatures forming the pseudoaromatic 1,2-dithiole-3-thiones.[1] An interesting example of this reaction is the formation of a mixture of 4-methyl-5-*t*-butyl-1,2-dithiole-3-thione and 4-neopentyl-1,2-dithiole-3-thione by reaction of sulfur with diisobutylene (a mixture of 2,4,4-trimethylpentene-1 and 2,4,4-trimethylpentene-2) at 200°.[2]

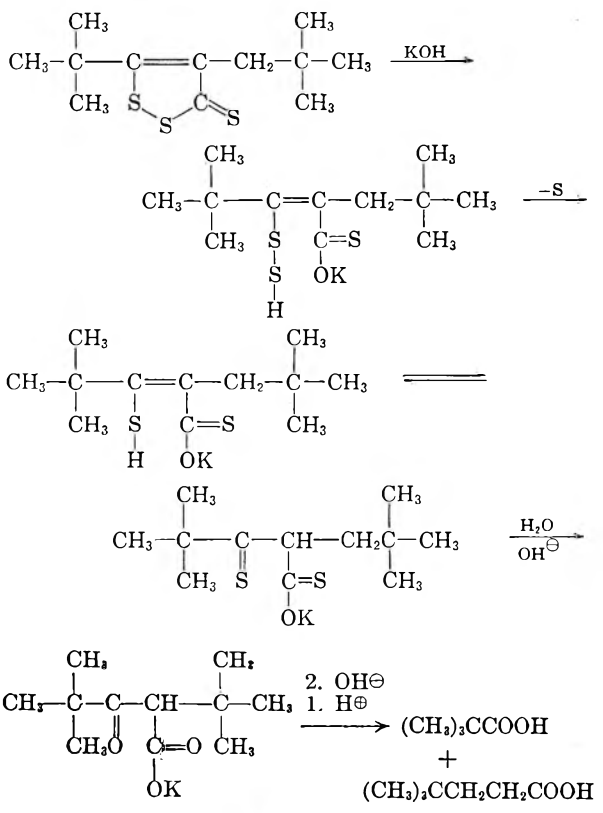
Triisobutylene is a readily obtainable olefin consisting primarily of 2,2,4,6,6-pentamethylheptene-3 and 1,1-dineopentylethylene.[3] Since terminal olefins are isomerized to the methyl compound before reaction with sulfur in the formation of 1,2-dithiole-3-thiones,[1] reaction of triisobutylene with sulfur should give only 4-neopentyl-5-*t*-butyl-1,2-dithiole-3-thione, I.



I

Reaction of triisobutylene with sulfur at 200° was carried out by dropping the olefin onto heated sulfur at atmospheric pressure. By-product hydrogen sulfide was passed out of the condensing system and measured with a Wet Test Meter in which the water had previously been saturated with hydrogen sulfide. Unchanged triisobutylene was returned to the reaction flask by means of an efficient condenser. The reaction can be facilitated by the addition of preformed sulfurized triisobutylene to the sulfur charge. This serves to reduce the viscosity of the sulfur and provides better olefin-sulfur contact, measurably increasing the rate of reaction.

Vacuum distillation of the product from this reaction gave a red oil distilling at 150–160° at 1 mm. The distilled product had a refractive index (using the hydrogen red line) of 1.6475 and its empirical formula was $C_{12}H_{20}S_3$. A 100-gram sample was fractionated under vacuum using a Piros-Glover spinning band column. Eighteen approximately equal fractions were taken. Fractions 4–15 (72% of the total distillate) had identical infrared spectra. Fractions 16–18 (10% of the total distillate) showed a small band developing at 9.92 μ. If this contaminant is an isomer of the parent sulfur compound it must be present in less than



(1) B. Böttcher and A. Lüttringhaus, *Ann.*, **557**, 89 (1945); A. Lüttringhaus, H. Koenig, and B. Böttcher, *Ann.*, **560**, 201 (1947); N. Lozac'h, *Bull. soc. chim. France*, 840 (1949); B. Böttcher, *Ber.*, **81**, 376 (1948); M. Voronkov, A. Broun, and G. Karpenko, *J. Gen. Chem. (U.S.S.R.)*, **19**, 1927 (1949).

(2) R. S. Spindt, D. R. Stevens, and W. E. Baldwin, *J. Am. Chem. Soc.*, **73**, 3693 (1951).

(3) F. Whitmore, *Organic Chemistry*, D. Van Nostrand Co., New York (1951), p. 49.

5% of these fractions or less than 0.5% of the total distillate.

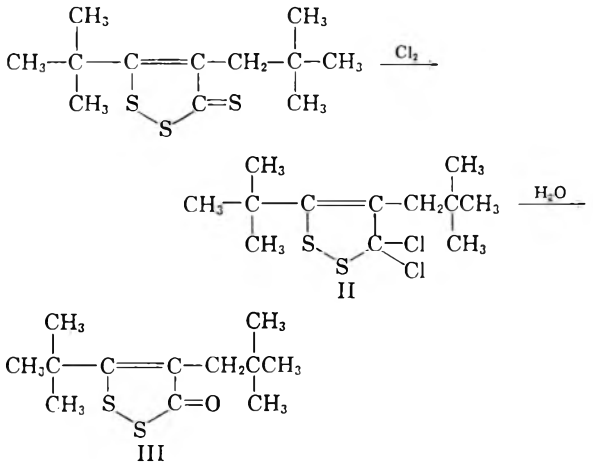
The structure of I is strongly supported by hydrolysis with alcoholic potassium hydroxide, whereby two organic acids were obtained, 2,2-dimethylpropionic and 4,4-dimethylvaleric acids.

Further support of the structure is obtained from spectra. Only two types of protons are observed in the NMR spectra of I. The methyl peak occurs as a doublet with a chemical shift (with reference to water as an external standard) of 129 and 148 cps. The doublet results from two *t*-butyl groups with different environments. The methylene peak has a chemical shift of 66 cps. The CH_3 to CH_2 proton ratio is 8.4 to one.

Ultraviolet and infrared spectra of I were obtained and compared with the ultraviolet spectra of the analogs from diisobutylene. Strong absorption maxima at 230, 248, 275, 321 and 414 mμ are characteristic of the dithiole-3-thiones and attest to the aromaticity of this structure.

A comparison of the infrared spectra of I with 4-neopentyl-1,2-dithiole-3-thione and 4-methyl-5-*t*-butyl-1,2-dithiole-3-thione was made. In all cases there is evidence for a carbon-carbon double bond, a thione group, and a carbon-sulfur bond.

Chlorination of I produced the dichloro-desthio derivative II which was readily hydrolyzed to the carbonyl compound III.



I also undergoes reactions typical of 1,2-dithiole-3-thiones. It forms oximes and hydrazones with hydroxylamine and hydrazine reagents, quaternary salts with alkyl halides, and well defined complexes with metal salts such as mercuric chloride, silver nitrate, bismuth trichloride, antimony trichloride, stannic chloride, cadmuim chloride, and lead diacetates. Nitric acid cleaves the dithiole ring yielding white solids which have not been characterized.

EXPERIMENTAL

The stoichiometric equation for the preparation of 4-neopentyl-5-*t*-butyl-1,2-dithiole-3-thione is

$$C_{12}H_{24} + 5\,S \longrightarrow C_{12}H_{20}S_3 + 2H_2S$$

It was found expedient to catalyze the reaction with added sulfurized triisobutylene. This served to decrease the viscosity of the sulfur, provide better surface contact between olefin and sulfur, and measurably increased the rate of reaction. In addition, the catalyzed reaction gave little or no tarry residue.

Preparation of 4-neopentyl-5-t-butyl-1,2-dithiole-3-thione. Catalyzed reaction. In a typical experiment 1280 g. of sulfur (40 moles) and 600 g. of sulfurized triisobutylene (from a previous run) were placed in a four-necked 5-l. flask fitted with an efficient condenser, a water-cooled stirrer, a thermometer, and a dropping funnel. A Wet Test Meter containing water saturated with hydrogen sulfide was connected to the condenser. With the flask contents heated at 200–215°, 1344 g. (8 moles) of triisobutylene was added dropwise in 7.5 hr. Reaction was continued at 200° for 9 hr. and a total of 16.4 moles of hydrogen sulfide was evolved. The crude product was then vacuum distilled and the fraction (2476 g., 93% based on sulfur) boiling in the range 140–165° at 1–3 mm. was collected. The product contained 36.5% S and had a molecular weight of 255. Fractionation of 100 g. through a Piros-Glover spinning band column gave 75 g. of oil, b.p. 152° at 1 mm. An additional 10 g., b.p. 157–159° at 1.3 mm., was obtained and was identical with the main fraction except for a small shoulder at 9.92 μ in the infrared. Physical properties measured include $d_4^{20°}$ 1.18 and $n_D^{20°}$ 1.6478.

Anal. Calcd. for $C_{12}H_{20}S_3$: C, 55.33; H, 7.74; S, 36.93; mol. wt., 260. Found: C, 55.14; H, 7.79; S, 36.74; mol. wt., 265.

Uncatalyzed reaction. From 160 g. of sulfur and 168 g. of triisobutylene, treated as in the preceeding example except that 8.5 hr. reaction time was used after addition of the triisobutylene, there was obtained 147 g. (55%) of red oil, b.p. 155–185° at 1–3 mm.

Anal. Calcd. for $C_{12}H_{20}S_3$: S, 36.93; mol. wt., 260. Found: S, 36.50; mol. wt., 255.

Methyl iodide adduct of I. A solution of 3.0 g. of I in 20 g. of methanol mixed with 3.0 g. of methyl iodide gave yellow crystals on standing. Recrystallization from methanol gave pale yellow crystals, m.p. 159–161°.

Anal. Calcd. for $C_{13}H_{23}S_3I$: S, 23.90; I, 31.54. Found: S, 22.59; I, 31.50.

Metal complexes. Mercuric chloride complex. To a solution of 12 g. of I in 30 ml. of acetone there was added 14 g. of mercuric chloride in 200 ml. of acetone. After stirring 5 min. a heavy yellow precipitate formed. The precipitate was filtered, washed with hot acetone, and dried in a desiccator; yield, 20.5 g., m.p. 218–221 dec.

Anal. Calcd. for $C_{12}H_{20}S_3HgCl_2$: S, 18.08; Hg, 37.71. Found: S, 17.89; Hg, 39.00.

Cadmium iodide complex. The addition of 3.3 g. of cadmium iodide in 100 ml. of isopropyl alcohol to a solution of 5.2 g. of I in 100 ml. of isopropyl alcohol gave 6.7 g. of a yellow precipitate. The precipitate was filtered, washed with solvent and dried, m.p. 145–148°.

Anal. Calcd. for $(C_{12}H_{20}S_3)_2CdI_2$: S, 21.68; Cd, 12.68. Found: S, 21.10; Cd, 12.2.

A number of other complexes have been prepared including $ZnCl_2 \cdot C_{12}H_{20}S_3$, m.p. 189–194°; $PtCl_4 \cdot 2C_{12}H_{20}S_3$, m.p. 168–171°; and $AgNO_3 \cdot 2C_{12}H_{20}S_3$, m.p. 145–149°.

Preparation of II. Chlorination of 25 g. of I in 100 ml. of carbon tetrachloride maintaining the temperature at 30° by external cooling gave 25.5 g. of a light yellow solid, m.p. 149–151°. Recrystallization from absolute alcohol raised the m.p. to 151–152°.

Anal. Calcd. for $C_{12}H_{20}S_2Cl_2$: S, 21.42; Cl, 23.70. Found: S, 22.1; Cl, 24.7.

Preparation of 4-neopentyl-5-t-butyl-1,2-dithiole-3-one, III. The hydrolysis of the dichloro compound II was accomplished by merely refluxing 200 g. of II with 2000 ml. of water for 32 hr. After discarding the acidic water layer the red residual

oil was vacuum distilled collecting 92.5 g. of III, b.p. 132–135° at 0.6–0.8 mm.

Anal. Calcd. for $C_{12}H_{20}S_2O$: C, 58.98; H, 8.24; S, 26.23. Found: C, 59.13; H, 8.03; S, 26.06.

Alcoholic hydrolysis of I. In a 4-l. flask there was placed 260 g. of I, 1200 ml. of 20% potassium hydroxide and 1200 ml. of 95% ethanol. This mixture was refluxed for 40 hr. and then carefully acidified with concd. sulfuric acid keeping the temperature below 50°. Copious amounts of hydrogen sulfide were liberated on acidification and a small amount of sulfur was isolated by filtration. The acidified solution was separated and extracted with 1 l. of ether and the ether solution evaporated on a water bath at 60°. The residue, 140 g., was fractionated and gave two major acidic fractions: A, b.p. 149–152°, 36.2 g.; B, b.p. 179–185°, 30.5 g.

A was identified as trimethyl acetic acid by conversion first to the acid chloride, b.p. 135–140°, using thionyl chloride, and then to the anilide by refluxing with aniline, m.p. 131°, reported m.p. 129° for trimethylacetanilide.

Anal. Calcd. for $C_{11}H_{15}ON$: N, 7.91. Found: N, 7.86.

The *p*-bromophenacyl ester of A (from 95% ethanol) melted at 75–76°, reported m.p. 76°.

Anal. Calcd. for $C_{12}H_{15}O_3Br$: Br, 27.83. Found: Br, 27.78.

B was identified as 4,4-dimethylvaleric acid by conversion to the amide and the anilide. B was refluxed with thionyl chloride and the acid chloride distilled. A solution of 5 g. of aniline in 50 ml. of benzene was added to 5 g. of the acid chloride, the solution refluxed 30 min., washed with water, 10% hydrochloric acid and 10% sodium hydroxide, and finally concentrated to 20 ml. total volume. White crystals separated from solution and were recrystallized from ethanol, m.p. 141–142°. The reported melting point for 4,4-dimethylvaleranilide is 141°.

Anal. Calcd. for $C_{13}H_{19}ON$: N, 6.82. Found: N, 6.83.

Conversion of the acid chloride of B to the amide with cold concd. ammonia gave white platelets, recrystallized from water, m.p. 139–141°; reported m.p. 140–141° for 4,4-dimethylvaleramide.

Anal. Calcd. for $C_7H_{15}ON$: N, 10.85. Found: N, 10.30.

PAULSBORO, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF APPLIED CHEMISTRY, COLLEGE OF ENGINEERING, UNIVERSITY OF OSAKA PREFECTURE]

Organic Polysulfides. II.[1] Polymorphism in Dibenzhydryl Tetrasulfide

JITSUO TSURUGI AND TAKESHIGE NAKABAYASHI

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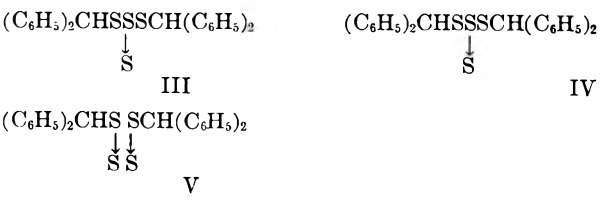
Two polymorphs of dibenzhydryl tetrasulfide were found. Observations of mutual convertibility and of their melting behaviors and determinations of ultraviolet and infrared absorption spectra support the conclusion that the two forms are rotational isomers in the solid state.

Synthesis of a series of dibenzhydryl polysulfides from mono- to hexasulfide was reported in the previous paper,[1] in which the sulfur-sulfur linkages in these polysulfides were linear. Dibenzhydryl tetrasulfide had been prepared[2] by condensation of two moles of the thiol with sulfur monochloride in carbon disulfide solution. The condensation reaction was exothermic. When all the procedures were carried out at temperatures below 30° by cooling, white pillars (I) were obtained. On the other hand, when the reaction temperature exceeded 30°, a mixture of white pillars and pale yellow needles (II) was obtained. The higher the temperatures, the greater was the proportion of yellow needles. Recrystallization of a mixture of pillars and needles from a solvent mixture of ether-petroleum ether led to an increase in the proportion of II. After two recrystallizations the white pillars disappeared completely and all the crystals were composed of the yellow needles (II). Such polymorphism was not found in other polysulfides previously reported,[1] *e.g.*, dibenzhydryl tri- and tetrasulfides and dibenzyl tri-, tetra-, and pentasulfides.

The ultraviolet absorption spectrum and molar refraction of benzhydryl tetrasulfide II were reported in the previous paper.[1] The spectrum of I overlapped with that of II within the experimental error. As II had[1] linear sulfur-sulfur linkages, by analogy, I would be expected to have the same sulfur linkages as II. Isomers such as III, IV and V are unlikely for the structure of I, as such a structure should have a different ultraviolet absorption spectrum from that of the linear one. Moreover, if the polymorphism resulted from such branched type isomers, the other polysulfides should have similar polymorphs. As stated above, such polymorphism could not be found in the other polysulfides.



The remaining possibilities are either that these polymorphs are rotational isomers of each other (possibility A) or that molecules having the same configuration aggregate to different crystal structures I and II (possibility B). In order to decide whether the polymorphism of dibenzhydryl tetrasulfide can be ascribed to possibility A or B, mutual

(1) Part I. J. Tsurugi and T. Nakabayashi, *J. Org. Chem.*, **24**, 807 (1959).

(2) J. Tsurugi and T. Nakabayashi, *Nippon Kagaku Zasshi*, **77**, 583 (1956).

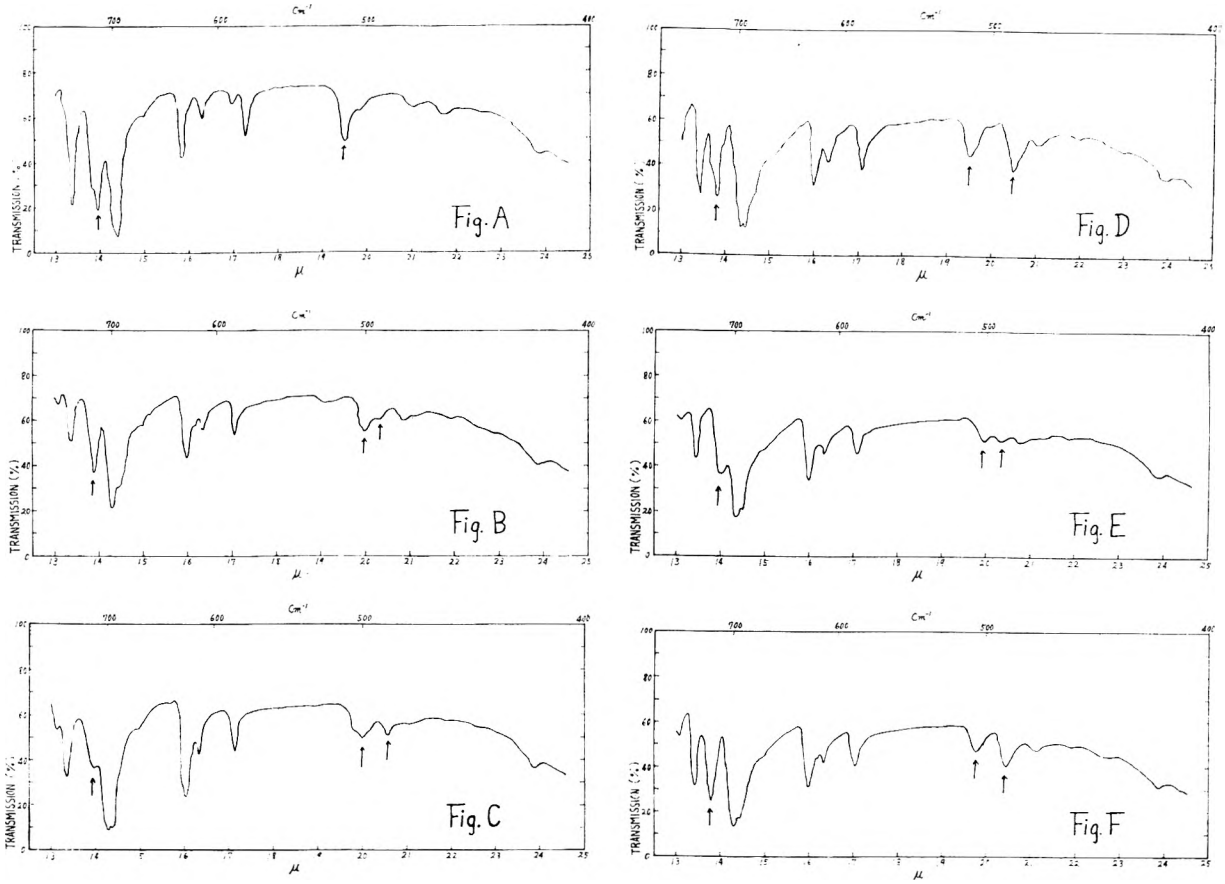


Fig. 1. A. Dibenzhydryl monosulfide. B. Dibenzhydryl disulfide. C. Dibenzhydryl trisulfide D. Dibenzhydryl tetrasulfide (I). E. Dibenzhydryl tetrasulfide (II). F. Dibenzhydryl pentasulfide

convertibility was attempted, and infrared absorption spectra of I and II and of the related compounds were determined. X-ray diffraction patterns of I and II were also determined.

The melting point of II was in the range of 82–83°,[1] while I began to melt at 73°, and in the range of 73–83°, solid remained mixed with melted substance. It melted completely at the same temperature as the melting point of II, *i.e.*, at 83°. However, when I was heated extremely slowly on the microscope hot stage, white pillars changed to pale yellow needles as soon as the former melted at 73°. The latter melted at 83°. This indicates that I was converted to II at 73°. Transformation of I to II was observed on recrystallization as stated above. The melt formed by heating I or II over 83° did not crystallize and remained as yellow viscous oil even after being kept at room temperatures. However, when one pillar of I or one needle of II was added to the oil at the temperatures near 70°, the oil crystallized to yellow needles (II). Transformation from II to I was also successful by adding one pillar of I to a saturated solution of the melted compound in petroleum ether below 30°. Observations mentioned above indicate that two polymorphs are easily interconvertible, and II is more stable than I. Easy convertibility with each other again precludes the possibility of isomers having branched sulfur chains. However, these observations do not decide whether possibility A or B is applicable.

Infrared absorption spectra of dibenzhydryl polysulfides, including I and II, were determined with a potassium bromide prism (12–25 μ) and indicated in Fig. 1a-f. In general, assignment of C—S and S—S vibrations are considered to be difficult because of their very weak intensities and wide range of the absorptions and because of the tendency to be shifted easily by neighboring groups. Moreover, only a few examples in this range can be found in the literature. Therefore, it is necessary here to determine the spectra of the homologous compounds and to compare them with each other, in order to correlate an absorption band to a given structural bond. Of the three spectral bands which appeared in the range of 700–770 cm.$^{-1}$ in Fig. 1, the central band near 716–727 cm.$^{-1}$ can be correlated with C—S vibration, and the other two to C—H out-of-plane deformations of monosubstituted aromatic ring in benzhydryl group. The latter two are well defined as such[3] and the former is observed in each spectrum of the polysulfides including the monosulfide. Moreover, no vibration

(3) J. L. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd Ed., London, 1958, p. 350.

except those of C—H out-of-plane deformations of phenyl groups can be expected with respect to dibenzhydryl polysulfides. Absorption bands in the region of 590–625 cm.$^{-1}$ can be correlated with the dibenzhydryl group, because all these bands for each compound are observed in the same frequency except for those of the monosulfide. Moreover, infrared spectrum of dibenzhydryl ether was determined in potassium bromide region, and three bands (578, 601, and 617 cm.$^{-1}$) were observed. Absorption bands near 500 cm.$^{-1}$, which do not appear in the spectrum of dibenzhydryl ether, are correlated with C—S and S—S vibrations respectively, and that which does not appear in the spectrum for the monosulfide must be correlated to S—S vibration. The above considerations are summarized in Table I, in which some absorption bands are correlated to C—S and S—S bonds.

The identity period along the *c* axis of I and II were also determined by the x-ray rotating crystal method; these were 8.0 and 5.7 A for I and II respectively.

Whether possibility A or B is applicable to explain the polymorphism may be decided by considering the results obtained above and by referring to some literature references on sulfur chemistry. Table I indicates that I and II have C—S and S—S vibrations different from each other, and Fig. 1 indicates that absorption bands of I have stronger intensities than those of II, in general. This difference may be explained by an assumption that two polymorphs are rotational isomers of each other, and that II has better symmetry than I. Cymerman and Willis[4] reported that weak S—S vibration was found in a spectrum of diphenyl disulfide, while the corresponding vibration could not be found in that of diphenyl disulphone because of its symmetrical center. Woodrow, Carmack, and Miller[5] concluded from determination of dipole moments that *n*-hexadecyl tetrasulfide in benzene has three pairs of conformers, which result from rotation of S—S bonds. Thus, if one assumes that I is composed of one specific configuration among these conformers and II another, the slight shift of the infrared absorption bands from I to II could be explained. The weaker intensities of bands of II than those of I could be attributed to a better symmetry of the former, while possibility B predicts nothing about the infrared spectra. The observations that the melted tetrasulfide does not crystallize even after long standing at room temperatures and that I, II, or their mixture is obtained depending on the temperatures during preparation are explained by assuming that polysulfides in liquid state or solution are in equilibrium of several configurations, and that the tetrasulfide can take two specific configurations depending on conditions under which it solidifies or crystallizes. The reason why benzhydryl tetrasulfide has such rotational isomers in the solid state may be found in a similar example in the study of a series of polymethylene dihalides [X-$(CH_2)_n$X]. Brown and Sheppard[6] found that trimethylene diiodide alone has two solid rotational isomers, one stable (TT) and one metastable (TG) isomer, while no other polymethylene dihalides have such metastable solid isomers. In this case, the bulky iodine atoms located at both ends of the molecule and the specific chain length of methylenes may lead to a metastable solid rotational isomer. The same situation may hold for the series of benzhydryl polysulfides. The bulky benzhydryl end groups and specific sulfur chain length of the tetrasulfide may lead to such a metastable rotational isomer as well.

TABLE I

ASSIGNMENT OF C—S AND S—S VIBRATIONS IN DIBENZHYDRYL POLYSULFIDES

	C—S, Cm.$^{-1}$		S—S, Cm.$^{-1}$
$[(C_6H_5)_2CH]_2S$	716.8	512.3	—
$[(C_6H_5)_2CH]_2S$	719.4	501.3	492.6
$[(C_6H_5)_2CH]_2S$	716.3	500.5	486.1
$[(C_6H_5)_2CH]_2S$, I	726.2	511.8	487.8
$[(C_6H_5)_2CH]_2S$, II	714.3	501.3	491.4
$[(C_6H_5)_2CH]_2S$	725.7	506.3	489.5

Palmer[7] reported the configuration of sulfur monochloride, in which the dihedral angle between Cl—SS—Cl is near 100°. When the synthesis of benzhydryl tetrasulfide is carried out at lower temperatures, the product may be assumed to maintain the same or similar dihedral angles between $<S_1S_2S_3$ and $<S_2S_3S_4$ as that of sulfur monochloride. This configuration corresponds to I. On the other hand, at higher temperatures S—S bond rotation may occur owing to steric repulsion of each bulky dibenzhydryl group. This leads to a more coiled and more stable configuration, which corresponds to II. The x-ray diffraction pattern and infrared spectra which indicate better symmetry of II are in accord with the above assumption.

In summary, polymorphism of dibenzhydryl tetrasulfide may be interpreted as due to rotational isomerism, and all the experimental results and literature references cited support this assumption.

EXPERIMENTAL

Preparation of I. White pillars of I were prepared by condensation of a slight excess of benzhydryl mercaptan (b.p. 98–99°/0.03 mm.) and freshly distilled sulfur monochloride.[2] In a stream of nitrogen gas and protected against moisture, sulfur monochloride in carbon disulfide was

(4) J. Cymerman and J. B. Willis, *J. Chem. Soc.*, 1332 (1951).

(5) C. C. Woodrow, M. Carmack, and J. G. Miller, *J. Chem. Phys.*, 19, 951 (1951).

(6) J. K. Brown and N. Sheppard, *Proc. Roy. Soc.*, 231, 555 (1951).

(7) K. J. Palmer, *J. Am. Chem. Soc.*, 60, 2360 (1938).

stirred into the mercaptan in carbon disulfide maintained in a cooling bath below 30°. After standing for 4 hr., the solvent was evaporated under vacuum and the remaining oil was taken up in ether. The ether solution was stored in a refrigerator and white pillars were obtained from the yellow solution a few days later.

Anal. Calcd. for $C_{26}H_{22}S_4$: C, 67.49; H, 4.79; S, 27.72. Found: C, 68.00; H, 4.86; S, 27.30.

Preparation of II. Yellow needles of II were obtained by recrystallization of the white pillars from ether-petroleum ether (b.p. 33–46°). The analysis and physical properties of II, including ultraviolet spectrum, have been reported.[1,2] The ultraviolet spectrum of I was identical with that of II within experimental error.

Infrared spectra of a series of dibenzhydryl polysulfides and dibenzhydryl ether in the range of potassium bromide were determined by using a Perkin-Elmer 21. Specimens were measured in a potassium bromide disk.

X-ray diffraction patterns of single crystals of I and II were determined by the rotating crystal method. An iron target was used (λ = 1.93728 A), and the radius of the casset was 50 cm. Distances between equatorial line and first layer line and between the former and second layer line were 12 and 27.5 mm. respectively in the case of I, and those of II 18 and 46 mm. respectively.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

S-Alkylmercaptosuccinic Acids as Solid Derivatives of Olefins, Alkyl Bromides, and Mereaptans

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Solid *S*-alkylmercaptosuccinic acids have been prepared from olefins, mercaptans, and alkyl bromides and their melting points and solubilities have been studied as a function of the structure of the alkyl group. These properties vary with structure in a predictable manner. The acids are satisfactory solid derivatives for primary olefins and mercaptans and both primary and secondary alkyl bromides because of the ease with which the reaction can be effected, the good yields obtained, and the ease of purification. They have the added advantage of being acids; thus their neutralization equivalents may be obtained for confirmatory characterization.

In the present era of instrumental analyses by which compounds are characterized with scarcely a trace of chemistry, it may seem archaic to propose a new reagent for the preparation of a solid derivative to be used as an aid in compound characterization. There are times, however, when a good crystalline derivative is highly desirable, but hard to find. This is especially true with the olefins, mercaptans, and alkyl bromides.

2,4-Dinitrobenzenesulfenyl chloride[2,3] is the most generally useful reagent for olefins[4] and mercaptans.[5] Other reagents which have been proposed include nitrosyl chloride, 4-mercaptobiphenyl,[6] other sulfhydral compounds,[7] and silver 3,5-dinitrobenzoate plus iodine.[8]

The initial purpose of this investigation was to develop a satisfactory solid derivative for liquid olefins. The free radical addition of mercaptosuccinic acid to an olefin appeared to offer several desirable features. The reaction goes readily to give solid derivatives which are acids and can be titrated to confirm their identity. These derivatives also have the added advantage of ready synthesis by two independent methods. They can be formed by the free radical addition of the ap-

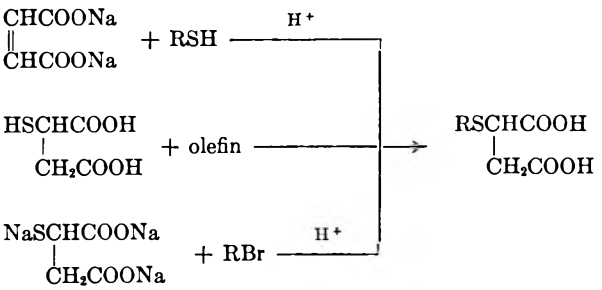

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TABLE I

S-Alkylmercaptosuccinic Acids

$$\begin{array}{l} R{-}SCHCOOH \\ \quad\;\; | \\ \quad\;\; CH_2COOH \end{array}$$

			Source							Neut. Equiv.		Analyses			
			Olefin		Mercaptan		Bromide					Found		Calcd.	
	R	Olefin	Yield, %	M.P.	Yield, %	M.P.	Yield, %	M.P.	Lit., M.P.	Found	Calcd.	C	H	C	H
C_1	Methyl								133[a]						
C_2	Ethyl								119.5[a]						
									126–128[b]						
C_3	1-Propyl						78	118.4–118.8	118–119[c]						
									112[a]						
C_4	1-Butyl				43	103.7–104.0			144.5[a]			46.45	6.83	46.58	6.84
	2-Butyl						60	134.9–135.1				46.59	6.86		
	Isobutyl						41	120.9–121.4		102.8	103.1	46.76	6.79		
	tert-Butyl								164[a]						
C_5	1-Pentyl	1-Pentene	85	107.3–107.6	100	107.7–108.0	60	107.0–107.6	99.5[a]			48.86	7.26	49.06	7.32
	2-Pentyl						50	134.8–135.4		110.0	110.1	49.09	7.09		
	3-Pentyl						39	153.8–154.1				48.84	7.22		
	2-Methylbutyl	2-Methyl-1-butene	85	122.3–122.6								49.18	7.20		
	Isopentyl						65	115.6–116.0	215[a]			48.89	7.13		
	1,2-Dimethylpropyl	2-Methyl-2-butene	75	153.7–154.0								48.87	7.11		
C_6	1-Hexyl	1-Hexene	100	95.4–95.7	79	96.0–96.2	91	96.3–96.5		117.8	117.1	51.41	7.62	51.25	7.74
	2-Hexyl						31	123.9–125.0				51.53	7.65		
	3-Hexyl						24	143.4–143.5		118.0		51.01	7.78		
	3-Methylpentyl						84	111.9–112.3		117.0		51.01	7.52		
	4-Methylpentyl	4-Methyl-1-pentene	92	102.6–102.9								51.08	7.43		
	1-Isopropylpropyl	2-Methyl-2-pentene	60	152.1–152.6								51.36	7.58		
	2-Ethylbutyl						75	132.4–132.8		117.9		50.15	7.74		
C_7	1-Heptyl	1-Heptene	88	103.4–103.9	82	105.8–106.2				124.2	124.1	52.89	7.99	53.20	8.12
	2-Heptyl						31	128.0–129.1				52.93	8.11		
	3-Heptyl						21	144.9–145.4				52.37	8.05		
	4,4-Dimethylpentyl	4,4-Dimethyl-1-pentene	90	119.0–119.5								53.22	8.13		
	1-Methyl-2-ethylbutyl	3-Ethyl-2-pentene	45	148.9–149.9								53.14	7.84		
C_8	1-Octyl	1-Octene	96	96.1–96.6					81[a]	133.1	131.2	54.98	8.36	54.93	8.45
	2-Octyl						50	128.0–129.0				54.68	8.19		
	3-Octyl	2-Octene	94	142.9–143.5						131.7		54.58	8.17		
	2-Ethylhexyl	2-Ethyl-1-hexene	81	101.9–102.7			59	103.7–104.2		128.5		54.66	8.37		

TABLE I (*Continued*)

	R	Olefin	Source: Olefin Yield, %	Olefin M.P.	Mercaptan Yield, %	Mercaptan M.P.	Bromide Yield, %	Bromide M.P.	Lit., M.P.	Neut. Equiv. Found	Neut. Equiv. Calcd.	Analyses Found C	Found H	Calcd. C	Calcd. H
	2-Cyclohexylethyl						47	126.3–126.8		130.4	130.1	55.21	7.71	55.37	7.74
C_9	1-Nonyl				85	105.0–106.0	43	105.0–105.5	103–105[d]	137.0	138.1	56.55	8.54	56.47	8.75
	3-Phenylpropyl				98	114.9–115.7				133.6	134.1	57.89	5.87	57.76	5.78
C_{10}	1-Decyl	1-Decene	82	93.5–93.8						145.5	145.2				
C_{11}	1-Undecyl						37	110.4–110.6	104–105[d]			58.99	9.13	59.18	9.27
C_{12}	1-Dodecyl								97.5[a]						
									102–103[d]						
C_{14}	1-Tetradecyl	1-Tetradecene	76	104.0–104.8					103–104[d]	174.8	173.5				
C_{16}	1-Hexadecyl	1-Hexadecene	84	105.0–105.8					105–106.5[d]	188.6	187.0				
C_{18}	1-Octadecyl				100	102–103			103–104[d]						
Cyclic Compounds															
C_5	Cyclopentyl	Cyclopentene	75	142.8–143.1						110.2	109.3	49.03	5.91	49.51	6.46
C_6	Cyclohexyl	Cyclohexene	83	150.5–151.1			9	149.0–149.9	148.0–148.5[e]	116.5	116.1				
C_7	2-Methylcyclohexyl	2-Methylcyclohexene	73	187.0–187.3								53.66	7.27	53.63	7.36
	4-Methylcyclohexyl				6	148.7–149.3						53.43	7.10		
Miscellaneous Compounds															
	Benzyl				97	188.4–188.9			189–190·192[g]	115.2	113.0				
	p-Chlorophenyl								163–164[h]						
	3-Thienyl								130–131[i]						
	3-Chloropropyl	Allyl chloride	35	108.5–108.8						113.6	113.3	37.37	4.80	37.09	4.89

[a] W. B. Chilcote, U. S. Patent **2,481,514** (1952). [b] P. Fitger, *Ber.*, **54B**, 2945 (1921). [c] M. Mantell, *Arkiv Kemi*, **3**, 129 (1951). [d] V. C. Berry, L. O'Rourke, and D. Towmey, *Proc. Roy. Irish Acad.*, **51B**, 223 (1947). [e] B. Weibull, *Arkiv Kemi, Mineral. Geol.*, **23-A**, No. 18, 1947, 25 pp. [f] K. D. Gundermann, *Chem. Ber.*, **90**, 72 (1957). [g] J. L. Szabo and E. T. Stiller, *J. Am. Chem. Soc.*, **70**, 3667 (1948). [h] E. W. Bousquet, U. S. Patent **2,434,100** (1948). [i] J. W. Brooks, E. G. Howard, and J. J. Wehrle, *J. Am. Chem. Soc.*, **72**, 1289 (1950).

propriate mercaptan to disodium maleate and by the reaction of an alkyl bromide and the trisodium salt of mercaptosuccinic acid. These same reactions are also useful for the preparation of solid derivatives of alkyl bromides and mercaptans.

The various *S*-alkylmercaptosuccinic acids prepared during this investigation and their physical properties are given in Table I.

Olefins. Prior to this work, cyclohexylmercaptosuccinic acid was the only olefin derivative of mercaptosuccinic acid obtained directly from the olefin.[9] This derivative was prepared by refluxing the olefin and mercaptosuccinic acid dissolved in acetic acid for ten hours or by irradiating the mixture for 117 hours using ultraviolet light. This did not appear to be a promising method for routine work.

The thermal addition of thioglycolic acid to olefins has been studied by Hoog and Eichwald.[10] The reaction was quantitative with primary olefins but low yields were obtained with highly hindered olefins. The free radical addition of thiolacetic acid to cyclic olefins has been reported by Bordwell and Hewett.[11]

The addition of mercaptosuccinic acid to olefins was initiated by various compounds capable of furnishing free radicals under the prevailing reaction conditions. The reaction rates as a function of the catalyst were in the order: benzoyl peroxide > ascardole > α,α'-bisisobutyronitrile > peracetic acid. Benzoyl peroxide was used because of its greater catalytic activity. Methanol was the best reaction medium due to the solubility of the reactants in it and its ease of removal from the reaction product.

Good yields of pure adducts were obtained with primary olefins. The 2-alkenes gave a mixture of two products which melted over a range of 5 to 10° between the melting points of the 2-alkyl- and 3-alkylmercaptosuccinic acids. With 2-octene it was possible to isolate the 3-octyl isomer by recrystallization. The more highly hindered olefins such as 2,6-dimethyl-2-heptene and 2,4,4-trimethyl-2-pentene did not react; yet 2-methyl-2-pentene and 3-ethyl-2-pentene gave satisfactory yields. A mixture of equal amounts of 1-octene and 2,4,4-trimethyl-2-pentene gave a good yield of the *n*-octyl derivative. Polymers were formed with styrene, indene, and 2-phenyl-2-butene. Butyl vinyl ether and allyl alcohol apparently reacted, but solid derivatives could not be isolated. The following vinyl halides did not react: 2-chloro-2-butene, 2-bromo-2-butene, 1,3-dichloro-2-butene, and β-bromostyrene. Allyl bromide apparently did not react, but allyl chloride gave a useful product in low yield (35%).

Mercaptans. The formation of *S*-alkylmercaptosuccinic acids by the addition of a mercaptan to disodium maleate followed the general procedure described by Chilcote[12] and Bousquet.[13]

The present study was limited to the primary mercaptans between C_4 and C_7, and nonyl, benzyl, and 3-phenylpropyl mercaptan. The yields were uniformly high. Suitable derivatives could not be obtained from higher molecular weight mercaptans because of emulsion formation. Tertiary mercaptans did not react.

Alkyl bromides. *S*-Alkylmercaptosuccinic acids were obtained from twenty-one primary and secondary alkyl bromides and from two cyclohexyl bromides by reaction with trisodium mercaptosuccinate. The highest yields were obtained from the primary bromides, but satisfactory yields were also obtained from the secondary bromides. Tertiary bromides did not produce products which could be isolated. The two cyclohexyl bromides gave low yields (6% and 9%). The reaction mixtures were refluxed from four to twenty-four hours and the free acid was liberated by concentrated hydrochloric acid.

Recrystallization. The solubility of a number of *S*-alkylmercaptosuccinic acids was determined in toluene at 50°. Some of these solubilities are given in Table II and others are in Fig. 1. The data in Fig. 1 show that the solubility of the *S*-alkylmercaptosuccinic acids is dependent upon the nature of the group attached to the sulfur atom forming the sulfide linkage. The 1-alkyl compounds are about twice as soluble as the 2-alkyl and several times more soluble than the 3-alkyl isomer. This difference in solubility has made it possible to separate 3-octylmercaptosuccinic acid from its mixture with 2-octylmercaptosuccinic acid.

TABLE II

THE SOLUBILITY OF S-ALKYLMERCAPTOSUCCINIC ACIDS IN TOLUENE AT 50.0°

RSCHCOOH
|
CH_2COOH

R	Grams per 100 G. Toluene
1-Propyl	0.30
2-Butyl	0.46
Isobutyl	0.87
2-Methylbutyl	4.00
2-Methyl-2-butyl	0.14
2-Ethylbutyl	2.59
Octadecyl	3.70
Cyclohexyl	0.25
2-Cyclohexylethyl	1.90
3-Chloropropyl	0.67

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(13) E. W. Bousquet, U. S. Patent 2,434,100 (1948).

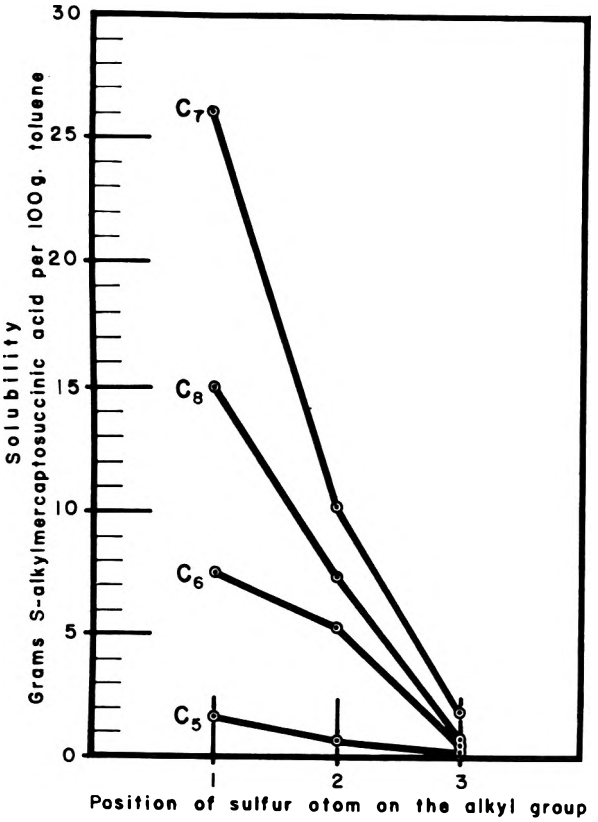

Fig. 1. Influence of the type of alkyl group on the solubility of *s*-alkylmercaptosuccinic acid in toluene at 50.0°C.

The *S*-alkylmercaptosuccinic acids retain both polar and nonpolar solvents very tenaciously. The best results were obtained by dissolving the derivative in diethyl ether and precipitating it with *n*-pentane. Usually one crystallization was sufficient to give an acceptable product, and the overall recovery was about 70%. Compounds with a C_{12} or higher alkyl group were recrystallized from acetic acid. About twenty milliliters of solvent was used per gram of solid.

Melting points. The melting point of an *S*-alkylmercaptosuccinic acid is a function of the position of the substitution on the alkyl group (Fig. 2). The *n*-alkyl compounds have a melting point range of about 95° to 110°; the 2-alkyl isomers have a melting point range between 125° and 135° and the 3-alkyl isomers have a melting point range between 142 and 153°. There is the expected variation in melting points of the straight-chain alkyl compounds with change in carbon content. Those with odd number of carbon atoms melt higher than the next higher, even numbered, homologue. There is also a correlation between melting point and the position of a methyl group on the alkyl group. There is a decrease of 7 to 10° in melting point as the methyl group moves from the 2 to 3 to 4 positions in respect to the carbon-sulfur linkage.

The cycloalkylmercaptosuccinic acids have a melting point range of 142 to 153° when there are no alkyl groups adjacent to the carbon-sulfur linkage. 2-Methylcyclohexylmercaptosuccinic acid has a melting point of 181°. 2-Cyclohexylethylmercaptosuccinic acid, however, melts at 117°.

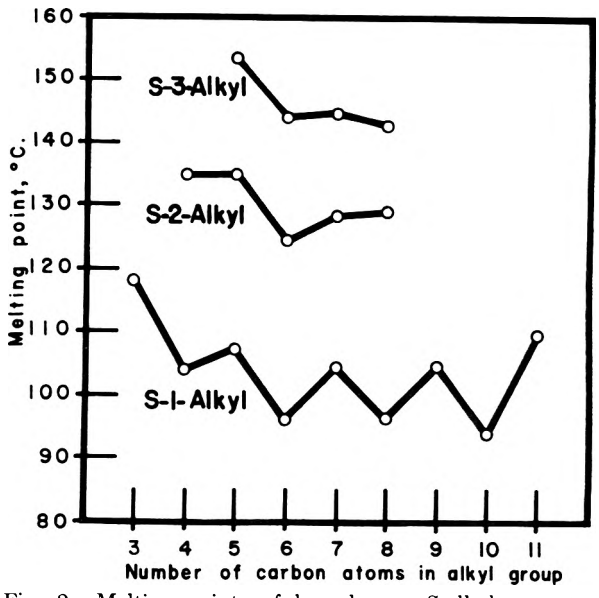

Fig. 2. Melting points of homologous *S*-alkylmercaptosuccinic acids

Many of the melting points of the *S*-alkylmercaptosuccinic acids reported by Chilcote[12] are incorrect (Table I).

EXPERIMENTAL

All melting points were taken using conventional melting point apparatus with calibrated Anschutz thermometers. All the reagents were commercial grade and used without further purification.

Olefins. Two grams of mercaptosuccinic acid and 3 ml. of methanol were heated in a 10 × 75 mm. test tube until the acid had completely dissolved. The solution was cooled and 1.00 ml. of olefin plus 0.10 g. of benzoyl peroxide were added. The test tube was tightly stoppered with a cork and shaken vigorously for 5 min. Because the olefin and methanol solution initially formed a two phase system, it was necessary to use vigorous shaking to insure a high yield of derivative. The test tube was then allowed to stand at room temperature until the desired amount of product had been formed. The crude crystals were washed into a 4 oz. bottle with 25 ml. of water and then treated with 25 ml. of 6*N* hydrochloric acid. The yield of product from this initial isolation was 1.3 to 1.9 g.

The crystals were recovered by vacuum filtration and washed with 25 ml. of 3*N* hydrochloric acid. They were dried for 15 min. on the filter and then for 12 hr. at room temperature. One gram of the derivative was dissolved at room temperature in 10 to 15 ml. of diethyl ether; then, *n*-pentane was added until turbidity resulted. After approximately 10% of the anticipated total amount of derivative had crystallized, the material was filtered and the crystals discarded. *n*-Pentane was then added to the filtrate until essentially all of the derivative had crystallized. These crystals were filtered and were sufficiently pure for melting point determinations and analyses.

Mercaptans. The following materials were placed in a 50 ml. Erlenmeyer flask: 20 ml. of 1.0*M* disodium maleate, 2.0 ml. of ethyl alcohol, 1.00 ml. of the mercaptan, and three or four boiling chips. The flask was equipped with a snugly fitting finger condenser and the contents were refluxed for 2 to 4 hr. After the reaction mixture was cooled, the lower

layer was separated and diluted with 10 ml. of concd. hydrochloric acid. The mercaptan derivative precipitated and was purified in the same manner as the products from the mercaptosuccinic acid–olefin reaction. The yield was usually in the range of 0.8 to 2.0 g.

Alkyl bromides. The following materials were placed in a 50-ml. Erlenmeyer flask: 1.00 ml. of mercaptosuccinic acid, 2 ml. of *n*-propyl alcohol, 1.00 ml. of the alkyl bromide, 25 ml. of 1.33*N* potassium hydroxide, and several boiling chips. The flask was fitted with a finger condenser and the mixture refluxed for 4 to 24 hr. If two layers were obtained upon cooling the reaction mixture, the aqueous layer was extracted with an equal volume of *n*-pentane. Ten milliliters of concd. hydrochloric acid was added to the aqueous layer and the precipitated derivative was recrystallized in the usual manner.

Neutralization equivalent. The *S*-alkylmercaptosuccinic acids were titrated with 0.07*N* potassium hydroxide to a phenolphthalein end-point in the presence of 5 ml. of ethyl alcohol and 40 ml. of water. The higher molecular weight derivatives (from 1-decene and higher) were titrated in a warm solution because of their limited solubility.

AUSTIN 12, TEX.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, THE HEBREW UNIVERSITY-HADASSAH MEDICAL SCHOOL]

Synthesis of 6-Thiouric Acid and Its Derivatives[1]

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6-Thiouric acid and its derivatives are obtained in high yield and excellent purity by direct thiation of suitable 4-oxo-5,6-diaminopyrimidines and subsequent cyclization with urea. Phosphorus pentasulfide attacks the 4-position selectively.

6-Thiouric acid (IIIa) is a substance of considerable biological interest, because it represents the main metabolite of 6-mercaptopurine,[3] a drug used for the treatment of leukemia. The synthesis of IIIa has proved a difficult task. Isolation of pure material from the reaction of uric acid with phosphorus pentasulfide required the use of anion exchangers,[4,5] because of the formation of side-products, *e.g.* the participation of the 8-position in the reaction.[5] These difficulties could be overcome if the mercapto group could be introduced at an earlier stage, *i.e.*, before the purine ring is formed. Therefore, the thiation of appropriate pyrimidines, which—as far as we are aware—has not been studied previously, was attempted.

We have found that a smooth reaction takes place at the 4-keto group of 5,6-diaminopyrimidines, when heated with phosphorus pentasulfide. The difference in reactivity of the 2- and 4-keto groups of the aforementioned compounds is similar to the differences of reactivity of keto groups in equivalent positions in xanthines.[6] Using this observation, the following syntheses were carried out: 1. 2,4-Dihydroxy-5,6-diaminopyrimidine (Ia)[7] was converted to 2-hydroxy-4-mercapto-5,6-diaminopyrimidine (IIa), the latter then being cyclized by fusion with urea to 6-thiouric acid (IIIa) in high yield. The product, as obtained, is practically pure, and can be easily recrystallized by acidification of a dilute solution of its sodium salt, without necessitating the use of an ion exchange column. 2. The same method, when applied to 1,2-dihydro-1-methyl-2-oxo-4-hydroxy-5,6-diaminopyrimidine (Ib)[8] gave 3-methyl-6-thiouric acid (IIIb) in high yield and excellent purity. 3. Because of the great difference in reactivity of the 2- and 4-keto group in I, *dithiation* of Ia or Ib in a one-step reaction with phosphorus pentasulfide is not a suitable procedure. Therefore, the following syntheses started with pyrimidines, already bearing a 2-thio group.

2-Mercapto-4-hydroxy-5,6-diaminopyrimidine (Ic)[9] reacted smoothly with phosphorus pentasulfide to give the dithio derivative (IIc).[10] The latter then was cyclized with urea to 2,6-dithiouric acid (IIIc). The spectral properties of our product are identical with those given by Elion, *et al.*,[5] who have prepared this compound by interaction of 2,6-dichloro-8-hydroxypurine with thiourea,[11] but differ from the data reported by Noell and Robins who obtained IIIc by thiation of 2-thiouric

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TABLE I

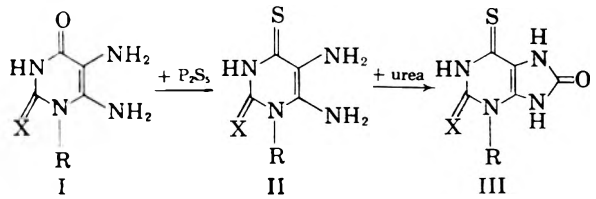
PHYSICAL PROPERTIES OF 6-THIOURIC ACID AND ITS DERIVATIVES

Compound	λ_{max}, mμ, pH 1	ϵ_m	λ_{max}, mμ, pH 8	ϵ_m	λ_{max}, mμ, pH 11	ϵ_m	R_F[a]	Fluorescence[b]
6-Thiouric acid (IIIa)	260	8,550	244	10,700	235	17,980	0.28	Blue
	355	28,730	347	27,270	344	22,000		
3-Methyl-6-thiouric acid (IIIb)	258	5,940	247	10,230	266	9,900	0.40	Blue
	358	23,960	357	26,730	344	20,990		
2,6-Dithiouric acid (IIIc)	261	9,100	245	23,450	252	26,000	0.44	Blue
	298	21,100	283	20,100				
	366	17,800	357	19,000	352	13,200		
3-Methyl-2,6-dithiouric acid (IIId)	262	11,030	255	24,180	241	13,420	0.57	Violet
	296	23,640	281	16,480	285	25,640		
	366	19,520	363	26,420	351	24,500		

[a] Descending method. Solvent used: isopropyl alcohol, 65 vol.; dimethylformamide, 25 vol.; water, 10 vol. [b] Observed under a Mineralight ultraviolet lamp, emitting light of about 255 mμ.

acid[12,13] (see Table I). 4. The same series of reactions, when applied to 1,2-dihydro-1-methyl-2-thio-4-hydroxy-5,6-diaminopyrimidine (Id),[14] led to 3-methyl-2,6-dithiouric acid (IIId) in 75% yield.

The spectral data and the R_f values of the uric acid derivatives described are summarized in Table I.



I II III

a. X = O; R = H
b. X = O; R = CH_3
c. X = S; R = H
d. X = S; R = CH_3

EXPERIMENTAL

2-Hydroxy-4-mercapto-5,6-diaminopyrimidine (IIa). Crude 2,4-dihydroxy-5,6-diaminopyrimidine (Ia), as obtained by reduction of the corresponding crude 5-nitroso derivative,[7] (2.0 g.), and phosphorus pentasulfide[15] (6.0 g.) in pyridine (100 ml.) were refluxed for 2.5 hr. with continuous stirring. The solvent was removed under reduced pressure and the residue decomposed by heating with water (50 ml.) during 40 min. Upon standing overnight in the refrigerator, brown crystals (1.5 g.) precipitated. By recrystallization from dilute sulfuric acid, yellow prisms of the neutral sulfate of IIa were obtained, which decomposed slowly above 270°. For cyclization, however, the crude precipitate is suitable.

Anal. Calcd. for $C_4H_6N_4OS \cdot {}^1/_2H_2SO_4 \cdot {}^1/_2H_2O$: C, 22.2; H, 3.7. Found: C, 22.5; H, 3.6.

6-Thiouric acid (IIIa). An intimate mixture of the diamine IIa (1.0 g.) and urea (1.5 g.) was heated for 20 min. at 180–200°. The solid cake was dissolved in 5% sodium hydroxide, treated with Norit, and the filtrate acidified with dilute sulfuric acid. 6-Thiouric acid was obtained as yellow, microcrystalline precipitate (1.0 g.; 90%). When a very dilute solution of this material in 5% sodium hydroxide was acidified with dilute sulfuric acid, slow crystallization took place, yielding analytically pure IIIa as yellowish plates, dec. >300°. The product showed properties identical with those reported in the literature.[4,5]

1,2-Dihydro-1-methyl-2-oxo-4-mercapto-5,6-diaminopyrimidine (IIb). Crude 1,2-dihydro-1-methyl-2-oxo-4-hydroxy-5,6-diaminopyrimidine (Ib)[8] (1.5 g.), phosphorus pentasulfide (5.0 g.) and pyridine (75 ml.) were refluxed for 4 hr. under continuous stirring. The starting material dissolved completely in the beginning and somewhat later the product (IIb) started to precipitate. After cooling, the crystals were filtered and boiled with water (30 ml.) for 15 min. Finally, the mercapto derivative was dissolved in 5% sodium hydroxide and precipitated with glacial acetic acid: yield 1.0 g. (60%). For analysis the product was recrystallized from dilute ethanol to give yellowish prisms, dec. >300°.

Anal. Calcd. for $C_5H_8N_4OS$: C, 34.9; H, 4.7. Found: C, 35.2; H, 4.7.

3-Methyl-6-thiouric acid (IIIb). An intimate mixture of the diamine (IIb) (0.3 g.) with urea (0.45 g.), was heated to 180–195° for 20 min. The solid cake was dissolved in 5% sodium hydroxide, treated with charcoal, and the product precipitated by acidification with hydrochloric acid. Purification was effected by redissolving in sodium hydroxide and acidification with glacial acetic acid. Pure IIIb consists of yellowish needles, which decompose >300°; yield 0.3 g. (75%).

Anal. Calcd. for $C_6H_6N_4O_2S$: C, 36.3; H, 3.0; N, 28.3. Found: C, 36.2; H, 3.1; N, 28.4.

2,4-Dithio-5,6-diaminopyrimidine (IIc). 2-Mercapto-4-hydroxy-5,6-diaminopyrimidine (Ic)[9] (3.0 g.) and phosphorus pentasulfide (9.0 g.) in pyridine (150 ml.) were heated as described for IIa. Acidification of a solution of crude IIc in 5% sodium hydroxide with glacial acetic acid gave golden prismatic needles; yield 2.4 g. (73%). The product proved identical with the product obtained from 2,4-dichloro-5-nitro-6-aminopyrimidine.[10]

2,6-Dithiouric acid (IIIc). Cyclization of IIc (0.5 g.) with urea (0.75 g.), as described above, gave 0.4 g. (69%) of yellow needles, dec. >300° The product was identical in every respect with the one described by Elion, *et al.*[5]

1,2-Dihydro-1-methyl-2-thio-4-hydroxy-5,6-diaminopyrimidine (Id).[14] The method used deviates from the original procedure of Traube and Winter,[14] but gives better yields. 1,2-Dihydro-1-methyl-2-thio-4-hydroxy-6-aminopyrimidine (4.2 g.) was dissolved in 5% sodium hydroxide (42 ml.), then sodium nitrite (2.3 g.) was added, and the mixture heated to 40°. Under continuous stirring, glacial acetic acid (45 ml.) was added slowly, the bath temperature raised to 75° for 2

(12) C. W. Noell and R. K. Robins, *J. Am. Chem. Soc.*, **81**, 5997 (1959).

(13) We have observed that aqueous solutions of IIIc decompose, when standing at room temperature for about half an hour, as recognized by increasing turbidity. Therefore, spectral measurements require always the use of freshly prepared solutions.

(14) W. Traube and F. Winter, *Arch. Pharm.*, **244**, 11 (1906).

(15) A gift of Oldbury Electro-Chemical Co., Niagara Falls, N. Y.

hr. and to 100° for 10 min. After cooling, the greenish-violet 5-nitroso derivative was filtered and, while still wet, was added portionwise with stirring to 80 ml. of water, kept at 60–70°. Alternating with the nitroso compound, portions of sodium hydrosulfite were added in such a manner that complete reduction of each charge was effected before introduction of a fresh lot of nitroso derivative. Upon cooling, the yellowish diamine (Id) crystallized in polyhedric prisms, m.p. 278–280°; yield 3.5 g. (76%).

1,2-Dihydro-1-methyl-2,4-dithio-5,6-diaminopyrimidine (IId). Thiation of Id (2.0 g.) with phosphorus pentasulfide (7.0 g.) in pyridine (100 ml.) was carried out by the method described above. IId was obtained in yellow, prismatic needles, which decomposed above 300°; yield 1.9 g. (87%).

Anal. Calcd. for $C_5H_8N_4S_2$: C, 31.9; H, 4.3. Found: C, 32.4; H, 4.5.

3-Methyl-2,6-dithiouric acid (IIId). Ring closure with urea was carried out as described above. By reprecipitation with 5% sodium hydroxide and acetic acid, yellow plates decomposing above 300° were obtained; yield 85%.

Anal. Calcd. for $C_6H_6N_4OS_2$: N, 26.2. Found: N, 26.1.

JERUSALEM, ISRAEL

[CONTRIBUTION FROM THE DIVISION OF PHYSICAL SCIENCES, UNIVERSITY OF CALIFORNIA AT RIVERSIDE]

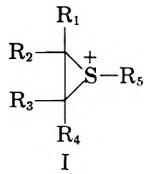
Stereochemistry of the Desulfurization of Thiiranes with Methyl Iodide[1]

GEORGE K. HELMKAMP AND DAVID J. PETTITT[2]

Received April 11, 1960

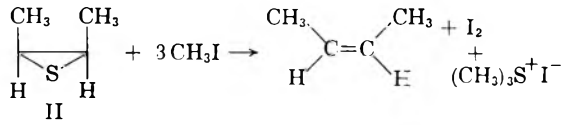
The reaction of isomers of 2,3-dimethylthiirane with methyl iodide results in the formation of 2-butene, with greater than 97% stereoselective desulfurization.

The reaction of thiiranes with methyl iodide leads to the formation of trimethylsulfonium iodide,[3,4] but little information has been given in literature concerning the olefin formed in the reaction.[5] This desulfurization has been investigated with regard to its stereochemistry, since a probable cyclic sulfonium intermediate (I) was of interest for studying generalized thiirane ring-openings.



I

When *cis*-2,3-dimethylthiirane (II) was treated with methyl iodide in refluxing acetone, *cis*-2-butene, iodine, and trimethylsulfonium iodide were formed in approximately equivalent amounts. The



II

progress of such reactions was usually determined by gravimetric analysis of the sulfonium halide which precipitated from solution. Although yields of butene and iodine were occasionally higher than that of the salt, measurements of butene were limited to volume estimations, and titration or photometric methods for iodine were somewhat unsatisfactory because of chemical instability of the acetone solutions. Yields of sulfonium iodide varied from about 15% to 40%, the higher values arising from low methyl iodide/thiirane ratios in the reaction mixtures.

The entire reaction sequence involved the conversions *cis*-2-butene→*meso*-2,3-dimethyloxirane (*meso*-2,3-epoxybutane)→*cis*-2,3-dimethylthiirane →*cis*-2-butene. Trace chromatographic analysis showed less than 0.2% *trans*-2-butene in the starting olefin and only 1.6% in the final product. In a somewhat parallel synthetic sequence, the *meso*-epoxide was prepared from recrystallized *meso*-2,3-butanediol, and the final olefin was found to contain 3.0% *trans*-2-butene. The results of reactions of *meso*- and DL-isomers are given in Table I. The processes appear to have a high degree of stereospecificity, for the small amount of con-

TABLE I

PRODUCTS OF DESULFURIZATION OF 2,3-DIMETHYLTHIIRANES

Thiirane Isomer	Source of Thiirane	Composition of Butenes, %[a]		
		1-	*cis*-2-	*trans*-2-
meso	*cis*-2-Butene	0	98.4	1.6
meso	*meso*-2,3-Butanediol	0	97.0	3.0
DL	Epoxide distilled from mixed isomers[b]	1.0	0.6	98.4

[a] Infrared spectra of the butenes showed no trace of isobutylene. [b] Low-boiling fraction of Dow Chemical Co's Butylene Oxides S.

(1) This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund.

(2) Taken in part from the B.A. thesis of David J. Pettitt, University of California at Riverside.

(3) M. Delépine and P. Jaffeux, *Compt. rend.*, **172**, 158 (1921).

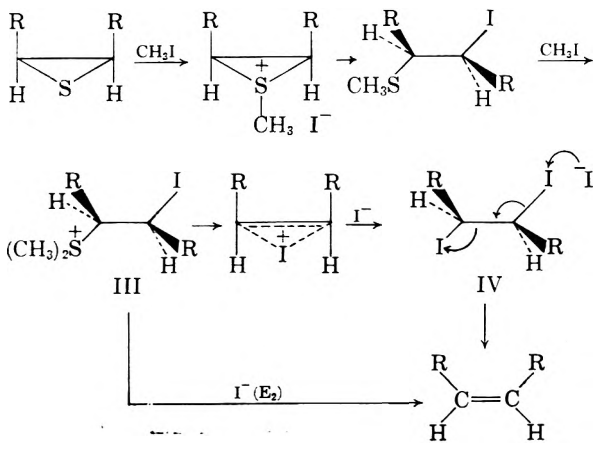
(4) C. J. Culvenor, W. Davies, and N. S. Heath, *J. Chem. Soc.*, **1949**, 284.

(5) R. D. Schuetz and R. L. Jacobs, Abstracts of Papers of the Division of Organic Chemistry, April, 1960. Mention is made of the fact that 2-alkoxymethylthiiranes react with methyl iodide to yield an olefinic compound corresponding to the thiirane employed.

taminating isomer has arisen through an accumulation of racemized materials of a reasonably long series of synthetic intermediates. In the case of the DL-thiirane, the commercial mixed epoxide isomers used as starting materials contained major amounts of 1,2-epoxide and *cis*-2,3-epoxide, and distillation processes were ineffective for complete separation.

The low yields in the reactions can be accounted for by side reactions, the principal one probably involving molecular iodine and the thiirane, for iodine reacted quite rapidly with the thiirane in hydroxylated solvents such as ethanol or in acetone containing water.[6] In these same solvents the desulfurization took place reasonably well, as indicated by formation of trimethylsulfonium iodide precipitate, but no iodine color developed until after prolonged reaction times. In very poor reaction solvents, such as saturated hydrocarbons, color again failed to develop. In this instance, it is proposed that the iodine never attained sufficient concentration for detection, as the rate of its reaction with thiirane, although low, was considerably greater than its rate of formation.

A series of reaction intermediates proposed by Culvenor, Davies, and Heath[4] accounts satisfactorily for the steric course of the desulfurization process if their diiodo compound (IV) is formed from its sulfonium precursor (III) with net retention of configuration, and this is followed by a *trans*-elimination. However, it is unnecessary to proceed as far as the dihalide, for the sulfonium precursor itself can lead directly to the appropriate alkene by an elimination reaction initiated by iodide ion attack on the secondary iodine atom.[8,9]



(6) Although bromine and chlorine have been shown to react with thiiranes,[7] no mention is made of iodine.

(7) J. M. Stewart and H. P. Cordts, *J. Am. Chem. Soc.*, **74**, 5880 (1952).

(8) S. Winstein, D. Pressman, and W. G. Young, *J. Am. Chem. Soc.*, **61**, 1645 (1939).

(9) J. Hine and W. H. Brader, Jr., *J. Am. Chem. Soc.*, **77**, 361 (1955).

(10) C. E. Wilson and H. J. Lucas, *J. Am. Chem. Soc.*, **58**, 2397 (1936).

EXPERIMENTAL

meso-2,3-Epoxybutane. cis-2-Butene containing less than 0.2% of other butene isomers was converted by way of the chlorohydrin to *cis*-2,3-epoxybutane according to the method of Wilson and Lucas[10]: yield, 30%; b.p. 58–60°, 735 mm.

In an alternate procedure, the *meso*-epoxide was prepared from recrystallized *meso*-2,3-butanediol, m.p. 33.5–34.0°, by the same sequence of reactions previously used for the active isomer.[11]

DL-*2,3-Epoxybutane.* This epoxide isomer pair was isolated by fractional distillation of straight-chain butylene oxide isomers[12] in a 2-meter column packed with glass helices: b.p. 53–54° (735 mm.). The original mixture of isomers contained about 40% each of *meso*-2,3-epoxybutane and 1,2-epoxybutane. As the desulfurization took place stereospecifically, the product composition (Table I) was considered sufficient criterion of isomer purity. The conversion to thiiranes and treatment with methyl iodide actually served as a convenient tool for determining isomer distribution in the epoxides.

2,3-Dimethylthiiranes. The *cis* and *trans* isomers were prepared from the corresponding epoxides by the thiourea method of Bordwell and Andersen.[13] Yield and physical constants of the *trans* isomer were similar to those previously reported for optically active 2,3-dimethylthiirane.[14] Redistilled *cis* isomer gave the following constants: b.p. 98.5° (735 mm.); n_D^{25} 1.4684 (lit.,[15] b.p. 51.0–51.5° at 130 mm.; n_D^{20} 1.4765).

Desulfurization. Although the reaction between thiirane and methyl iodide could be carried out in the absence of solvent, the yields were low. Ordinarily, the two reactants were added to acetone and the mixture was allowed to stand at room temperature, or the solution was refluxed in an apparatus designed for butene collection. In a typical reaction, to 20 ml. of dry acetone were added 5.0 g. of 2,3-dimethylthiirane and 24.5 g. of methyl iodide. The mixture was refluxed, and after 10–15 min. iodine color began to appear. The yield after 24 hr. of trimethylsulfonium iodide was obtained gravimetrically, of butenes volumetrically, and of iodine spectrophotometrically: trimethylsulfonium iodide, 16% (1.9 g.); butenes, 41% (2.0 ml.); iodine, 36%. After the trimethylsulfonium iodide had been recrystallized three times from ethanol, it decomposed smoothly and completely at 204–210° without any discoloration. Infrared and NMR spectra were consistent with the structure of the salt. Butene analyses were made on an Aerograph vapor phase fractometer.

When an identical reaction was carried out at room temperature, iodine color began to appear after 0.5 hr., and the yield of iodine after 24 hr. was only 7.4%. Under these conditions, the sulfonium salt, formed in 19% yield, showed traces of impurities, for some decomposition took place at 100°. The bulk of the precipitate, however, exhibited the same features of decomposition as the trimethylsulfonium iodide.

RIVERSIDE, CALIF.

(11) G. K. Helmkamp, C. D. Joel, and H. Sharman, *J. Org. Chem.*, **21**, 844 (1956).

(12) The authors are indebted to the Dow Chemical Co., Midland, Mich., for a generous sample of the mixed epoxide isomers.

(13) F. G. Bordwell and H. M. Andersen, *J. Am. Chem. Soc.*, **75**, 4959 (1953).

(14) G. K. Helmkamp and N. Schnautz, *Tetrahedron*, **2**, 304 (1957).

(15) N. P. Neureiter and F. G. Bordwell, *J. Am. Chem. Soc.*, **81**, 578 (1959).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XXXVIII. Alkylating Agents Related to Phenylalanine Mustard. II

W. A. SKINNER, KAREN A. HYDE, HELEN F. GRAM, AND B. R. BAKER

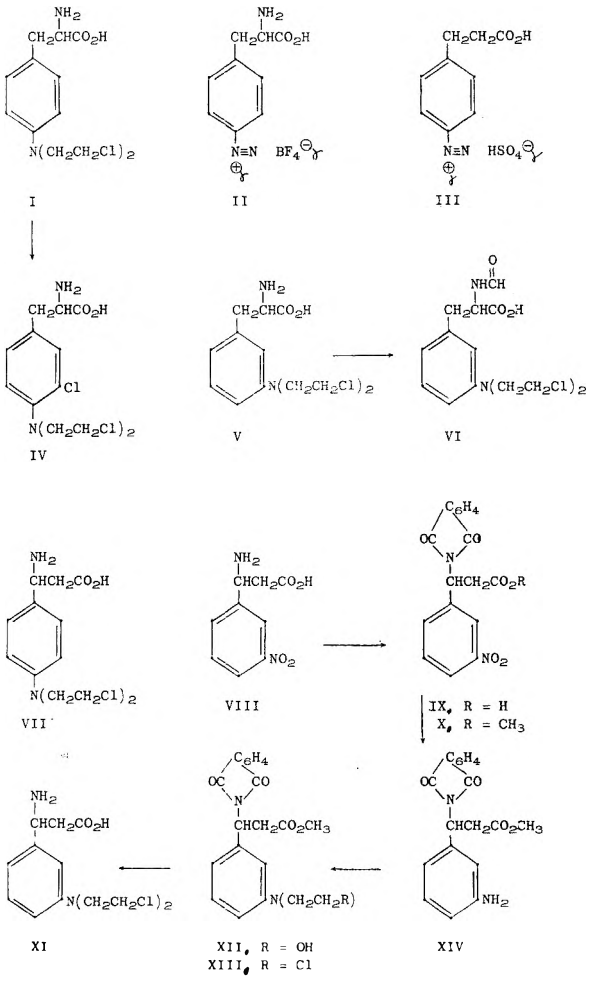
Received March 4, 1960

Three alkylating agents related to phenylalanine mustard have been synthesized, namely, 3-{*m*-[bis(2-chloroethyl)amino]-phenyl}-β-alanine (XI), 3-{4-[bis(2-chloroethyl)amino]-3-chlorophenyl}-DL-alanine (IV), and 3-{*m*-[bis(2-chloroethyl)-amino]phenyl}-*N*-formyl-DL-alanine (VI).

The increased selectivity of antitumor activity of phenylalanine mustard[2,3] (I) over that of some of the other nitrogen mustards (HN_2, Chlorambucil, Nitromin) would indicate that the phenylalanine moiety is a good carrier for alkylating groups. Replacement of the nitrogen mustard group of phenylalanine mustard with the diazonium group[4] gave a compound (II) effective against Ehrlich ascites and Leukemia L-1210 whereas 3-(*p*-diazoniumphenyl)propionic acid bisulfate III,[5] an analog of chlorambucil, was found to be inactive against Leukemia L-1210 and much less effective against Ehrlich ascites than was the diazonium compound derived from phenylalanine.

Biological test results[6] on the *meta*-isomer of phenylalanine mustard (V)[4] show that it has a more favorable chemotherapeutic index on Carcinoma-755, Ehrlich ascites, and Cloudman melanoma S-91 than does phenylalanine mustard (I), that it is equally effective against Sarcoma 180, and Dunning rat leukemia,[12] but that it is less effective against Leukemia L-1210.

Recently, the synthesis of 3-{*p*-[bis(2-chloroethyl)amino]phenyl}-β-alanine (VII), the β-amino acid isomer of phenylalanine mustard has been reported.[7,8] This compound was reported[8] to inhibit completely the growth of the Walker-256 tumor in rats when given at a dose of 20 mg./kg. of animal weight. It also inhibited Sarcoma 180 at a dose of 50 mg./kg. of animal weight.



This paper reports the synthesis of 3-{*m*-[bis(2-chloroethyl)amino]phenyl}-β-alanine (XI) by a synthetic route analogous to that used in this Laboratory for the synthesis of *meta*-phenylalanine mustard[4] (V); however, as is usually encountered with the synthesis of nitrogen mustards, the sequence had its individual idiosyncrasies to be overcome. In addition to XI, two other nitrogen mustards related to phenylalanine mustard were synthesized, namely, 3-{4-[bis(2-chloroethyl)-amino]-3-chlorophenyl}-DL-alanine (IV) and 3-

(1) This program is under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper of this series, *cf.* E. J. Reist, I. G. Junge, and B. R. Baker, *J. Org. Chem.* **25**, 1673 (1960).

(2) F. Bergel, V. C. E. Burnop, and J. A. Stock, *J. Chem. Soc.*, 1223 (1955); F. Bergel and J. A. Stock, *J. Chem. Soc.*, 2409 (1954).

(3) L. F. Larinov, A. S. Khokhlov, E. N. Shkodinskaia, O. S. Vasina, V. I. Trusheikina, and M. A. Novikova, *Lancet* **269**, 169 (1955).

(4) H. F. Gram, C. W. Mosher, and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 3103 (1959).

(5) W. A. Skinner, Helen F. Gram, and B. R. Baker. Paper XXXII of this series, *J. Org. Chem.*, **25**, 777 (1960).

(6) M. O. Greene, B. R. Baker, and J. Greenberg, manuscript submitted to *Cancer Research*.

(7) N. G. Chernov, L. S. Yagushinskii, and A. Ya. Barlin, *Doklady Akad. Nauk S.S.S.R.*, **126**, 802 (1959).

(8) F. Bergel, J. M. Johnson, and J. A. Stock, *Chem. and Ind.*, **47**, 1487 (1959).

{*m*-[bis(2-chloroethyl)amino]phenyl}-*N*-formyl-DL-alanine (VI).

The synthesis of 3-(*m*-nitrophenyl)-β-alanine (VIII) from *m*-nitrobenzaldehyde, ammonium acetate, and malonic acid according to the method used for the synthesis of β-phenyl-β-alanine[9] gave VIII in 67% yield. Earlier attempts to prepare VIII by the method of Rodionov, *et al.*,[10] using *m*-nitrobenzaldehyde, aqueous ammonia, and malonic acid resulted in lower yields of VIII contaminated with *m*-nitrocinnamic acid. Paper chromatography[11] proved to be useful in detecting whether samples of VIII were free of *m*-nitrocinnamic acid. Compound VIII traveled with an R_f of 0.68 in solvent A and was ninhydrin-positive while *m*-nitrocinnamic acid had an R_f of 0.91 in the same system when detected by its ultraviolet absorption.

3-(*m*-Nitrophenyl)-β-alanine (VIII) was converted to crystalline IX in quantitative yield using phthalic anhydride in pyridine followed by treatment with acetic anhydride. Esterification of IX with methanol saturated with hydrogen chloride afforded crystalline methyl β-(*m*-nitrophenyl)-1,3-dioxo-2-isoindolinepropionate (X) in 58% yield. Catalytic hydrogenation of X using 5% palladium on charcoal gave a quantitative yield of methyl β-(*m*-aminophenyl)-1,3-dioxo-2-isoindolinepropionate (VIV) as a crystalline solid.

Hydroxyethylation of XIV with ethylene oxide in aqueous acetic acid afforded methyl β-{*m*-[bis(2-hydroxyethyl)amino]phenyl}-1,3-dioxo-2-isoindolinepropionate (XII) in 85% yield as an analytically pure oil. This material traveled as a single spot (R_f 0.74) when chromatographed in solvent D[11] while the starting compound (XIV) had an R_f of 0.59 in the same system. Chlorination of XII using thionyl chloride in refluxing chloroform solution gave methyl β-{*m*-[bis(2-chloroethyl)amino]phenyl}-1,3-dioxo-2-isoindolinepropionate (XIII) in 49% yield. This compound traveled as a single spot (R_f 0.51) in solvent D on paper. The technique[4] of dissociation of the hydrochloride of XIII, produced upon chlorination of XII with thionyl chloride—namely, evaporation of a methanolic solution of the hydrochloride—allowed the crystalline free base of XIII to be obtained.

Previous experience in this laboratory with acid hydrolysis of the *N*-phthalyl blocked methyl ester of *m*-phenylalanine mustard was extremely useful in the hydrolysis of XIII to XI. When XIII was refluxed for three hours in concentrated hydrochloric acid, the solution chilled and filtered to remove phthalic acid, then neutralized with sodium acetate to *p*H5, a yellow gum separated which could be extracted with chloroform. Concentration of the chloroform extracts gave a sirup which on crystallization from acetone afforded 3-{*m*[bis(2-chloroethyl)amino]phenyl}-β-alanine (XI) as a white solid, m.p. 178–182°, in 45% yield. An analytical sample of XI, m.p. 185–188°, was obtained by solution of the crude solid in 20% hydrochloric acid followed by neutralization with sodium acetate to reprecipitate XI.

Ring chlorination of aromatic compounds often has a profound effect on their biological activities; hence, it was of interest to modify the structure of phenylalanine mustard by ring chlorination and determine what effect this had on its antitumor activity. In order to prevent over-chlorination and avoid the problem of separation of mixtures of mono- and dichlorinated mustard, I was chlorinated with one equivalent of sulfuryl chloride in acetic acid. From this reaction, a monochloro derivative of phenylalanine mustard, m.p. 166–173°, was obtained in 41% yield. As the amine group of I could be expected to control the orientation of the incoming chlorine, the structure of the compound is probably 3-{4-[bis(2-chloroethyl)amino]-3-chlorophenyl}-DL-alanine (IV). The elementary analysis of IV would not allow one to distinguish it from the hydrochloride of phenylalanine mustard (I). That the compound isolated was not the hydrochloride was shown by the low ionic chloride value (0.45%). The absence of free carboxyl absorption in the infrared also supports structure IV as a zwitterion rather than the mustard (I) hydrochloride with an unionized carboxyl.

Knunyants, Kil'disheva, and Golubeva[12] reported the synthesis of *N*-formylphenylalanine mustard in 1956. The *N*-formyl derivative of L-phenylalanine mustard has been reported to be more effective on Dunning Leukemia than was phenylalanine mustard.[13] Peptides of *N*-formylphenylalanine mustard have been synthesized and are reported to be less toxic then the parent mustard yet still show decided antitumor activity.[14]

This paper reports the synthesis of 3-{*m*-[bis(2-chloroethyl)amino]phenyl}-*N*-formyl-DL-alanine (VI) in 91% yield by treatment of *m*-phenyl-

(9) T. B. Johnson and J. E. Livak, *J. Am. Chem. Soc.*, **58**, 299 (1936).

(10) W. M. Rodionov and E. Th. Malewinskaja, *Ber.*, **59**, 2952 (1926).

(11) Paper chromatograms were run by the descending technique on Whatman No. 1 paper in solvent A, *n*-butyl alcohol-acetic acid–water (5:2:3); solvent B, *n*-butyl alcohol saturated with water; or solvent C, ammonium sulfate–isopropyl alcohol–water (2:28:70); and on Schleicher and Schuell No. 2495 acetylated paper in solvent D, benzene-methanol-water (2:6:1). The compounds were detected by their ultraviolet absorption, and in the case of the amino acids, by the use of ninhydrin reagent.

(12) J. L. Knunyants, O. V. Kil'disheva, and N. E. Golubeva, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, **1956**, 1418.

(13) R. Jones, Jr., paper presented at the Clinical Symposium of the Cancer Chemotherapy National Service Center in Washington, D. C., Nov. 11, 1959; to be published.

(14) N. E. Golubeva, O. V. Kil'disheva, and J. L. Knunyants, *Doklady Akad. Nauk S.S.S.R.*, **119**, 83 (1958); L. F. Larionov and Z. P. Sophina, *Doklady Akad. Nauk S.S.S.R.*, **114**, 1070 (1957).

alanine mustard (V)[4] with formic acid in acetic anhydride. The *N*-formyl derivative (VI) was obtained as an analytically pure solid, m.p. 151–152°. The absence of any appreciable amount of *m*-phenylalanine mustard (V) as contaminant was shown by movement of VI as a single ninhydrin-negative spot (R_f 0.93) in solvent system A when spotted at 200 γ whereas V could be detected at 5 γ using ninhydrin reagent and had an R_f of 0.85 in the same solvent system.[11]

EXPERIMENTAL[15]

3-(m-Nitrophenyl)-β-alanine (VIII). A mixture of 30.2 g. (0.20 mole) of *m*-nitrobenzaldehyde, 20.8 g. (0.20 mole) of malonic acid, and 30.8 g. (0.40 mole) of ammonium acetate in 50 ml. of 95% ethanol was heated on a steam bath under reflux for 5 hr. The mixture was cooled to room temperature and filtered. The yellow solid was washed with 20 ml. of 95% ethanol and the washings discarded. The remaining solid was partially dissolved in 150 ml. of 2*N* hydrochloric acid at room temperature and the undissolved solid (*m*-nitrocinnamic acid) removed by filtration and washed with 10 ml. of water. The combined filtrate and washings were neutralized with 20 ml. of 15*N* ammonium hydroxide solution. As the solution was cooled, a precipitate formed; yield, 28.0 g. (67%), m.p. 224–226° (lit.,[10] m.p. 226–227°); $\lambda_{max(\mu)}^{Nujol}$ 4.75 (NH_3^+); 6.20 (aryl); 6.32, 7.12 (CO_2^-); 6.50, 7.35 (NO_2); 12.1 (*m*-disubstituted benzene). The compound traveled as a single spot (R_f 0.68) in solvent system A[11] and was ninhydrin-positive. The acid insoluble by-product, *m*-nitrocinnamic acid, had an R_f of 0.91 in the same system when detected by its ultraviolet absorption.

The method of Radionov and Malewinskaja[10] gave 20–30% yields.

β-(m-Nitrophenyl)-1,3-dioxo-2-isoindolinepropionic acid (IX). A mixture of 9.42 g. (0.045 mole) of 3-(*m*-nitrophenyl)-β-alanine (VIII) and 6.62 g. (0.045 mole) of phthalic anhydride in 100 ml. of pyridine was refluxed until all the solid had dissolved (4.5 hr.). The solution was concentrated *in vacuo* to a yellow oil which was dissolved in 30 ml. of acetic anhydride and refluxed for 10 min. The resulting solution was poured onto ice and acidified to *p*H 2 with concd. hydrochloric acid. The gum which formed was triturated with the acid solution until solidification occurred; yield, 15.3 g. (100%), m.p. 108–115°, of solvated crystals that were pure enough for the next step. Several recrystallizations from chloroform-petroleum ether (b.p. 30–60°) gave an analytical sample, m.p. 158°; $\lambda_{max(\mu)}^{Nujol}$ 5.63, 5.83 (phthaloyl and carboxyl C=O); 6.53, 7.42 (NO_2); 13.85 (phthaloyl). The compound traveled as one spot (R_f 0.95) in solvent system A[11] (ninhydrin negative). In solvent D, IX traveled as a single spot (R_f 0.56). The starting material VIII had an R_f of 0.66 in the same system (ninhydrin positive).

Anal. Calcd. for $C_{17}H_{12}N_2O_6$: C, 60.0; H, 3.55; N, 8.23; Found: C, 60.0; H, 3.44; N, 8.28.

Methyl β-(m-nitrophenyl)-1,3-dioxo-2-isoindolinepropionate (X). To 20 ml. of methanol saturated with hydrogen chloride was added 3.05 g. (9.0 mmoles) of β-(*m*-nitrophenyl)-1,3-dioxo-2-isoindolinepropionic acid (IX). The mixture was refluxed for 2 hr., then cooled to room temperature whereupon white crystals separated. The mixture was concentrated *in vacuo* to about 10 ml., then chilled in ice to yield 1.86 g. (58%) of white solid, m.p. 117–121°, suitable for the next step.

An analytical sample was prepared by recrystallization from absolute ethanol, m.p. 116.5–118°; $\lambda_{max(\mu)}^{Nujol}$ 5.75, 5.84 (phthaloyl and ester C=O); 6.50, 7.38 (NO_2); 8.28 (ester C—O—C); 13.78 (phthaloyl). The compound traveled as a single spot (R_f 0.94) in solvent system A[11] and as a single spot (R_f 0.26) in solvent system D.

Anal. Calcd. for $C_{18}H_{14}N_2O_6$: C, 61.0; H, 3.98; N, 7.91. Found: C, 61.0; H, 4.15; N, 8.02.

Methyl β-(m-aminophenyl)-1,3-dioxo-2-isoindolinepropionate (XIV). A mixture of 14.2 g. (0.040 mole) of methyl β-(*m*-nitrophenyl)-1,3-dioxo-2-isoindolinepropionate (X) and 1.5 g. of 5% palladium on charcoal (moistened with about 10 ml. of methyl cellosolve) was suspended in 200 ml. of methanol and hydrogenated at 53 psig at room temperature until no more hydrogen was absorbed (2 hr.). The catalyst was filtered from the reaction mixture and washed well with methanol. The filtrate was concentrated *in vacuo* to a yellow solid; yield 13.0 g. (100%), m.p. 130–132°, suitable for the next step.

An analytical sample, m.p. 131–133°, was obtained by recrystallization from methanol, then from chloroform–petroleum ether (b.p. 30–60°); $\lambda_{max(\mu)}^{Nujol}$ 2.93, 2.99 (NH); 5.63, 5.73, 5.82 (phthaloyl and ester C=O); 6.21, 6.67 (aryl); 8.27 (ester C—O—C); 13.8 (phthaloyl). The compound traveled as a single spot (R_f 0.59) in solvent system D[11] (ninhydrin negative).

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.7; H, 4.97; N, 8.64. Found: C, 66.5; H, 4.92; N, 8.80.

Methyl β-{m-[bis(2-hydroxyethyl)amino]phenyl}-1,3-dioxo-2-isoindolinepropionate (XII). To a solution of 13.0 g. (0.040 mole) of methyl β-(*m*-aminophenyl)-1,3-dioxo-2-isoindolinepropionate (XIV) in 80 ml. of glacial acetic acid were added 60 ml. of water and 22 ml. (0.44 mole) of ethylene oxide. The flask was stoppered and allowed to stand at room temperature for 24 hr. The solution was poured into 200 ml. of water and neutralized with solid sodium hydrogen carbonate. The oil which separated was extracted with ethyl acetate, the extracts dried over anhydrous magnesium sulfate, then concentrated *in vacuo* to a red-brown oil; yield, 14 g. (85%); $\lambda_{max(\mu)}^{film}$ 2.95 (OH); 5.62, 5.72, 5.82 (phthaloyl and ester C=O); 6.23, 6.63 (aryl); 8.50 (ester C—O—C); 9.30, 9.85 (C—OH); 12.81 (*m*-disubstituted benzene); 13.83 (phthaloyl). The compound traveled as a single spot (R_f 0.74) in solvent system D.[11]

Anal. Calcd. for $C_{22}H_{24}N_2O_6$: C, 64.1; H, 5.87; N, 6.79. Found: C, 64.0; H, 5.94; N, 6.63.

Methyl β-{m-[bis(2-chloroethyl)amino]phenyl}-1,3-dioxo-2-isoindolinepropionate (XIII). To a solution of 19.0 g. (0.047 mole) of methyl β-{*m*-[bis(2-hydroxyethyl)amino]-phenyl}-1,3-dioxo-2-isoindolinepropionate (XII) in 65 ml. of chloroform was added 9.0 ml. (0.124 mole) of thionyl chloride in 20 ml. of chloroform. This solution was refluxed for 2 hr. and then concentrated *in vacuo* to a dark sirup. Four 50-ml. portions of methanol were added and the solution evaporated after each addition. After standing overnight under methanol, the sirup had solidified and was recrystallized from ethanol to give 10.3 g. (49%) of a white solid, m.p. 105–111°, that was suitable for the next step.

A small portion was recrystallized three times from ethanol to give a constant melting solid, m.p. 115–116°; $\lambda_{max(\mu)}^{Nujol}$ 5.64, 5.74, 5.82 (phthaloyl and ester C=O); 6.22, 6.67 (aryl); 8.32, 8.51 (ester C—O—C); 12.18 (*m*-disubstituted benzene); 13.80 (phthaloyl); and no OH near 3 or 9–10 μ. The compound moved as a single spot (R_f 0.51) in solvent system D.[11]

Anal. Calcd. for $C_{22}H_{22}Cl_2N_2O_4$: C, 58.7; H, 4.90; Cl, 15.8; N, 6.23. Found: C, 59.0; H, 5.15; Cl, 15.6; N, 6.43.

3-{m-[Bis(2-chloroethyl)amino]phenyl}-β-alanine (XI). A solution of 7.5 g. (0.021 mole) of methyl β-{*m*-[bis(2-chloroethyl)amino]phenyl}-1,3-dioxo-2-isoindolinepropionate (XIII) in 75 ml. of concd. hydrochloric acid was refluxed for 3 hr. The solution was chilled in ice and the phthalic acid removed by filtration. The filtrate was neutralized with a saturated aqueous sodium acetate solution to *p*H 5. The yellow gum which formed was extracted with three 25-ml. portions of chloroform. The combined extracts were

(15) Melting points were taken on a Fisher-Johns block and are uncorrected.

dried over anhydrous magnesium sulfate, then concentrated *in vacuo* to a brown sirup. This sirup was dissolved in 50 ml. of hot acetone and the solution allowed to stand overnight at room temperature. The white, powdery solid which had separated was collected and washed with acetone; yield 2.3 g. (45%); m.p. 178–182°. A portion of this solid was dissolved in 20% hydrochloric acid and neutralized with a saturated aqueous solution of sodium acetate causing a white solid to separate. The filtrate upon partial concentration *in vacuo* yielded an analytical sample of VII, m.p. 185–188°; $\lambda_{max(\mu)}^{Nujol}$ 6.21, 6.30, 6.40 (NH_3^+, CO_2^-, aryl); 6.63 (aryl, NH_3^+); 7.06 (CO_2^-); 12.8 (*m*-disubstituted benzene); 13.5 (C—Cl). The compound (XI) traveled as a single ninhydrin and ultraviolet absorbing positive spot (R_f 0.84) in solvent system A.[11]

Anal. Calcd. for $C_{13}H_{18}Cl_2N_2O_2$: C, 51.2; H, 5.92, Cl, 23.2; N, 9.18. Found: C 51.1; H, 6.06, Cl, 23.3; N, 9.20.

*3-{4-[Bis(2-chloroethyl)amino]-3-chlorophenyl}-*DL*-alanine* (IV). To a stirred suspension of 3.05 g. (0.010 mole) of 3-{*p*-[bis-(2-chloroethyl)amino]phenyl}-DL-alanine (I) in 30 ml. of glacial acetic acid heated to 50° was added dropwise in about 2–3 min. 0.85 ml. (0.010 mole) of sulfuryl chloride, maintaining the temperature between 50–55° by external cooling. Ten minutes after all the sulfuryl chloride had been added, the solution was concentrated *in vacuo* to 5 ml., diluted with 10 ml. of water, and neutralized with saturated sodium acetate solution. The gum which separated was triturated with water until it solidified. Solution of the solid in 25 ml. of methanol and addition of water caused a dark gum to separate. After removal of this gum, further addition of water yielded a granular solid upon chilling; yield 1.4 g. (41%), m.p. 166–173°; $\lambda_{max(\mu)}^{Nujol}$ 4.80 (NH_3^+); 6.09 (amino acid I); 6.65 (amino acid II); 6.31, 7.13 (CO_2^-). The compound (IV) traveled as a single ninhydrin positive spot (R_f 0.72) in solvent system C.[11] The starting material (I) traveled nearly the same (R_f 0.68) in that system.

Anal. Calcd. for $C_{13}H_{17}Cl_3N_2O_2$: C, 45.9; H, 5.04; Cl, 31.3. Found: C, 45.5; H, 5.18, Cl, 31.3. An analysis for ionic chloride, carried out at 0°, gave 0.45%.

*3-{m-[Bis(2-chloroethyl)amino]phenyl}-N-formyl-*DL*-alanine* (VI). To a solution of 0.60 g (2.0 mmole) of 3-{*m*-[bis-(2-chloroethyl)amino]phenyl}-DL-alanine (V) in 4 ml. of 90% formic acid was added 1.2 ml. of acetic anhydride. The red colored solution was warmed at 50–55° for 30 min. After cooling, the reaction mixture was diluted with 20 ml. of water and the product slowly crystallized; yield; 0.61 g. (91%), m.p. 145–150°. A sample for analysis was prepared by recrystallization from absolute ethanol, m.p. 151–152°; $\lambda_{max(\mu)}^{Nujol}$ 2.99 (NH); 5.80 (acid C=O); 6.19 (amide C=O); 6.64 (amide NH); 12.9 (*m*-disubstituted benzene). This compound (VI) traveled as a single spot (R_f 0.93) in solvent system A[11] and had an R_f of 0.71 in solvent system B. The chromatograms were ninhydrin negative at 200 γ while the starting amino acid (V) was detectable at 5 γ using ninhydrin reagent, thus showing less than 3% of (V) could have been present. Compound V had an R_f of 0.85 in solvent system A and R_f of 0.48 in solvent system B.[11]

Anal. Calcd. for $C_{14}H_{18}Cl_2N_2O_3$: C, 50.4; H, 5.42; Cl, 21.3; N, 8.40. Found: C, 50.5; H, 5.44; Cl, 21.0; N, 8.34.

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MENLO PARK, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, SCHOOL OF MEDICINE, YALE UNIVERSITY]

Synthesis of Some 8-Purinyl Nitrogen Mustards[1]

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As part of a program concerned with the preparation of nitrogen mustards intended to exhibit biological specificity, the 8-bis(β-chloroethyl)amino derivatives of xanthine, hypoxanthine, and adenine were synthesized.

In recent years large numbers of nitrogen mustards, *i.e.*, compounds containing the bis-(β-chloroethyl)amino grouping, have been synthesized as potential antitumor agents. In the hope of increasing the biological specificity of these compounds the mustard group has been attached to various carrier molecules such as antimalarial drugs,[3] amino acids[4,5] steroids,[6] and carbohydrates,[7] to name only a few.

In view of the hypothesis that double armed mustards exert their carcinostatic effects by reacting with the phosphate groups of nucleic acids, thus causing cross-linking between adjoining double helices,[8] it seemed of interest to synthesize compounds which would facilitate the likelihood of such cross-linking occurring.

This problem was approached in two ways, (a) by synthesizing 8,8′-bispurines,[9] and (b) by synthesizing the 8-purinyl nitrogen mustards described in this communication. Incorporation of 8,8′-bispurines (or their deoxyribonucleosides) in neighboring deoxyribonucleic acid double helices might result in direct crosslinking, while incorporation of

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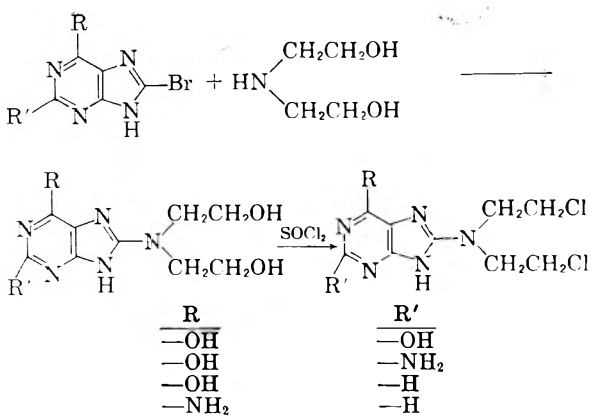
8-purinyl mustards might result in subsequent cross-linking by chemical reaction. The 8-position was chosen since bulky and reactive substituents in the 2- and 6-positions of purines would interfere with the hydrogen bonding required to form the Watson-Crick double helix, while the 9-position is required for deoxyribonucleosidation. Recently the synthesis of 5-bis(β-chloroethyl)aminouracil, a compound with considerable antitumor activity,[10] has been reported. Here again the mustard group is attached in a position where interference with hydrogen-bonding or with ribonucleosidation is minimized. It would seem reasonable to assume that whenever reactive groupings are attached to metabolites to form "toxophoric antimetabolites," these groups should not replace substituents required for attachment to the receptor site but should be located in their vicinity.[11,12]

The following synthetic scheme was utilized:



R	R′
—OH	—OH
—OH	—NH_2
—OH	—H
—NH_2	—H

The reaction of 8-bromopurines with diethanolamine proceeded smoothly in boiling ethylene glycol monomethyl ether under nitrogen. The 8-chloro-compounds were considerably less reactive. Reaction of the bis(β-hydroxyethyl)amino compounds with thionyl chloride then yielded the desired mustards in the form of hydrochlorides. The only exception proved to be 8-bis(β-hydroxyethyl)aminoguanine which, on being treated with thionyl chloride, did not yield the desired guanine-mustard. Considerable difficulties were encountered in obtaining analytical samples of all the bis-(β-chloroethyl)amino compounds reported on herein

Biological work with these compounds is now in progress and will be described elsewhere.

EXPERIMENTAL

8-Bromopurines. 8-Bromoadenine and 8-bromohypoxanthine were prepared by the method of Kruger[13] and 8-bromoguanine and 8-bromoxanthine by the method of Fischer and Ruse.[14]

8-Bis(β-hydroxyethyl)aminoadenine. A mixture of 5.3 g. (0.0248 mole) of 8-bromoadenine and 25 g. of diethanolamine in 50 ml. of ethylene glycol monomethyl ether was stirred mechanically and heated to boiling over a period of 20 hr., while being kept under nitrogen. The solvent was removed under vacuum and the residue extracted five times with 25-ml. portions of hot acetone. Ethanol was added to the residual oil, and the resulting solid removed by filtration. Concentration of the combined washings and filtrate resulted in the separation of more material, the combined yield being 3.0 g. (50%). The product was recrystallized from hot water to yield a white powder melting at 245–249°.[15] Ultraviolet spectrum. *p*H 1, λ_{max} 300 mμ, ϵ_{max} 16,700.

Anal.[16] Calcd. for $C_9H_{14}N_6O_2$: C, 45.36; H, 5.92; N, 35.27. Found: C, 45.58; H, 6.01; N, 35.13.

8-Bis(β-hydroxyethyl)aminohypoxanthine. This material was obtained from 8-bromohypoxanthine and diethanolamine in 49% yield and recrystallized from water to yield delicate white needles m.p. 250–255° dec. Ultraviolet spectrum. *p*H 1, λ_{max} 260 mμ, ϵ_{max} 16,800.

Anal. Calcd. for $C_9H_{13}N_5O_3.H_2O$: C, 42.01; H, 5.87; N, 26.22. Found: C, 42.18; H, 5.94; N, 25.78.

Water could be removed by heating the sample at 170° for 30 seconds.[16]

Calcd. for $C_9H_{13}N_5O_3$: N, 29.28. Found: N, 29.30.

8-Bis(β-hydroxyethyl)aminoguanine. This compound was obtained in 89% yield by the reaction of 8-bromoguanine with diethanolamine in methyl cellosolve and recrystallized from a large volume of water; m.p. 321° dec. Ultraviolet spectrum. *p*H 1, λ_{max} 253 mμ, ϵ_{max} 17,000.

Anal. Calcd. for $C_9H_{14}N_6O_3$: C, 42.51; H, 5.55; N, 33.05. Found: C, 42.59; H, 5.61, N, 32.96.

8-Bis(β-hydroxyethyl)aminoxanthine. This compound was obtained in 47% yield by the reaction of 8-chloroxanthine with diethanolamine in methyl cellosolve and recrystallized from water; m.p. 246° dec. Ultraviolet spectrum. *p*H 1, λ_{max} 299 mμ, ϵ_{max} 101,000.

Anal. Calcd. for $C_9H_{13}N_5O_4$: C, 42.35; H, 5.13; N, 27.44. Found: C, 42.37; H, 5.28; N, 27.32.

8-Bis(β-chloroethyl)aminoadenine hydrochloride. A mixture of 0.4 g. (0.001678 mole) of 8-bis(β-hydroxyethyl)aminoadenine, 10 ml. of thionyl chloride, and 0.5 ml. of dimethylformamide in 30 ml. of chloroform was refluxed under nitrogen for 3 hr. The solvent was removed under vacuum and the residue dissolved in absolute ethanol which was saturated with anhydrous hydrogen chloride. After cooling, 0.5 g. (85.5%) of white product was obtained and recrystallized four times from ethanol-ether, m.p., 155–162°. Ultraviolet spectrum. Methanol, λ_{max} 295 mμ, ϵ_{max} 15,900.

Anal. Calcd. for $C_9H_{14}Cl_4N_6$: C, 31.02; H, 4.05; N, 24.11; Cl, 40.73. Found: C, 30.95; H, 4.61; N, 24.19; Cl, 39.28.

8-Bis(β-chloroethyl)aminohypoxanthine hydrochloride. This material was obtained from 8-bis(β-hydroxyethyl)aminohypoxanthine and thionyl chloride in chloroform in 88% yield and recrystallized from ethanol-ether to yield white crystals m.p. 190–193° dec. Ultraviolet spectrum. Methanol, λ_{max} 271 mμ, ϵ_{max} 14,600.

Anal. Calcd. for $C_9H_{12}N_5Cl_3O \cdot {}^1/_2H_2O$: C, 33.61; H, 3.91; N, 21.77, Cl, 33.07. Found: C, 33.43; H, 4.04; N, 21.68; Cl, 33.44.

8-Bis(β-chloroethyl)aminoxanthine hydrochloride. This ma-

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(15) All melting points are uncorrected.

(16) Microanalyses were performed at Midwest Microlabs, Minneapolis, Ind., and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

terial was obtained by an analogous procedure in 19% yield and recrystallized from ethanol-ether to yield white crystals, m.p. 155° dec. Ultraviolet spectrum. Methanol, λ_{max} 296 mμ, ϵ_{max} 13,000.

Anal. Calcd. for $C_9H_{12}Cl_3N_3O_2$: C, 32.89; H, 3.68. Found: C, 33.14; H, 3.94.

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[CONTRIBUTION FROM THE INSTITUTE OF INDUSTRIAL MEDICINE, NEW YORK UNIVERSITY MEDICAL CENTER]

Epoxidation and Cyclization of Squalene[1]

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The epoxidation of squalene, isosqualene and tetracyclosqualene was examined. It is shown that epoxidation of squalene with peracetic acid proceeds stepwise. Di-, tetra- and hexaepoxysqualenes and diepoxytetracyclosqualene were isolated and studied. Some of the lead tetraacetate cleavage products of the diols derived from these epoxides were identified.

In a recent report from this laboratory[3] the isolation and identification of squalene and isosqualene from cigarette smoke condensate was described. In view of the possibility that epoxides of squalene and isosqualene, which may also be present in cigarette smoke, may exhibit biological activity, these compounds were prepared. The rate of epoxidation of squalene and the preparation and examination of squalene epoxides are described in this report. These compounds are currently being examined for carcinogenic activity to mouse skin. In the course of this work isosqualene and tetracyclosqualene were prepared and some properties and reactions of these compounds were studied.

Raymond[4] utilized the autoxidation of benzaldehyde to epoxidize a number of unsaturated compounds including squalene. The products of the epoxidation were not isolated or identified.

Some studies on the rate of the peracetic acid oxidation of squalene were carried out in our work. Squalene was epoxidized at −12° with chloroform as solvent. Two moles of peracid are consumed within fifteen minutes; another two moles of peracid are consumed only after two hours. For consumption of the last two moles of peracid it was necessary to allow reaction to proceed at 3° overnight.

Squalene was then treated with two, four, and six moles of peracetic acid in three experiments. The diepoxy product could not be purified as such. The crude product was catalytically hydrogenated and then purified by molecular distillation. The product had the correct analysis for diepoxyoctahydrosqualene. From the other two experiments there were obtained a tetra- and a hexaepoxysqualene. Tetraepoxysqualene absorbed two moles of hydrogen to give a product which had the correct analysis for tetraepoxytetrahydrosqualene. The crude epoxides showed in their infrared absorption spectra weak bands in the hydroxyl and carbonyl regions indicative of impurities. The pure distilled epoxides showed no absorption in the 3 μ and 6 μ regions but showed bands between 7.95 and 8.08 μ characteristic for 1,2-epoxides.[5] Other infrared bands which are known to be characteristic for 1,2-epoxides[6−8] *e.g.*, at 11.0, 11.7 and 12.1 μ, do not appear in the squalene epoxides.

Early attempts to purify the epoxides by chromatography on acid washed alumina or on florisil were unsuccessful. The chromatographed products were usually viscous yellow sirups which showed intense hydroxyl (3 μ) and carbonyl (5.8 μ) absorption in the infrared spectra.

Epoxidation of squalene with six moles of perbenzoic acid gave a product which from its elementary analysis was a mixture of the tetra- and hexaepoxides. The product decomposed on vacuum distillation but by molecular distillation gave a liquid tetraepoxide. The hexaepoxide could not be obtained in pure form by the perbenzoic acid oxidation. Carbonyl, hydroxyl and aromatic absorption in the infrared spectrum of the crude products suggested oxirane ring opening to hydroxybenzoate structures and possibly rearrangement reactions to keto-carbonyl–containing products. Filler and co-workers[9] studied the nature of these side reactions in the epoxidation of 1-substituted cyclohexenes.

Because of the difference in the rate of consumption of two, four, and six moles of peracid it became of interest to examine the partly epoxidized prod-

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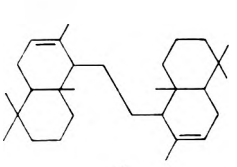
ucts in more detail. Several workers[10-12] have reported poor yields of tetrahydroxystearic acid from the hydrolysis of the corresponding epoxy compound. With monoepoxy compounds, quantitative yields are usually obtained. Similarly, it was found in the present work that when the squalene epoxides were treated with aqueous acid, products were obtained which from their infrared absorption spectra contained carbonyl impurities. The viscous, resinous products could not be purified and were cleaved directly with aqueous lead tetraacetate. The aldehydes and ketones obtained were examined by paper chromatography of their 2,4-dinitrophenylhydrazones and by the ultraviolet absorption spectra of the eluted spots. Quantitative recovery studies on the 2,4-dinitrophenylhydrazones of acetone and formaldehyde using these procedures showed that these derivatives can be recovered quantitatively. Hexaepoxysqualene gave only 10% of the expected yield of acetone. The hydrogenated di- and tetraepoxides each gave in different experiments 5 to 8.5% yields of acetone, assuming that in these two epoxides the double bonds at the ends of the squalene molecule were epoxidized. Both the di- and tetraepoxides gave traces of formaldehyde. Both these epoxides gave prominent high R_F spots suggesting the presence of the 2,4-dinitrophenylhydrazones of long chain carbonyl compounds. These results do not exclude the possibility that the di- and tetraepoxides are mixtures in which different double bonds have been epoxidized. Such random epoxidation appears unlikely because of the rate data. The double bonds in squalene are all the same [C—CH=C(CH_3)—C, *trans*] and should be equally susceptible to epoxidation. On the other hand, the double bonds at the ends of the squalene molecule may be more accessible and therefore epoxidize more rapidly. A similar observation was made in a study of the epoxidation of linolenic acid.[10b] In linolenic acid, the double bonds are in the 1,4-position from each other and in squalene they are in the 1,5-position. One would not expect considerable electronic effects from an epoxide group in diepoxylinolenic acid or in di- or tetraepoxysqualene upon the rate of epoxidation of the remaining double bonds in these compounds. Such electronic interaction probably does account for the epoxidation of 1,3-butadiene to give exclusively a monoepoxide.[13,14]

Using Heilbron's procedure[15] isosqualene was obtained in this study from the isomeric hexachlorosqualanes by treatment with pyridine. The products were the same from both the hexachlorosqualanes by refractive indices and infrared spectra. It was found in this work that hexachlorosqualane is also readily dehydrohalogenated on a column of activated alumina to give a product which is very similar to isosqualene by its infrared absorption spectrum and refractive index. The absence of cyclized materials in isosqualene was established by quantitative hydrogenation with a rhodium-on-alumina catalyst (with platinum as a catalyst hydrogenation was much slower). Six moles of hydrogen were absorbed. Iodine values also indicated six double bonds, *i.e.*, very little or no cyclized material is present. Squalane obtained by the hydrogenation of squalene was identical in infrared spectrum, density, and refractive index with that obtained from isosqualene.

A pure hexaepoxide of isosqualene could not be obtained. The product invariably decomposed on attempted molecular distillation. The crude epoxide was treated with dilute sulfuric acid and then cleaved with lead tetraacetate. Paper chromatography of the 2,4-dinitrophenylhydrazones indicated the presence of both formaldehyde and acetone. This result is expected from the infrared data concerning the positions of the double bonds in isosqualene.[16]

In the course of his studies, Heilbron[15] found that squalene on treatment with 98% formic acid gave a new viscous high boiling liquid, named tetracyclosqualene, which from its iodine absorption was concluded to have only two double bonds. Büchi[17] proposed structure I for this compound.



I

In our experiments, it was found that tetracyclosqualene absorbs two moles of iodine and in a quantitative hydrogenation, two moles of hydrogen were absorbed. A Kuhn-Roth analysis gave 2.5 carbon-methyl groups. Low carbon-methyl values were also obtained for squalene and isosqualene by Dauben and co-workers.[16] Epoxidation of tetracyclosqualene with peracetic acid gave a viscous oil which had the correct analysis for diepoxytetracyclosqualene.

The infrared absorption spectrum shows only very weak carbon-carbon double bond absorption in the 6 μ region. A band at 12 μ is suggestive of trisubstituted ethylenic structures. There is no

(10) (a) D. Swern and G. B. Dickel, *J. Am. Chem. Soc.*, **76**, 1957 (1954); (b) D. Swern and W. E. Parker, *J. Org. Chem.*, **22**, 583 (1957).

(11) A. F. Mackay and A. R. Bader, *J. Org. Chem.*, **13**, 75 (1948).

(12) T. G. Green and T. P. Hilditch, *Biochem. J.*, **29**, 1552 (1935).

(13) D. Swern, *J. Am. Chem. Soc.*, **69**, 1692 (1947).

(14) D. Swern, *Chem. Revs.*, **45**, 1 (1949).

(15) I. M. Heilbron, E. D. Kamm, and W. M. Owens, *J. Chem. Soc.*, 1630 (1926).

(16) W. G. Dauben, H. L. Bradlow, N. K. Freeman, D. Kritchevsky, and M. Kirk, *J. Am. Chem. Soc.*, **74**, 4321 (1952).

(17) See L. Ruzicka, *Experientia*, **9**, 357 (1953).

absorption at 11.25 μ, suggesting the absence of terminal methylene structures.

Further information about the structure of tetracyclosqualene was obtained by comparison of the NMR spectra of squalene and tetracyclosqualene in carbon tetrachloride solution. The spectrum of squalene shows the signals from the three types of protons in this molecule at 95 (=C—CH_3), 118 (=C—CH_2—) and 300 cps. (=CH) relative to tetramethylsilane as internal reference. Tetracyclosqualene showed peaks at 93, 116, and 300 cps. due to the same three types of protons and in addition a peak at 57 cps. which is ascribed to the methyl protons of the grouping: $H_3C—\overset{|}{\underset{|}{C}}—$. These data are consistent with the proposed structure for tetracyclosqualene, but this does not exclude the possibility that other double bond isomers are present.

Treatment of isosqualene with formic acid under the same conditions used for the cyclization of squalene[15] gave a product which was indistinguishable from tetracyclosqualene by its spectra, physical, and chemical properties.

In the course of this work a sample of the 2,4-dinitrophenylhydrazone of levulinaldehyde was required. Attempts to prepare levulinaldehyde from 2-methylfuran by acid hydrolysis[18] led mainly to resinous products. A convenient method for the preparation of levulinaldehyde was by the hydrogenation of acetylacrolein. This substance could be readily prepared from 2-methylfuran *via* 2,5-dimethoxy-2,5-dihydro-2-methylfuran.[19,20]

EXPERIMENTAL

All melting points are corrected; boiling points are uncorrected.

Squalene. Commercial squalene (Eastman Kodak Co., 90% squalene) was chromatographed on activated alumina, eluted with petroleum ether (b.p. 30–60°), and distilled in vacuum. The fraction boiling at 188–190°/0.2 mm. (reported,[16] b.p. 213°/1 mm.) was collected; n_D^{25} 1.4904, d^{25} 0.8570, $(R)_D$ 134.92; $(R)_D$ calcd. for $C_{30}H_{50}$, 6 C=C: 137.92 (reported[15] n_D^{20} 1.4965, d^{18} 0.8596, $(R)_D$ 139.6–139.9; n_D^{20} 1.4962[16]). Squalene prepared in this manner absorbed 5.9 moles of hydrogen.[21]

Isosqualene. (a) *Pyridine method.* Isosqualene was prepared from a mixture of the hexachlorosqualanes,[15] chromatographed on activated alumina, and distilled in vacuum under nitrogen. The product, n_D^{25} 1.4890 (reported,[15] n_D^{20} 1.4990), absorbed 5.1 moles of iodine and in a quantitative hydrogenation 6 moles of hydrogen were absorbed.

(b) *Alumina method.* One gram of hexachlorosqualane[15] (mixture of isomers) was dissolved in a minimum of chloroform and chromatographed on activated alumina with petroleum ether (b.p. 30–60°) as eluent. A number of colored bands rapidly developed at the top of the column and a colorless oil was eluted. The product, 0.51 g. (81% yield), was distilled in vacuum under nitrogen, n_D^{25} 1.4902.

Anal. Calcd. for $C_{30}H_{50}$: C, 87.66; H, 12.26. Found: C, 87.35; H, 12.44.

This material absorbed 6 moles of hydrogen and its infrared and ultraviolet absorption spectra were identical with that of isosqualene prepared by the pyridine method.

Tetracyclosqualene. Squalene was cyclized with 98% formic acid as described by Heilbron.[15] The dark brown crude product was chromatographed on activated alumina using petroleum ether (b.p. 30–60°) as eluent. The residue from the eluate was distilled in vacuum under nitrogen to give a 58% yield of a colorless viscous oil, b.p. 204–210°/0.4 mm., n_D^{25} 1.5088, d^{28} 0.943, $(R)_D$ 129.5. $(R)_D$ calcd. for $C_{30}H_{50}$, 2 C=C: 131.00 [reported,[15] b.p. 230–232°/3 mm., n_D^{15} 1.5211, d^{15} 0.9359, $(R)_D$ 133.2].

Anal. Calcd. for $C_{30}H_{50}$: C, 87.66; H, 12.26; 6 C—CH_3: 21.95%. Found: C, 87.77; H, 12.37; Kuhn-Roth: 9.719 mg. required 6.00 ml. 0.01*N* sodium hydroxide, 9.27% C—CH_3, 2.5 C—CH_3 groups. The product absorbed 2.0 moles of hydrogen and 1.7 moles of iodine.

Cyclization of isosqualene. Isosqualene was cyclized with formic acid and the product worked up as described above for squalene. The light yellow viscous product, n_D^{25} 1.5083, absorbed 2 moles of hydrogen and 2 moles of iodine in double bond estimations. The infrared absorption spectrum was identical with that of tetracyclosqualene.

Catalytic hydrogenation of squalene and isomers. Squalene, isosqualene, and tetracyclosqualene were all rapidly hydrogenated at atmospheric pressure. The catalyst-compound ratio was 2:1. The hydrogenation products were purified by chromatography on activated alumina followed by vacuum distillation. All three products were colorless oils. The products were as follows: (a) *Squalane:* obtained from squalene with the absorption of 6 moles of hydrogen, n_D^{25} 1.4462, d^{25} 0.8076, $(R)_D$ 139.3; $(R)_D$ calcd. for $C_{30}H_{62}$: 140.74 [reported[22]: n_D^{20} 1.4534, d^{20} 0.810; $(R)_D$ 140.9]. (b) *Squalane:* obtained by the hydrogenation of isosqualene with the absorption of 6 moles of hydrogen, n_D^{25} 1.4470, d^{25} 0.8121, $(R)_D$ 138.5. (c) *Tetrahydrotetracyclosqualene:* obtained from tetracyclosqualene, with the absorption of 2 moles of hydrogen, n_D^{25} 1.4968, d^{25} 0.9452, $(R)_D$ 128.0, $(R)_D$ calcd. for $C_{30}H_{54}$: 131.94.

Tetraepoxysqualene. A chloroform solution of perbenzoic acid, 307 ml. (0.181 mole; 0.0815 g. of perbenzoic acid/ml.) was added slowly to 10 g. (0.024 mole) of squalene in 10 ml. of chloroform cooled in an ice bath. The temperature was kept below 20°. After the addition was completed, the mixture was allowed to stand at 0° for 17 hr. The reaction mixture was washed with cold 5% sodium hydroxide and then with cold water. The chloroform solution was dried over anhydrous sodium sulfate, filtered, and the solvent removed at room temperature. The pale yellow oil was distilled in a Hickman type molecular still at 2 microns with a bath temperature of 100°. A clear mobile oil was obtained.

Anal. Calcd. for $C_{30}H_{50}O_4$: C, 75.85; H, 10.61. Found: C, 76.07; H, 10.80.

Tetraepoxytetrahydrosqualene. Squalene, 2 g. (0.00488 mole), was dissolved in 100 ml. of chloroform and cooled to −10°. Peracetic acid,[23] 4 ml. (0.0195 mole) saturated with sodium acetate was added with vigorous shaking. The peracid was added at such a rate that the temperature did not rise above −10°. The addition required 1 hr. Shaking and cooling was then continued for 30 min. at −10° and between −5° and 0° for another 15 min. The reaction mixture was washed well with cold 5% aqueous sodium bicarbonate

(18) C. Harries, *Ber.*, **31**, 37 (1898).

(19) N. Clauson-Kaas and F. Limborg, *Acta Chem. Scand.*, **1**, 619 (1947).

(20) D. G. Jones, Brit. Patent **595,041**, Nov. 25, 1947; *Chem. Abstr.*, **42**, 2992 (1948).

(21) Except where stated otherwise catalytic hydrogenations were carried out in tetrahydrofuran or dioxane with 5% rhodium-on-alumina (Baker and Co., Inc.) as catalyst.

(22) I. M. Heilbron, T. P. Hilditch, and E. D. Kamm, *J. Chem. Soc.*, 3131 (1926).

(23) The peracetic acid used in this work was purchased from Becco Chemical Division, Food Machinery and Chemical Corp., and contained 380 g./l. of peracetic acid in glacial acetic acid.

solution and then with cold water. The chloroform solution was dried over anhydrous sodium sulfate and the chloroform removed at room temperature. A colorless oil, 1.8 g., was obtained. The crude epoxide was hydrogenated in dioxane with Adams catalyst and distilled at 0.1 mm., bath temperature 230°.

Anal. Calcd. for $C_{30}H_{54}O_4$: C, 75.22; H, 11.36. Found: C, 75.39; H, 11.37.

Diepoxyoctahydrosqualene. Squalene, 2 g. (0.00488 mole), was dissolved in 100 ml. of chloroform and the solution cooled to −10°. Peracetic acid, 1.95 ml. (0.00975 mole), saturated with sodium acetate was added slowly and with stirring to the squalene at −10°. After the addition was complete, the mixture was agitated for an additional 5 min. The reaction mixture was extracted twice with cold 10% aqueous sodium bicarbonate solution and washed with cold water. The chloroform solution was dried over anhydrous sodium sulfate and the solvent removed at room temperature. Two grams of a clear oil was obtained. One gram of the crude squalene epoxide was hydrogenated in dioxane with platinum as catalyst; 4.0 moles of hydrogen were absorbed. The product was chromatographed on florisil, and distilled from a molecular still at 1 micron, bath temperature 100°.

Anal. Calcd. for $C_{30}H_{58}O_2$: C, 79.89; H, 12.96. Found: C, 79.96; H, 13.09.

Diepoxytetracyclosqualene. Tetracyclosqualene, 2 g. (0.00488 mole), in 200 ml. of chloroform was cooled to −10° and peracetic acid, 1.95 ml. (0.00975 mole), saturated with sodium acetate added slowly and with stirring at −10°. The mixture was allowed to stand at 0° for 24 hr. The reaction mixture was washed first with cold 10% aqueous sodium bicarbonate and then with water. The chloroform solution was dried over anhydrous sodium sulfate and the solvent removed at room temperature. The oily product, 1.7 g., was distilled in vacuum at 0.4 mm., bath temperature 250°, to give a viscous colorless oil.

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.33; H, 11.38. Found: C, 81.21; H, 11.30.

Hexaepoxysqualene. Squalene, 5.1 g. (0.0125 mole), was dissolved in 500 ml. of chloroform, cooled to −10° and 15 ml. of peracetic acid (0.075 mole), saturated with sodium acetate, was added dropwise and with stirring. The mixture was agitated for 1 hr. at −10° and then stirred at 4° for 24 hr. The solution was washed with aqueous sodium bicarbonate and then with water, and dried over anhydrous sodium sulfate. Removal of the solvent left 5.3 g. of crude epoxide. The material was purified by molecular distillation at a bath temperature of 150°. A pale yellow oil was obtained.

Anal. Calcd. for $C_{30}H_{50}O_6$: C, 71.07; H, 9.94. Found: C, 72.03; H, 9.93.

Rate of epoxidation of squalene. Experiment A. One gram of squalene (0.0025 mole) dissolved in 50 ml. of chloroform was cooled to −5° in an ice-salt mixture and 4.0 ml. of peracetic acid (0.0195 mole), saturated with sodium acetate, added in one portion with stirring. The temperature increased to −3° and was maintained at this temperature. Aliquot portions were titrated at regular intervals for moles of peracid consumed. The results are given in Table I.

Experiment B. One gram of squalene (0.0025 mole) was dissolved in 150 ml. of chloroform and cooled to −12°; 1.0 ml. (0.005 mole) of peracetic acid, saturated with sodium acetate, was added with stirring. Aliquot portions were titrated at regular intervals. When 2 moles of peracid per mole of squalene was consumed another 1.0 ml. of peracid was added and the consumption of peracid followed by titration. When 4 moles of peracid were consumed, the last 2 moles of peracid were added. The rate of epoxidation decreased and the mixture was allowed to react at 3°. The results are shown in Table I.

TABLE I

RATE OF EPOXIDATION OF SQUALENE WITH PERACETIC ACID

Experiment A (−3°)		Experiment B (−12°)	
Reaction time, min.	Moles peracid used per mole of squalene	Reaction time, min.	Moles peracid used per mole of squalene
3	4.76	3	1.26
16	5.18	12	1.86
47	5.60	37	2.20
108	5.70	58	2.40
130	5.80	115	3.45
148	6.02	136	3.81
		186	4.50
		900[a]	6.20

[a] Allowed to react at 3° after 186 min.

Cleavage of squalene epoxides. All three of the squalene epoxides were hydrolyzed with aqueous sulfuric acid, cleaved with lead tetraacetate, and the aldehydes and ketones examined as follows:

(a) *Acid hydrolysis of epoxide.* Five hundred milligrams of the epoxide, dissolved in 10 ml. of benzene, was refluxed with stirring in the presence of 10 ml. of 15% aqueous sulfuric acid for 5 hr. This procedure was found necessary in order to obtain a minimum of rearrangement products as evidenced by the infrared spectra. After cooling, the benzene layer was separated and the aqueous layer extracted with benzene (2 × 10 ml.).

(b) *Lead tetraacetate cleavage of diols.* The combined benzene solutions were added to the calculated amount of lead tetraacetate in 20 ml. of water and stirred at 100° under reflux for 2 hr. The aldehydes and ketones were then steam-distilled directly into the calculated amount of 2,4-dinitrophenylhydrazine hydrochloride in aqueous-ethanolic solution. When the steam distillation was complete, the mixture in the receiver was heated to boiling, cooled, and extracted with benzene. The benzene extract was chromatographed on paper.

(c) *Paper chromatography of 2,4-dinitrophenylhydrazones.* The derivatives were chromatographed on Whatman No. 1 chromatographic paper using a system similar to that employed by Meigh.[24] After the application of the spots, the paper was allowed to equilibrate in the chromatography tank for 12 hr. in the presence of the developing solvent. The chromatograms were automatically started[25] and developed with a saturated solution of methanol in cyclohexane by the ascending technique. The spots were detected by their visible color, eluted with dioxane, and their ultraviolet absorption spectra determined in dioxane. Concentrations were determined by relating peak intensities of the longest wave-length band in the ultraviolet absorption spectrum with that of a solution of known concentration of the authentic compound. Where necessary, bands were rechromatographed. All solvents used were spectroscopically pure. The R_F values of the derivatives of known aldehydes and ketones are given in Table II.

In an attempt to determine the presence of levulinaldehyde and succindialdehyde derivatives, another chromatographic system was required because both these derivatives and the reagent showed zero R_F with the cyclohexane-methanol system. With hexane-ether-methanol (20:30:1)[26] as developing solvent, the reagent showed R_F 0.45 but the levulinaldehyde and succindialdehyde derivatives still remained at the origin. The concentrations of these two components were therefore not determined. The yields of acetone from the squalene epoxides are given in Table III.

Preparation of levulinaldehyde-2,4-dinitrophenylhydrazone. 2-Methylfuran was treated with bromine in methanol at −7° according to the procedure outlined by Clauson-Kaas

(24) D. F. Meigh, *Nature*, **170**, 579 (1952).
(25) B. L. Van Duuren, *Anal. Chem.*, **32**, 732 (1960).
(26) I. Martin, *Chem. & Ind. (London)*, 1439 (1958).

TABLE II

R_F VALUES OF 2,4-DINITROPHENYLHYDRAZONES

2,4-DNP of	R_F Value: Cyclohexane-methanol	R_F Value: Hexane-ether-methanol (20:30:1)
Formaldehyde	0.25	—
Acetaldehyde	0.27	—
Isobutyraldehyde	0.53	—
Acetone	0.45	—
Tiglaldehyde	0.40	—
Levulinaldehyde	0.0	0.0
Succindialdehyde	0.0	0.0
2,4-DNP-reagent	0.0	0.45

TABLE III

YIELDS OF ACETONE FROM CLEAVAGE OF SQUALENE EPOXIDES

Epoxide	Percentage Yield of Acetone on Basis of 2 Moles of Acetone Per Mole of Epoxide
Diepoxyoctahydrosqualene	5.1, 8.5
Tetraepoxytetrahydrosqualene	5.0, 6.5
Hexaepoxysqualene	10.0

and Limborg[19] to give 2,5-dimethoxy-2,5-dihydro-2-methylfuran, b.p. 60–63°/20 mm. (reported[19] b.p. 46–56°/8 mm.). Hydrolysis of this product with dilute sulfuric acid gave 3-acetylacrolein[19] which gave a red crystalline 2,4-dinitrophenylhydrazone, m.p. 270–271° dec. from pyridine-ethanol [reported for 3-acetylacrolein,[27] m.p. 269° dec.]. Ultraviolet in dioxane: λ_{max} 404 mμ, ϵ_{max} 16,000; λ_{max} 450 mμ, ϵ_{max} 15,220. The crude acetylacrolein was hydrogenated with Adams' catalyst in tetrahydrofuran. One mole of hydrogen was absorbed. After filtration and removal of solvent the residue was converted directly to a 2,4-dinitrophenylhydrazone. The yellow needles were recrystallized from pyridine-ethanol, m.p. 233° (reported[28] m.p. 234–235°). Ultraviolet in dioxane: λ_{max} 350 mμ, ϵ_{max} 7530; λ_{max} 420 mμ, ϵ_{max} 4530.

Anal. Calcd. for $C_{17}H_{16}N_8O_8$: C, 44.38; H, 3.51; N, 24.36. Found: C, 44.73; H, 3.64; N, 24.28.

Spectra. Infrared absorption spectra were measured with a Baird double-beam instrument with sodium chloride optics. Spectra were obtained of 5% solutions in chloroform and 5% solutions in carbon disulfide. In addition, spectra of liquids were determined qualitatively as thin films of pure liquids and spectra of solids were obtained from potassium bromide pellets.

Ultraviolet absorption spectra were obtained on a Process and Instruments automatic recording unit with a Beckman DU spectrophotometer.

NMR spectra were recorded and interpreted by Varian Associates, Palo Alto, Calif. Carbon tetrachloride was used as solvent with added tetramethylsilane as internal standard. Both the spectra reported were obtained at 60 M.C.

Acknowledgment. The authors are indebted to Dr. Norton Nelson for his interest and encouragement in this work and to Mr. C. A. Joseph for technical assistance.

NEW YORK 16, N. Y.

(27) K. G. Lewis, *J. Chem. Soc.*, 1083 (1956).

(28) H. Inoue, *Pharm. Bull. (Japan)*, **1**, 401 (1953); *Chem. Abstr.*, **49**, 10908 (1955).

[CONTRIBUTION FROM THE RESEARCH DIVISION, ARMOUR AND CO.]

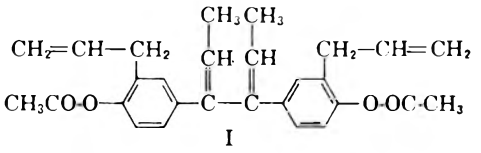
Preparation of New Derivatives of Synthetic Estrogens *via* the Claisen Rearrangement[1]

EMIL KAISER AND ELLEN GUNTHER

Received March 21, 1960

The preparation of 3,3′-diallyldienestrol diacetate from 3,4-bis(4-hydroxyphenyl)-3,4-hexanediol is described. In the course of this synthesis, it was demonstrated that the migratory aptitude of substituents affected the competition between pinacol rearrangement and dehydration in the treatment of a pinacol with acetyl chloride.

The recently reported[2] growth-promoting activity of 3,3′-diallyldiethylstilbestrol and 3,3′-diallylhexestrol[3] in ruminants made it desirable to synthesize other diallyl derivatives of synthetic estrogens. The preparation of 3,3′-diallyldienestrol diacetate (I) was of special interest as its parent compound, dienestrol diacetate, is in use as a poultry growth promotant.



I

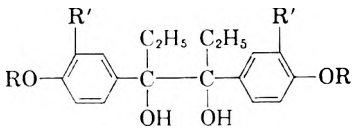
The synthesis of I was originally planned to start with 3,4-bis(4-allyloxyphenyl)-3,4-hexanediol (IIb) and proceed through the dehydration product of this pinacol, the dienestrol diallyl ether, to the 3,3′-diallyldienestrol and by subsequent acetylation to I.

By analogy with the dehydration of 3,4-bis(4-acetoxyphenyl)-3,4-hexanediol (IIc) to dienestrol diacetate,[4] we expected to obtain the dienestrol

(1) Presented at the 136th meeting of the American Chemical Society, Atlantic City, N. J., Sept. 13–18, 1959.

(2) O. O. Thomas, R. R. Woodward, J. T. Doty, and J. R. Queensberry, *J. Animal Sci.*, **18**, 1498 (1959); I. A. Dyer and A. T. Ralston, *J. Animal Sci.*, **18**, 1499 (1959).

(3) E. Kaiser and J. J. Svarz, *J. Am. Chem. Soc.*, **68**, 636 (1947).

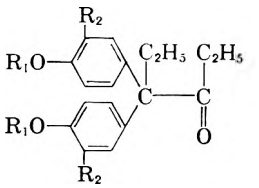


IIa. R = H R′ = H
IIb. R = C_3H_5 R′ = H
IIc. R = CH_3CO R′ = H
IId. R = H R′ = C_3H_5

diallyl ether by refluxing IIb with an acetyl chloride–acetic anhydride mixture. The product of this reaction was an oil which resisted all crystallization attempts. Nevertheless, it was subjected to the Claisen rearrangement in diethylaniline, and crystals with a melting point of 137–138° were isolated. However, this product was not the expected 3,3′-diallyldienestrol, which actually was obtained with a melting point of 123–124° by two other synthetic routes which will be discussed later.

The identity of the substance obtained on refluxing IIb with an acetyl chloride–acetic anhydride mixture was deduced from the infrared absorption spectra of the oily reaction product and its Claisen rearrangement product. In the spectrum of the oil, a peak appeared at 5.86 μ, and shifted to 6.02 μ for the compound which melted at 137–138°. These peaks indicated the presence of a keto group which resulted from a pinacolone rearrangement.[5]

The pinacolone was prepared by a different route to prove that the acetyl chloride–acetic anhydride treatment of IIb really yielded a pinacolone. In this process, the free phenolic pinacol (IIa), was rearranged to 4,4-bis(4-hydroxyphenyl)-3-hexanone (IIIa) with hydrogen chloride in an ether suspension according to Adler, *et al.*[6] With allyl bromide, the diallyl ether of IIIa, an oil, was prepared. This material had an infrared spectrum identical with that of the oil obtained from the acetyl chloride–acetic anhydride reaction mixture, indicating that the two were identical with 4,4-bis(4-allyloxyphenyl)-3-hexanone (III-b). The Claisen rearrangement products (melting point 137–138°) of both oils had identical infrared spectra and melting points. The mixed melting point showed no depression. These identical rearrangement products were 4,4-bis(3-allyl-4-hydroxyphenyl)-3-hexanone (IIIc) instead of 3,3′-diallyldienestrol. The presence of the *p*-allyloxy substituents in the aromatic groups of the pinacol caused pinacolone rearrangement to the corresponding diallyl ether during the acetyl chloride–acetic anhydride reaction. The expected dehydration to dienestrol diallyl ether did not take place.



IIIa. R_1 = H R_2 = H
IIIb. R_1 = C_3H_5 R_2 = H
IIIc. R_1 = H R_2 = C_3H_5

Lane and Spialter[7] used acidic reagents to study the competition between dehydration and pinacol rearrangement in the treatment of IIc and suggested a mechanism for dehydration with acetyl chloride. To Lane and Spialter's findings, we can now add that not only the components of the acidic reagents but also the migratory aptitudes[8] of the groups attached to the pinacol have a bearing upon the competition between pinacolone or diene formation. The rapidly migrating *p*-allyloxyphenyl groups direct the acetyl chloride reaction towards the pinacol rearrangement, and the retarding effect of the *p*-acetoxyphenyl groups permits the formation of the proposed monoacetate intermediate of Lane and Spialter,[7] which in turn dehydrates to a diene.

The hindering effect of the *p*-acetoxyphenyl group on the pinacol rearrangement was further demonstrated when IIc was treated with hydrogen chloride in an ether or methyl ethyl ketone suspension. Contrary to the behavior of IIa,[6] which contains a free phenolic hydroxyl group, the diacetate (IIc) did not undergo a pinacol rearrangement with hydrogen chloride, but was recovered unchanged.

The findings which point out the differences in the behavior of the diallyl ether IIb and the diacetate IIc towards various acidic reagents are summarized in Table I.

TABLE I

PRODUCTS FROM THE TREATMENT OF 3,4-BIS(4-HYDROXYPHENYL)-3,4-HEXANEDIOL (IIa), ITS DIALLYL ETHER (IIb) AND DIACETATE (IIc) WITH ACIDIC REAGENTS

Starting Material	Reagent	Product
Diacetate (IIc)	Acetyl chloride in acetic anhydride or methyl ethyl ketone	Dienestrol diacetate
Diacetate (IIc)	Hydrogen chloride in ether or methyl ethyl ketone	No reaction
Diallyl ether (IIb)	Acetyl chloride in acetic anhydride or methyl ethyl ketone	Pinacolone (IIIb)
Phenol (IIa)	Hydrogen chloride in ether	Pinacolone (IIIa)

According to the evidence presented in Table I, the dehydration of the 3,4-bis(4-allyloxyphenyl)-3,4-hexanediol to 3,3′-diallyldienestrol with acidic

(4) E. C. Dodds, L. Golberg, R. Robinson, and L. Lawson, *Nature*, **142**, 34 (1938); *Proc. Roy. Soc. (London)*, **B127**, 140 (1939).

(5) J. F. Lane and L. Spialter, *J. Am. Chem. Soc.*, **73**, 4408 (1951).

(6) E. Adler, G. J. Gie, and H. v. Euler, U. S. Patent 2,421,401 (1947).

(7) J. F. Lane and L. Spialter, *J. Am. Chem. Soc.*, **73**, 4411 (1951).

(8) G. H. Wheland, *Advanced Organic Chemistry*, second ed., John Wiley & Sons, Inc., New York, 1949, p. 515.

reagents was prevented by the rapid shifting of a *p*-allyloxyphenyl group from the 3 to the 4 position of the hexanediol. To avoid this pinacol rearrangement, the *p*-ether linkages had to be eliminated. This was accomplished *via* the Claisen rearrangement, which transformed IIb into the oily 3,4-bis(3-allyl-4-hydroxyphenyl)-3,4-hexanediol, IId. This was acetylated and dehydrated in one step by using an acetyl chloride-acetic anhydride mixture. The resulting crystalline product was the desired 3,3′-diallyldienestrol diacetate (I).

For structural confirmation, 3,3′-diallyldienestrol diacetate was also synthesized from dienestrol diallyl ether prepared from dienestrol with allyl bromide. The dienestrol diallyl ether was rearranged to the 3,3′-diallyldienestrol, a crystalline product, *via* the Claisen rearrangement. Subsequent acetylation of the rearranged compound yielded 3,3′-diallyldienestrol diacetate (I), identical in melting point and infrared spectrum with the product obtained from the oily 3,4-bis(3-allyl-4-hydroxyphenyl)-3,4-hexanediol.

The estrogenic activity of 3,3′-diallyldienestrol was found to be in the range of 0.2% of that of diethylstilbestrol. This assay, conducted by Dr. H. D. Lennon of the Research Division of Armour and Company, was done by the immature-mouse uterine weight method of Evans, *et al.*[9] The compound was injected subcutaneously in the test animals and its potency calculated from the standard dose-response curve of diethylstilbestrol according to the general method of Bliss.[10]

EXPERIMENTAL[11]

Meso-3,4-bis(4-allyloxyphenyl)-3,4-hexanediol (IIb). A mixture of *meso-* and *racemic*-3,4-bis(4-hydroxyphenyl)-3,4-hexanediols[12] was acetylated and the *meso*-diacetate separated from the racemic diacetate by crystallization from butanol. Saponification of the *meso*-diacetate yielded pure *meso*-II-a.[13] Twenty-four grams of *meso*-II-a and 26 g. of anhydrous potassium carbonate were stirred with 100 ml. of methyl ethyl ketone and, at reflux temperature, 15.6 ml. of allyl bromide was added dropwise. Refluxing was continued for 13 hr., the solid removed by filtration, and the filtrate evaporated. The residue was crystallized from ethanol and 24.5 g. of *meso*-3,4-bis(4-allyloxyphenyl)-3,4-hexanediol (IIb), m.p. 134–136°, was obtained.

Anal. Calcd. for $C_{24}H_{30}O_4$: C, 75.36; H, 7.90. Found: C, 75.14; H, 7.95.

4,4-Bis(4-allyloxyphenyl)-3-hexanone (IIIb). A 1.9-g. sample of 3,4-bis(4-allyloxyphenyl)-3,4-hexanediol (IIb) was refluxed with a mixture of 10 ml. of acetyl chloride and 10 ml. of acetic anhydride for 4 hr. The mixture was poured into 300 ml. of water, stirred, and extracted with ether. The organic layer was dried over sodium sulfate and the ether was evaporated. The residue was an oil which could not be crystallized. The infrared absorption spectrum of the oil showed a peak at 5.86 μ, indicating the presence of a keto group.

4,4-Bis(3-allyl-4-hydroxyphenyl)-3-hexanone (IIIc). The oil IIIb, obtained in the previous step, was refluxed for 4 hr. with 20 ml. of diethylaniline in an atmosphere of nitrogen. After it had been cooled, the reaction mixture was poured into 300 ml. of 2*N* hydrochloric acid, stirred vigorously, and then extracted with ether. The dried ether extract was reduced to a small volume. Petroleum ether (b.p. 40–60°) was added to the concentrated ether solution until a precipitate began to form. The precipitate was removed by filtration and discarded. The filtrate was mixed with sufficient petroleum ether (b.p. 40–60°) to produce turbidity. Crystals formed when the mixture was chilled. They were collected and dried. The yield of 4,4-bis(3-allyl-4-hydroxyphenyl)-3-hexanone (IIIc) was 0.6 g., m.p. 137–138°. A ketone peak at 6.02 μ was present in the infrared spectrum of the compound.

Anal. Calcd. for $C_{24}H_{28}O_3$: C, 79.08; H, 7.74. Found: C, 79.15; H, 7.68.

4,4-Bis(4-hydroxyphenyl)-3-hexanone (IIIa). This compound was prepared according to the process of Adler, *et al.*[6] by passing hydrogen chloride through an ether suspension of IIa. An oil (IIIa) was isolated from the ether solution. This oil solidified on standing. Compound IIIa showed a ketone peak at 5.93 μ.

4,4-Bis(4-allyloxyphenyl)-3-hexanone (IIIb) *from* IIIa. Five grams of compound IIIa was treated with allyl bromide in the same manner as described for the preparation of compound IIb from compound IIa.

An oil isolated from the reaction mixture had the same infrared absorption spectrum as the oil IIIb which had been obtained by the acetyl chloride-acetic anhydride treatment of 3,4-bis(4-allyloxyphenyl)-3,4-hexanediol. This identical spectrum proved that the compound was 4,4-bis(4-allyloxyphenyl)-3-hexanone.

4,4-Bis(3-allyl-4-hydroxyphenyl)-3-hexanone (IIIc) *from* IIIb. Five grams of compound IIIb prepared from IIIa was rearranged in diethylaniline as described for the preparation of compound IIIc from the oily product IIIb of the acetyl chloride-acetic anhydride reaction. A 4.3-g. sample of IIIc was obtained. This compound had the same melting point and infrared absorption spectrum as described previously, which identified it as 4,4-bis(3-allyl-4-hydroxyphenyl)-3-hexanone.

Treatment of meso-3,4-bis(4-acetoxyphenyl)-3,4-hexanediol (IIc) *with hydrogen chloride.* One gram of *meso*-3,4-bis(4-acetoxyphenyl)-3,4-hexanediol (IIc) was suspended in 20 ml. of ether, and hydrogen chloride gas was passed through the suspension for 8 hr. The suspension did not clear and the solid was collected from it on a filter. The melting point and infrared spectrum of the solid were identical with those of the starting material. The filtrate was evaporated to dryness. Only traces of an oil remained after the ether had been evaporated. The same treatment was carried out in a methyl ethyl ketone suspension and again unchanged IIc was recovered.

Dehydration of meso-3,4-bis(4-hydroxyphenyl)-3,4-hexanediol (IIc) *with acetyl chloride in methyl ethyl ketone.* Twenty grams of IIc was refluxed with a mixture of 100 ml. of acetyl chloride and 100 ml. of methyl ethyl ketone for 22 hr. All of the solid dissolved. Water and ether were added, and after the acetyl chloride decomposed, the solvent layer was separated from the aqueous layer. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was crystallized from ethanol and 5.2 g. of dienestrol diacetate, m.p. 120–122°, was obtained.

Dienestrol diacetate was obtained also from the racemic form of IIc with acetyl chloride in the methyl ethyl ketone dehydration process.

(9) J. S. Evans, R. F. Varney, and F. C. Koch, *Endocrinology*, **28**, 747 (1941).

(10) C. I. Bliss, *The Statistics of Bioassay*, Academic Press, Inc., New York, 1952, p. 566, ff.

(11) Microanalyses were performed by Midwest Microlab., Inc., Indianapolis 20, Ind.

(12) Mr. W. E. Irwin from the Miles Chemical Co., Elkhart, Ind., furnished a generous sample of the pinacol mixture.

(13) E. Adler, U. S. Patent **2,465,505** (1949).

3,3-Diallyldienestrol diacetate from IIb. To 15 ml. of diethylaniline, 1.91 g. of 3,4-bis(4-allyloxyphenyl)-3,4-hexanediol (IIb) was added and the solution refluxed under nitrogen for 6 hr. The reaction mixture was poured into 200 ml. of 2*N* hydrochloric acid, stirred, and then extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and the solvent evaporated. The residue, a viscous oil, was used without further purification for dehydration to 3,3′-diallyldienestrol diacetate. The dehydration was carried out by refluxing the oil, *meso*-3,4-bis(3-allyl-4-hydroxyphenyl)-3,4-hexanediol, with a mixture of 10 ml. of acetyl chloride and 10 ml. of acetic anhydride for 4 hr. Four hundred milliliters of water was added and the mixture extracted with ether. The ether extract was washed with a sodium bicarbonate solution, then with water, dried over sodium sulfate, and the ether evaporated. The residue was crystallized from ethanol and then recrystallized from an ether–petroleum ether (b.p. 40–60°) mixture. The 3,3′-diallyldienestrol diacetate melted at 145–147° and its yield was 0.25 g.

Anal. Calcd. for $C_{28}H_{30}O_4$: C, 78.11; H, 7.02. Found: C, 78.09; H, 7.18.

3,3′-Diallyldienestrol diacetate from dienestrol. Dienestrol was treated with allyl bromide in the same manner as described for the preparation of compound IIb. Dienestrol diallyl ether was rearranged in diethylaniline to form 3,3′-diallyldienestrol, which was then crystallized from an ether–petroleum ether (b.p. 40–60°) mixture and recrystallized from dilute ethanol. The 3,3′-diallyldienestrol melted at 123–125°.

Anal. Calcd. for $C_{24}H_{26}O_2$: C, 83.21; H, 7.28. Found: C, 83.12; H, 7.35.

The 3,3′-diallyldienestrol quickly discolored upon exposure to air but remained colorless when the hydroxyl groups were acetylated. Acetylation with acetic anhydride or a pyridine–acetic anhydride mixture gave very poor yields but acetylation of the sodium salt of the 3,3′-diallyldienestrol with acetic anhydride produced the diacetate in good yields. Six grams of 3,3′-diallyldienestrol was dissolved in 100 ml. of 30% aqueous ethanol containing 1.9 g. of sodium hydroxide. The solution was evaporated to dryness under reduced pressure and the residue refluxed for 7 hr. with 150 ml. of acetic anhydride. The acetic anhydride was decomposed with water and the remaining solid was collected on a filter and crystallized from ethanol. A 5.1-g. sample of 3,3′-diallyldienestrol diacetate was obtained. The compound was identical in melting point and infrared spectrum with the product obtained from the *meso*-3,4-bis(4-allyloxyphenyl)-3,4-hexanediol (IIb) through Claisen rearrangement, acetylation, and dehydration.

CHICAGO 9, ILL.

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY AND THE DEPARTMENT OF CHEMISTRY, ST. JOSEPHS COLLEGE[1]]

Steroidal Sapogenins. LXIII. Chiapagenin, a New Normal (25 L) Δ^5-12β-Hydroxysapogenin[2]

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Received April 8, 1960

A new normal Δ^5-12β-hydroxysapogenin, for which the name chiapagenin is proposed, has been isolated from the tubers of Dioscorea chiapasensis Matuda.[4] Unequivocal proof of structure was obtained by catalytic hydrogenation of chiapagenin followed by acidic isomerization at C_{25} to give the known 5α,12β-hydroxysapogenin rockogenin. Reduction of the known normal Δ^5-12-ketosapogenin correllogenin with lithium in liquid ammonia containing methyl alcohol gave chiapagenin. Therefore the latter must be 12β-hydroxyyamogenin.

During the course of investigations of the plant kingdom for steroidal sapogenins, a new sapogenin was isolated from *Dioscorea chiapasensis* Matuda[4] and identified. The two sapogenins present in this plant were separated by chromatography. The first product eluted was identified as the Δ^5-normal (25 L) sapogenin, yamogenin, by direct comparison with an authentic sample. Further elution gave a more polar, obviously polyhydroxy, sapogenin. The melting points of the latter compound and its acetate did not correspond to any previously known sapogenin. The structure of the new sapogenin, for which the name chiapagenin is proposed, was established in the following manner. Analysis of the new sapogenin and its acetate showed two hydroxyl groups present and the typical C_{27} skeleton found in steroidal sapogenins. The infrared spectrum of chiapagenin diacetate showed this sapogenin to have the normal spiroketal side chain[5,6] with bands characteristic of Δ^5-unsaturation.[7,8] This latter feature of the molecule

(1) Eastern Utilization Research and Development Division, Agricultural Research Service, United States Department of Agriculture, Philadelphia 18, Pennsylvania, and St. Joseph's College, Philadelphia 31, Pennsylvania.

(2) Previous paper in this series, Steroidal Sapogenins. LXII, M. E. Wall and S. Serota, *Tetrahedron*.

(3) (a) Eastern Utilization Research and Development Division, Philadelphia 18, Pennsylvania. Abstracted from a thesis submitted to the Department of Chemistry, St. Joseph's College, Philadelphia 31, Pennsylvania, in partial fulfillment of the requirements for the degree of Master of Science. (b) Professor of Chemistry, St. Joseph's College, Philadelphia 31, Pennsylvania. (c) Eastern Utilization Research and Development Division, Philadelphia 18, Pennsylvania.

(4) Identified by Dr. E. Matuda, Instituto Biologico, University of Mexico, Villa Obregón, Mexico, D. F.

(5) M. E. Wall, C. R. Eddy, M. L. McClennan, and M. E. Klumpp, *Anal. Chem.*, **24**, 1337 (1952).

(6) R. N. Jones, E. Katzenellenbogen, and K. Dobriner, *J. Am. Chem. Soc.*, **75**, 158 (1953).

(7) R. N. Jones, P. Humphries, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **73**, 3215 (1951).

(8) C. R. Eddy, M. E. Wall, and M. K. Scott, *Anal. Chem.*, **25**, 266 (1953).

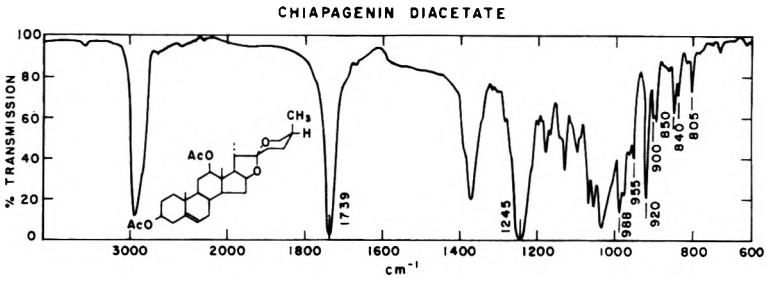

Figure 1

was confirmed by the high negative optical rotation.[9]

The entire structure of chiapagenin was established by two independent paths. Catalytic hydrogenation of chiapagenin gave a normal sapogenin

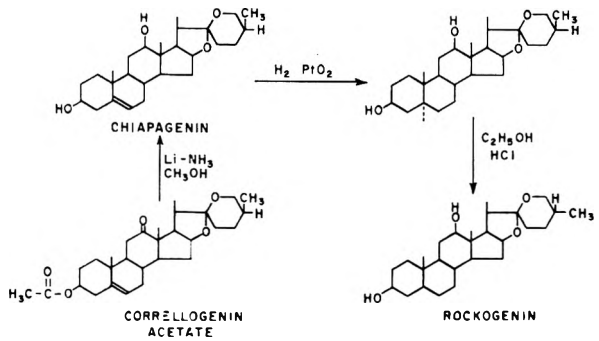

Figure 2

with the 5α-ring A/B fusion. This compound was not further characterized but was subjected to prolonged heating at reflux temperature in ethanolic hydrochloric acid. This is the well known iso reaction which converts normal sapogenins with the axial methyl group to the corresponding isosapogenin (25 D) with the more stable equatorial methyl group.[10] The crude reaction product was chromatographed and the major product, after acetylation, was shown to be rockogenin diacetate,[11,12] identical with an authentic specimen. As the iso reaction inverts only the asymmetric center at C_{25},[10] and as under the experimental conditions used catalytic hydrogenation affects only the Δ^5 moiety,[13] chiapagenin must be 12β-hydroxyyamogenin.

The second independent proof of structure involved the normal Δ^5-12-keto sapogenin correllogenin,[14] which was reduced with lithium metal in liquid ammonia in the presence of methanol.[15] This reaction when applied to hindered ketones gives the most stable hydroxyl[15] which, in the case of the 12-ketone, should be the equatorial 12β-hydroxyl group. In accordance with this prediction, correllogenin acetate reduced in the above manner gave chiapagenin in excellent yield.

Steroidal sapogenins with a 12-hydroxyl group are of rare occurrence in nature. The only examples to date are rockogenin[11] and agavogenin,[11] which occur in a limited group of *Agave* species and are 5α,12β-hydroxysapogenins with the iso side chain. The isolation from *D. chiapasensis* Matuda of chiapagenin represents the first case of a 12-hydroxy sapogenin to be found in this genus. Oxygenation at C_{12} of any type is rare in the *Dioscorea*. In contrast to the *Agave* genus, where many species contain the 12-keto sapogenins hecogenin and/or manogenin,[11] the 12-ketones gentrogenin and correllogenin have to date been found only in *D. spiculiflora*.[14]

EXPERIMENTAL

Melting points were obtained with a Kofler[16] micro melting-point apparatus. Optical rotations were determined in chloroform solution. Infrared spectra were obtained with a Perkin-Elmer Model 21 double beam spectrophotometer with sodium chloride prism and cells.

Isolation of chiapagenin. Tubers of *D. chiapasensis* Matuda were collected[17] at the Finca Monte Bella of Sr. Cristobal above San Sebastian, Guatemala. The sample was received dry and was ground to give 5.2 kg. of dry material. This material was boiled, with stirring, for 1 hr. with two separate 5-gallon portions of 70% isopropyl alcohol, the extract being drawn off each time; 5 gallons of 90% isopropyl alcohol was used for the third extraction. These alcoholic extracts were combined and concentrated by distillation to 8.6 l. which was refluxed 4 hr. with 1.3 l. of concd. hydrochloric acid. The crude precipitate was filtered, washed with 10 l. of 5% sodium bicarbonate solution followed by 6 l. of water, and the solids dried in a forced-air oven. This material was extracted in a soxhlet extractor with 4 l. of heptane for 60 hr. The heptane solution of crude sapogenins was concentrated by distillation to 700 ml. and after standing at room tem-

(9) D. H. R. Barton and W. Klyne, *Chem. & Ind. (London)*, 755 (1948).

(10) For a comprehensive review of the iso reaction, *cf.* Fieser and Fieser, *Steroids*, Reinhold Pub. Corp., New York, 1959, pp. 818–22.

(11) R. E. Marker *et al.*, *J. Am. Chem. Soc.*, 69, 2167 (1947).

(12) R. Hirshmann, C. S. Snoddy, Jr., C. F. Hiskey, and N. L. Wendler, *J. Am. Chem. Soc.*, 76, 4013 (1954).

(13) M. E. Wall, and S. Serota, *J. Am. Chem. Soc.*, 78, 1747 (1956).

(14) H. A. Walens, S. Serota, and M. E. Wall, *J. Am. Chem. Soc.*, 22, 182 (1957).

(15) F. Sondheimer, O. Mancera, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, 75, 1282 (1953).

(16) Specification of brand names of equipment and material used does not imply endorsement over similar commercial products.

(17) Tubers were collected by Dr. Ernest P. Imle, present address, Director of Research, American Cocoa Research Institute, 1741 K Street, N.W., Washington, D. C.

perature for several days 3.8 g. of crude crystalline material was deposited. This was chromatographed on a Florisil column using benzene as solvent. The benzene eluates gave 1.4 g. of a monohydroxy sapogenin. This material (0.2 g.) was refluxed for 30 min. in 5 ml. of acetic anhydride in pyridine (1:1). The solution was evaporated to dryness *in vacuo* and the residue recrystallized from methyl alcohol to give needles, m.p. 194–197°. These crystals were identified as yamogenin acetate by comparison of its infrared spectra with that of an authentic specimen. Elution with benzene-chloroform (1:1) and chloroform gave 1.8 g. of chiapagenin which, after recrystallization from methyl alcohol, melted at 249–251°, $[\alpha]_D^{24°}$ −126°.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.25 H, 10.06.

Acetylation of 0.2 g. of chiapagenin, as in the previously described manner, and recrystallization of the product from methyl alcohol yielded 0.14 g. rectangular needles, m.p. 191–193°, $[\alpha]_D^{24°}$ −127°. The infrared spectrum shows strong bands at 1739 and 1245 cm.$^{-1}$ (acetate carbonyl and —C—O—C— stretching respectively) and bands at 988 and 920 (strong), 900 and 850 (weak) cm.$^{-1}$, all four bands attributed to the normal spiroketal system. Bands at 840 and 805 cm.$^{-1}$ are due to Δ^5 unsaturation.

Anal. Calcd. for $C_{31}H_{46}O_6$: C, 72.34; H 9.01. Found: C, 72.65; H, 9.22.

Conversion of chiapagenin to rockogenin. A 0.272-g. sample of chiapagenin was dissolved in a solution of 100 ml. of a 5% solution of glacial acetic acid in ethyl alcohol to which was then added 0.272 g. of platinum oxide. The mixture was hydrogenated at 3 atm. for 21 hr. at room temperature. The platinum was filtered and all the solvent removed *in vacuo*. Infrared analysis showed the double bond had been saturated (absence of 805 and 840 cm.$^{-1}$ bands). The white amorphous looking material which resulted was dissolved in 47 ml. of absolute ethyl alcohol. Concentrated hydrochloric acid (7 ml.) was then added and the resulting solution was refluxed 48 hr. Solvent was removed *in vacuo* and the residue chromatographed on a Florisil column using benzene as solvent. Elution with chloroform gave a glass which on crystallization from acetone yielded 60 mg. of crystals. This crystalline fraction was acetylated in the usual manner and gave crystals from methyl alcohol, m.p. 200–203. The infrared spectrum was identical with that of authentic rockogenin diacetate.

Conversion of correllogenin to chiapagenin. A 0.33-g. sample of correllogenin acetate was dissolved in a mixture of 5 ml. of anhydrous ether and 5 ml. of anhydrous tetrahydrofuran in a 100 ml. two-necked round bottomed flask. The solution was added, with continued stirring, to a solution of liquid ammonia (25 ml.) containing 5 ml. of methyl alcohol. Lithium wire, 0.2 g., cut in small pieces, was added rapidly. After 5 min. 2.0 g. of ammonium chloride was added and the evaporation of ammonia was hastened by a warm water bath. Water (50 ml.) was then added and the aqueous slurry extracted twice with 20-ml. portions of methylene chloride. The solvents were evaporated and the residue acetylated, using the procedure previously described, to yield 0.21 g. of short rectangular needles from methyl alcohol, m.p. 191–193°, and an infrared spectrum identical with that of natural chiapagenin diacetate.

Acknowledgment. We gratefully acknowledge the assistance, in many botanical matters, of Dr. Bernice G. Schubert, Botanist of the Plant Introduction Section, Crops Research Division, U. S. Department of Agriculture, Beltsville, Maryland. We thank Miss Oksana Panasiuk for carbon and hydrogen analyses and Mr. Carl T. Leander, Jr., under the supervision of Dr. C. Roland Eddy, for the infrared spectra. We wish to express our deep appreciation to Dr. J. J. Willaman, formerly Chief of the Plant Products Laboratory, Eastern Utilization Research and Development Division, for his inspiring leadership and for his help in obtaining the tubers of *Dioscorea chiapasensis* (Matuda).

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1]]

Unique Fatty Acids from *Limnanthes douglasii* Seed Oil: The C_{20}- and C_{22}-Monoenes[2]

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The principal fatty acids of *Limnanthes douglasii* seed oil are shown to include two previously unknown components: *cis*-5-eicosenoic (65%) and *cis*-5-docosenoic acid (7%). The oil also contains *cis*-13-docosenoic (erucic) acid (13%) and 10% of an unknown C_{22}-acid.

Limnanthes douglasii or meadow-foam (fam. Limnanthaceae) is an annual herb native to coastal California and presently cultivated as an ornamental.[3] A recent paper from this laboratory[4] indicated that the seed oil of this species is highly unusual in containing 94% of fatty acids longer than C-18. The present paper will report isolation and characterization of three of the four principal fatty acids of *Limnanthes douglasii* seed oil.

Isolation of pure acids. Gas chromatographic analysis of the methyl esters of the mixed acids from *Limnanthes* oil indicated that the principal components were a C_{20}-monoene, a C_{22}-monoene

(1) One of the laboratories of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) Presented before the Division of Organic Chemistry, 137th Meeting, American Chemical Society, Cleveland, Ohio, April 5–14, 1960.

(3) L. Abrams, *Illustrated Flora of the Pacific States*, Vol. III, Stanford University Press, Stanford, Calif., 1951, p. 46.

(4) F. R. Earle, E. H. Melvin, L. H. Mason, C. H. VanEtten, and I. A. Wolff, *J. Am. Oil Chemists' Soc.*, **36**, 304 (1959).

TABLE I

GAS CHROMATOGRAPHIC ANALYSIS OF METHYL ESTERS OF *Limnanthes douglasii* SEED OIL AND VARIOUS DERIVED FRACTIONS

Percent Acid

Type of Acid	Original Oil	Hydrogenated Oil	Conc. B	Countercurrent Dist. Run I Trans. 310	Countercurrent Dist. Run I Trans. 340	Countercurrent Dist. Run II Trans. 640
C_{10}-sat.	—	tr	tr			
C_{12}-sat.	tr	tr	tr			
C_{14}-sat.	tr	0.1	0.1			
C_{16}-sat.	0.4	0.5	0.1	—	—	
C_{16}-monoene	0.3	—	—			
C_{18}-sat.	0.3	1.7	0.2	—	—	
C_{18}-monoene	1.7	tr	0.4			
C_{18}-diene	0.7	—	—	—	—	
C_{18}-triene	tr	—	—			
C_{20}-sat.	1.0	65	0.7	1.2	0.1	1.1
C_{20}-monoene	65	0.5	66	37.6	97.2	
C_{20}-unknown	0.3	0.3	—		—	
C_{21}-monoene (?)	—	—	tr	0.9		0.4
C_{22}-sat.	—	31	—	—	—	
C_{22}-unknown	10	—	2	—	0.4	
C_{22}-monoene	20	—	30	60.3	2.3	98.5
C_{24}-unknown	<1	—	—			

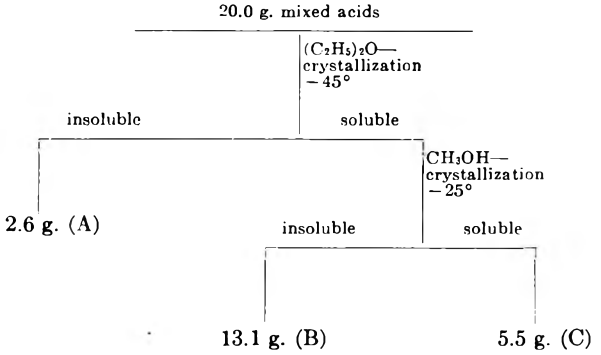

Fig. 1. Low-temperature crystallization of mixed fatty acids of *Limnanthes douglasii* seed oil

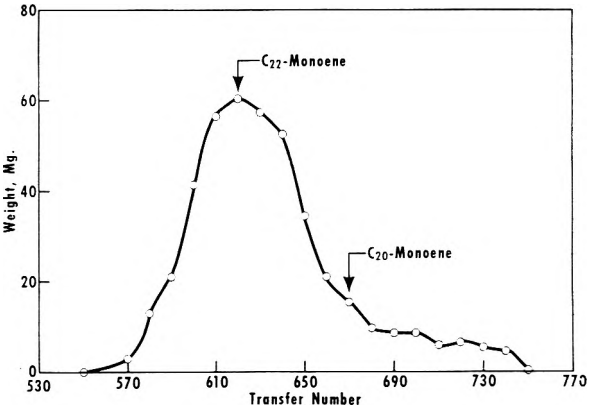

Fig. 2. Countercurrent distribution of methyl esters of *Limnanthes douglasii* seed oil fractions (Run I)

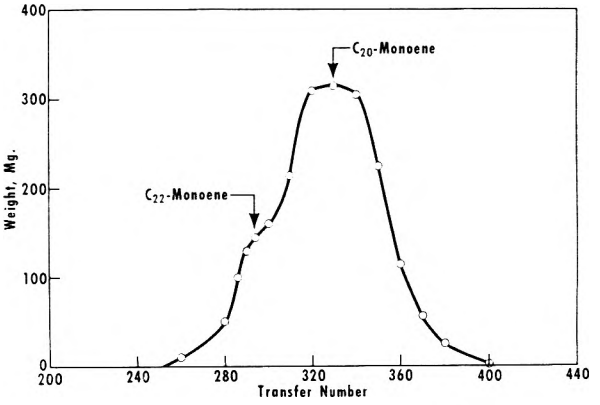

Fig. 3. Countercurrent distribution of methyl esters of *Limnanthes douglasii* seed oil fractions (Run II)

and a C_{22}-"unknown" (see Table I). When the mixed acids were hydrogenated, these unsaturated components were converted to eicosanoic (arachidic) and docosanoic (behenic) acids (Table I). Concentrates of the monoenes (A and B) and of the unknown (C) were obtained by a sequence of low-temperature crystallizations (Fig. 1 and Table I) and by countercurrent distributions (Figs. 2 and 3). Concentrate B from the low-temperature crystallization scheme was shown by gas chromatography to contain 66% C_{20}-monoene and 30% C_{22}-monoene (Table I). A portion of this concentrate B was subjected to countercurrent distribution (Run I) in a 200-tube automatic Craig-Post apparatus. The solvent system acetonitrile-hexane[5] was used and a total of 440 transfers were made by making use of an automatic fraction collector in which two transfers per tube were collected. This treatment effected only a partial resolution of the C_{20}- and C_{22}-monoene components (Fig. 2 and Table I); the C_{22}-monoene appeared as a shoulder on the peak formed by the slower-moving C_{20}-monoene. A concentrate of C_{20}-monoene suitable for structural determination was obtained by pooling material from transfers 342 to 390, having 90 to 97% purity. A C_{22}-monoene concentrate was obtained by pool-

(5) C. R. Scholfield, J. Nowakowska, and H. J. Dutton, *J. Am. Oil Chemists' Soc.*, **37**, 27 (1960).

ing material from appropriate tubes and was further fractionated by countercurrent distribution Run II (Fig. 3 and Table I). A small amount of C_{22}-monoene of *ca.* 98% purity was obtained by combining peak fractions from Run II. The presence of a single double bond in acids from these fractions was confirmed by quantitative hydrogenation or iodine value.

Characterization of monoethenoid acids. The purified C_{20}-monoene was subjected to oxidative cleavage by both the permanganate-periodate method[6] and the older permanganate–acetic acid method.[7] Efforts were concentrated on application of the permanganate–acetic acid technique because of solubility difficulties encountered with the permanganate-periodate method. When separation of the degradation products by steam distillation was attempted in the usual manner, there was obtained in the distillate a very slightly steam-volatile acid, which tended to solidify in the condenser and which unexpectedly proved to be pentadecanoic acid. The identity of this fragment was established by mixed melting point determinations on the free acid and on the *p*-bromophenacyl ester, and also by gas chromatographic analysis. The nonvolatile dicarboxylic acid fragment from the C_{20}-monoene was proved to be glutaric acid. These cleavage products, together with the infrared spectrum (no maxima in the 10–11 μ region), clearly established the structure of the C_{20}-monoene as the previously unknown *cis*-5-eicosenoic acid.

The purified C_{22}-monoene was also cleaved by permanganate-acetic acid oxidation and was shown to be a mixture of two isomers: *cis*-5-docosenoic, another previously unknown acid, in combination with the familiar *cis*-13-docosenoic (erucic) acid. The monobasic acid fragments from the C_{22}-monoene were separated from the dibasic acids by solvent partitioning. Gas chromatographic analysis of the resulting monobasic acid fraction indicated that the principal fragments were nonanoic and heptadecanoic acids in a ratio of about 2:1. Several other fragments were present in small amounts; the work of Begemann and coworkers[7] indicated that the permanganate–acetic acid method suffers from the drawback of formation of secondary degradation products. The nonanoic acid fragment was isolated from the monobasic acid fraction by steam distillation and characterized as a *p*-bromophenacyl ester. The heptadecanoic acid fragment was crystallized from the nonvolatile residue after steam distillation and characterized by mixed melting point determination. A tridecanedioic acid fragment, corresponding to nonanoic acid was isolated from the dibasic acid concentrate and identified by mixed melting point. A glutaric acid fragment, corresponding to heptadecanoic acid, was not isolated in a state of sufficient purity for characterization.

Isolation and partial purification of the C_{22}-unknown have also been accomplished. An account of this work and of structural studies now in progress on this acid will be given in a later paper.

DISCUSSION

The *cis*-5-eicosenoic acid found in *Limnanthes* oil appears to be unique. No other monoethenoid fatty acids with Δ^5-double bonds appear to have been recorded as triglyceride constituents in either the vegetable or animal kingdoms.[8] Two other monoethenoid C_{20}-acids in glycerides have been reported: the 9- and 11-isomers. The occurrence of *cis*-11-eicosenoic acid in a number of vegetable and marine animal oils is well established.[9] In contrast, 9-eicosenoic acid has thus far been found only in animal oils.[10] The melting point of *cis*-5-eicosenoic acid (26–27°) is about four degrees higher than melting points reported for the 9- and 11-isomers.[9b,11] 5-Docosenoic acid is also unique; C_{22}-monoenes in the fatty acid series previously reported as occurring naturally are the 11- and 13-isomers.[9a]

Correlations made by Lovern[12] and by Klenk and Debuch[13] have called attention to certain biogenetic patterns in unsaturated fatty acids. From their observations may be drawn the empirical generalization that double bonds in these acids tend to occur in positions $3n$ carbon atoms removed from one end of the chain (n being a small integer). Thus $n = 3$ for oleic and erucic acids and $n = 4$ for petroselinic acid. 5-Eicosenoic acid conforms to this pattern in the sense of having the integral value $n = 5$, counting the methyl group as C_1. In addition, it is significant that there are natural polyunsaturated C_{20}-fatty acids having

(6) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955); E. von Rudloff, *J. Am. Oil Chemists' Soc.*, **33**, 126 (1956).

(7) P. H. Begemann, I. G. Keppler, and H. A. Boekenoogen, *Rec. trav. chim.*, 69, 439 (1950), and references cited therein.

(8) Human hair oil has been reported to contain several unusual monounsaturated *free* fatty acids, including a 5-tetradecenoic acid [*cf.* A. W. Weitkamp, A. M. Smiljanic, and S. Rothman, *J. Am. Chem. Soc.*, 69, 1936 (1947)]. Note Added in Proof: A recent communication states that human fecal lipids contain several unusual C_{18}-monoethenoid acids, including 5-octadecenoic acid [*cf.* A. T. James, J. P. W. Webb, and T. D. Kellock, *Biochem. J.*, 74, 21P (1960)].

(9) (a) T. P. Hilditch, *Chemical Constitution of Natural Fats*, 3rd Ed., John Wiley & Sons, New York, 1956; (b) C. Y. Hopkins, M. J. Chisholm, and J. Harris, *Can. J. Res.*, **27B**, 35 (1949), and subsequent papers by Hopkins and Chisholm.

(10) Y. Toyama and T. Tsuchiya, *J. Soc. Chem. Ind., Japan*, **37**, Suppl. binding 14 (1934); *Chem. Abstr.*, **28**, 2208 (1934); W. Bergmann, S. M. Creighton, and W. M. Stokes, *J. Org. Chem.*, **21**, 721 (1956).

(11) B. W. Broughton, R. E. Bowman, and D. E. Ames, *J. Chem. Soc.*, 671 (1952).

(12) J. A. Lovern, *J. Sci. Food Agr.*, 9, 773 (1958).

(13) E. Klenk and H. Debuch in *Annual Reviews of Biochemistry*, Vol. 28, ed. by J. M. Luck *et al.*, Annual Reviews, Inc., Palo Alto, Calif., 1959, p. 39.

Δ^5-double bonds, *e.g.* the nutritionally essential 5,8,11,14-eicosatetraenoic (arachidonic) acid. Certain exceptions to this widespread biogenetic scheme are known, including 11-octadecenoic (vaccenic) acid and the Δ^4-unsaturated acids of the Lauraceae.[12] 5-Docosenoic acid, in common with these exceptions, does not conform to any biogenetic pattern that is now apparent.

EXPERIMENTAL

General methods. The gas chromatographic analyses were carried out with a Burrell Kromatog K-5 instrument.[14] The columns were U-shaped glass tubings 1.25 to 2.75 m. in length and $^1/_8$- to $^1/_4$-inch inner diameter, packed with LAC-2-R-446 (a polyester of diethylene glycol-pentaerythritol and adipic acid) or Apiezon L (a hydrocarbon grease) supported by Johns-Manville Celite 445. The carrier gas was helium and the operating temperature ranged from 185 to 250°, depending on the sample. For quantitative determination of composition, the areas under peaks were measured by the instrument's automatic integrator. Mixtures of acids were analyzed in the form of their methyl esters.

Except where otherwise noted, methyl esters were prepared by refluxing the desired mixture of acids 1 hr. in excess 1% sulfuric acid in methanol. Esters were isolated by ether extraction in the usual way; unchanged acids were removed by washing the ethereal solutions of esters with 5% potassium carbonate. When required for characterization work, fractionated esters were saponified by refluxing 1 hr. with 0.8*N* ethanolic potassium hydroxide.

Preparation of mixed fatty acids. Coarsely ground seeds of *Limnanthes douglasii* were extracted overnight in a Soxhlet apparatus with petroleum ether (b.p. 30–60°). The bulk of the solvent was evaporated on a steam bath under a nitrogen atmosphere, and the remainder was removed *in vacuo* with a rotating evaporator. The infrared spectrum of this oil showed no *trans* C=C adsorption (10.3 μ).

A 37.6-g. portion of *Limnanthes* oil was refluxed 30 min. with 240 ml. of 2*N* ethanolic potassium hydroxide under a nitrogen atmosphere. The resulting solution was diluted with water and extracted with ether. Combined ether extracts were, in turn, extracted by water which was combined with the original alkaline liquor. Free fatty acids (35.0 g.) were obtained by acidification of the alkaline liquor and extraction with ether. A sample of methyl esters was prepared for gas chromatographic analysis by esterification with diazomethane (see Table I).

A portion of these mixed fatty acids were hydrogenated in ethanol with platinum oxide catalyst at room temperature and atmospheric pressure. The saturated acids, as well as the methyl esters prepared from them, were white crystalline solids (see Table I).

Low-temperature crystallizations (Fig. 1). Mixed fatty acids (20.0 g.) were dissolved in 440 ml. of ether and the solution was cooled slowly to −45°. After standing 2 hr., the filtrate was removed with a filter stick. The solid was redissolved in 117 ml. and cooled to −46° for 2 hr., yielding 2.551 g. of crystals (fraction A), m.p. 25–26.5°, iodine number 77. Gas chromatographic analysis of similarly prepared material indicated 90% C_{20}-monoene and 6% C_{22}-monoene.

Combined mother liquors from crystallizations of fraction A were evaporated and the resulting residue was crystallized from 360 ml. of methanol; 14.5 g. of solid was obtained after keeping the solution at −25° for 2 hr. This product was similarly crystallized from 360 ml. of methanol, and a yield of 13.1 g. of solid (fraction B) resulted, iodine value 89 (see Table I for gas chromatographic analysis of a similarly prepared fraction).

The combined mother liquors from crystallizations of fraction B yielded 5.5 g. of liquid (fraction C), iodine number 125. According to gas chromatographic analysis, a similarly prepared fraction contained 37% C_{20}-monoene, 10% C_{22}-monoene, and 40% C_{22}-"unknown."

Fractionation by countercurrent distribution. (a) *Run I. Isolation of C_{20}-monoene.* Fraction B was esterified as described under Methods. Methyl esters thus obtained (10.0 g.) were subjected to a 440 transfer countercurrent distribution in a 200-tube Craig-Post apparatus. The solvent system used was mutually saturated acetonitrile and hexane[5] (8 to 1); 40 ml. of acetonitrile was placed in each of the 200 tubes. The methyl esters to be distributed were divided evenly among the first five tubes. The automatic operation of the instrument introduced 5 ml. of equilibrated hexane to tube 0 at each transfer stage. As hexane upper layers progressed past tube 200, they were decanted into an automatic fraction collector, combining two transfers per tube, and successively collected until 240 upper phases had been withdrawn. The weight curve obtained by evaporating solvent from contents of the various tubes is indicated in Fig. 2. Gas chromatographic analyses of selected tubes are indicated in Table I. On the basis of these analyses, contents of tubes 342–378 and 312–340 were combined and saponified to afford C_{20}-monoene for structural elucidation. Combined acids from transfers 342–378 had an iodine value of 83.0; calculated for one double bond, 81.8. A portion of combined acids from transfers 342–378 was hydrogenated in ethanol with platinic oxide catalyst at room temperature and atmospheric pressure. The product obtained by filtration and evaporation melted at 74° without recrystallization; the mixed melting point with authentic eicosanoic (arachidic) acid was 74–75°. Material from transfers 264–310, richest in C_{22}-monoene, was combined.

(b) *Run II. Isolation of C_{22}-monoene.* Material from transfers 264–310, Run I, was subjected to a second distribution in the same manner, except that the material was recycled so that a total of 770 transfers were made. The weight curve obtained is given in Fig. 3. Gas chromatographic analysis of the peak tube (transfer 640) is shown in Table I. Material from transfers 576–640 was combined and saponified for structural elucidation. These combined acids (0.0472 g.), when hydrogenated quantitatively with platinum oxide in ethanol (room temperature, 1 atm.), absorbed 0.85 mole of hydrogen. The hydrogenated product, 0.0393 g., melted at 71–78°. On recrystallization from ether-hexane, 0.016 g. was obtained, m.p. 78.5–79.5°; the mixed melting point with authentic docosanoic (behenic) acid was 78.5–79.5°.

Permanganate-periodate oxidation of C_{20}-monoene.[6] A 0.063-g. portion of C_{20}-monoene (97% pure) and 0.083 g. of potassium carbonate were dissolved in 40 ml. of water. To this was added 1.0 ml. of 0.04*M* potassium permanganate and 0.334 g. of sodium periodate in 40 ml. of water. The mixture was stirred 24 hr., then reduced with sodium metabisulfite, acidified with hydrochloric acid, and extracted with ether. The mixed acids obtained by this oxidation were esterified without fractionation and analyzed by gas chromatography. Pentadecanoic acid constituted 80% of the total monocarboxylic acids found. As the only dicarboxylic acid found was glutaric acid, it seems likely that the shorter chain monocarboxylic acids were secondary degradation products.

Permanganate-acetic acid oxidation of C_{20}-monoene.[7] C_{20}-monoene concentrate (1.09 g.) was dissolved in 20 ml. of purified acetic acid. Finely ground potassium permanganate (8 g.) was added in portions over a period of several hours, during which the mixture was stirred continuously. The temperature did not exceed 40°. The mixture was diluted with water after standing overnight, reduced with sodium metabisulfite, and acidified with hydrochloric acid. The strongly acid solution was extracted repeatedly with ether. The ether was largely removed from the combined extracts

(14) The mention of trade names or products does not constitute endorsement by the Department of Agriculture over those not named.

by distillation and the residue steam distilled 5 hr. During this time, a solid acid distilled over very slowly and incompletely. Undistilled acids were recovered from the aqueous liquor by extraction with ether and by evaporation of combined extracts. The residue thus obtained was triturated repeatedly with petroleum ether (b.p. 30–60°). The soluble portion was filtered to remove traces of suspended insoluble matter (dicarboxylic acid fragments). Upon evaporation, the petroleum ether extracts yielded 0.431 g. of monocarboxylic acid; an additional 0.182 g. was obtained from the steam distillate by extraction with ether. This cleavage fragment (0.034 g.) was recrystallized from aqueous methanol: 0.019 g. was obtained, m.p. 48–49°[15]; there was no depression on admixture with authentic pentadecanoic acid (m.p. 48–51°). A 0.123-g. portion was converted to the *p*-bromophenacyl ester. A yield of 0.116 g. of product was obtained, m.p. 68–72°; this yielded on recrystallization from aqueous ethanol 0.076 g., m.p. 75–76°; there was no depression on admixture with authentic *p*-bromophenacyl pentadecanoate (m.p. 75–77°).

The acidic aqueous liquors from the original oxidation mixture and those from the steam distillation were combined and extracted continuously with ether. A crude dicarboxylic acid fragment (0.172 g.) was obtained from the extract. Upon recrystallizing this from chloroform, 0.074 g. was obtained, m.p. 90–94°. Three additional recrystallizations from chloroform or chloroform-benzene had little effect on the melting point, but there was no depression when mixed with authentic glutaric acid (m.p. 96–97°). The identity of this fragment as glutaric acid was confirmed by x-ray diffraction.

The glutaric acid fragment was obtained in a purer form when the C_{20}-monoene was subjected to permanganate-periodate cleavage by the general procedure of Lemieux and von Rudloff.[6] Crude acid (0.056 g.), m.p. 86–90°, was recrystallized once from chloroform; a specimen was obtained having m.p. 94–95°. There was no depression of melting point on admixture with authentic glutaric acid. The permanganate-periodate method was abandoned, however, because of the limited solubility of the acid in the oxidizing medium.

Pure cis-5-eicosenoic acid. A 0.110-g. portion of acid, obtained by saponification of combined transfers 342–378, m.p. 26–27° (*ca.* 97% pure 5-eicosenoic acid—see Table I), was recrystallized twice from aqueous methanol without observable change in melting point. Its infrared spectrum showed no *trans* C=C absorption (10.3 μ).[16]

Anal. Calcd. for $C_{20}H_{38}O_2$: C, 77.4; H, 12.3. Found: C, 77.3; H, 12.6.

Permanganate-acetic acid oxidation of C_{22}-monoene. C_{22}-monoene concentrate (0.99 g.) was oxidized essentially as described for the C_{20}-monoene. Combined ether extracts from the bisulfite-reduced, acidified oxidation medium were concentrated so as to remove most of the solvent. The residue was dissolved in 30 ml. of methanol and 3 ml. of water. The resulting solution was extracted four times with 30-ml. portions of petroleum ether (b.p. 30–60°). The combined petroleum ether extracts were dried over sodium sulfate and evaporated, yielding 0.280 g. of semisolid, a concentrate of monocarboxylic acids. Upon evaporation, the aqueous methanol yielded 0.602 g. of dicarboxylic acids as a waxy solid.

Gas chromatographic analysis of the monocarboxylic acid concentrate indicated two principal fragments: nonanoic acid (27.8%) and heptadecanoic acid (21.9%). A portion (0.280 g.) of this material was separated by steam distillation. Nonanoic acid (0.067 g.) obtained by ether extraction of the distillate was converted to a *p*-bromophenacyl ester. The crude yield was 0.020 g., m.p. 50–54°. After two recrystallizations from aqueous ethanol and one from hexane, this derivative melted at 60–63°; the melting point was undepressed on admixture with authentic *p*-bromophenacyl nonanoate.

The nonvolatile monocarboxylic acid (0.110 g.) was obtained as a semisolid by petroleum ether extraction of the aqueous residue from steam distillation. After three recrystallizations from methanol, this acid melted at 54–58°, undepressed on admixture with authentic heptadecanoic acid (m.p. 56–59°). A considerable depression (m.p. 48–62°) was observed on admixture with palmitic acid (m.p. 62°).

The dicarboxylic acid concentrate obtained by cleavage of the C_{22}-monoene was dissolved in 10 ml. of chloroform. This solution was extracted repeatedly with 10-ml. portions of water, dried with sodium sulfate, and evaporated. A solid (0.111 g.), m.p. 77–95°, was obtained. This material was recrystallized twice from chloroform-hexane and once from aqueous ethanol; a sample was obtained, m.p. 110–111°; there was no depression on admixture with authentic tridecanedioic (brassylic) acid (m.p. 111–112°).

Combined acidified aqueous extracts from chloroform-water partitioning were extracted with ether. The product thus obtained, presumably containing glutaric acid, was not satisfactorily characterized.

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(15) Melting points were determined by a Fisher-Johns block and are uncorrected.

(16) Infrared spectra were measured as films on silver chloride plates with a Perkin-Elmer model 21 rock salt spectrophotometer.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

The Ultraviolet Absorption Spectra of Hydrazones of Aromatic Aldehydes

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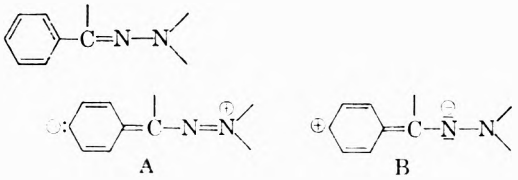
Ultraviolet absorption spectra are reported for a variety of hydrazones of benzaldehyde, substituted both on the terminal nitrogen and in the ring. The spectral features accord with the suggestion that the hydrazone group (>C=N—N<) is a strong electron-donor. *N*-alkyl- and *N*-acylhydrazone groups are also electron-donors. A close parallel exists between the spectral relationships of the aniline-acetanilide series, on the one hand, and the benzaldehyde hydrazone–benzaldehyde acylhydrazone series on the other. Explanations of properties of hydrazones based on assumptions of electron-withdrawal by the hydrazone group are shown to be unnecessary.

Benzaldehyde hydrazone and its derivatives which bear alkyl or acyl groups on the terminal nitrogen and no more than one nuclear substituent, have simple ultraviolet absorption spectra, characterized by two maxima, one in the region of 220–250 mμ, the other at longer wave lengths, 270–400 mμ. Benzophenone hydrazone and its nuclear-substituted derivatives have similar spectral features. When alkyl groups are introduced on the terminal nitrogen of benzaldehyde hydrazone, bathochromic and hyperchromic displacements are observed. This effect has been explained by invoking resonance forms of type A.[2] To explain the effect of ring substituents on the ultraviolet absorption spectra[3] and basicities[4] of a series of benzophenone hydrazones, resonance forms of type B have been used as well as those of type A. The latter would be aided by electron-withdrawing groups in the *ortho* and *para* positions, while the former would be favored by electron-donating substituents in the *ortho* and *para* positions.



A B

The earlier work dealt only with the effect of substituents on the terminal nitrogen of benzaldehyde hydrazone, while the later work was concerned only with the effects of nuclear substituents in a series of benzophenone hydrazones. While the two series would be expected to parallel each other fairly closely, it would be of interest to compare the effects of substituents on the terminal nitrogen and in the nucleus of one series of compounds. In the course of studies on the chemistry of hydrazines we have prepared a number of hydrazones of benzaldehyde and its nuclear-substituted derivatives. For the present study we have determined the ultraviolet absorption spectra of these materials, as well as additional hydrazones which together form a series in which the substituents on the ring and the terminal nitrogen have been systematically varied.

The results, summarized in Table I (with additional data from the literature), show that the hydrazone group (>C=N—N<) is a strong electron-donating group, in the sense of formula A. The *N*-alkyl hydrazones are in the same class, the alkyl groups facilitating electron-release. The spectral changes, which accompany changes in the substituents *para* to the hydrazone or alkylhydrazone groups, are closely related to the changes observed when substituents *para* to the more familiar electron-donating groups are varied.[5] In the case of the hydrazones considered here, the in-

(1) Present address: Union Carbide Research Institute, 32 Depot Plaza, White Plains, N. Y.

(2) D. Todd, *J. Am. Chem. Soc.*, **71**, 1353 (1949).

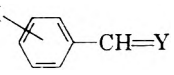
(3) H. H. Szmant and C. McGinnis, *J. Am. Chem. Soc.*, **74**, 240 (1952).

(4) H. F. Harnsberger, E. L. Cochran, and H. H. Szmant, *J. Am. Chem. Soc.*, **77**, 5048 (1955).

(5) L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, 69, 2714 (1947). The two bands which are observed in most of the spectra of hydrazones appear to be the displaced first and second primary bands of benzene, as described by Doub and Vandenbelt. Following their terminology, the band of longer wave length is referred to as the first primary band and that of shorter wave length as the second primary band. Throughout the discussion, references to displacements of peaks mean the first primary band, for which more data are available. The second primary bands show similar but smaller displacements. In their work the two primary bands were present (and the secondary band was absent) when the *para* substituents were of opposite and fairly strong electronic types (e.g. methoxyl and carbonyl).

Whether the bands of long and short wave length in the spectra of a series of *p*-disubstituted benzenes are in fact related to each other as first and second primary bands can be determined by the general method of G. N. Lewis and M. Calvin [*Chem. Rev.*, 25, 273 (1939)], as applied to the benzene case by W. D. Kumler [*J. Am. Chem. Soc.*, 68, 1184 (1946)]. This method states that the relationship is established if (1) the ratio of wave lengths of the first primary band (λ) to the second primary band (λ') is always less than 2 and increases as λ increases, and (2) the ratio of molar absorbancy indices ϵ'/ϵ decreases as λ increases. These criteria were adhered to sufficiently in the spectra of the hydrazones to serve as tentative establishment of the relationship. The hydrazones bearing nitro groups were anomalous although consistent within themselves. (Both Doub and Vandenbelt and Kumler have remarked the spectral anomalies introduced by nitro groups.) Furthermore, the semicarbazones do not fit the pattern established by the hydrazones, but are consistent within their own group.

TABLE I

ABSORPTION MAXIMA[a] OF AROMATIC ALDEHYDES AND HYDRAZONES: 

X	Y				
	O	NNH_2	$NNHCH_3$	$NN(CH_3)_2$	$NNHCONH_2$
p-$(CH_3)_2N$	342(4.47)[b]	--	312[c]	313(4.40)	334(4.34)
		—	225[c]	223(3.99)	233(4.02)
p-CH_3O	277(4.17)[d]	281[e]	284(4.32)	291(4.31)	292(4.35)[e]
		—	sh 215(4.08)	sh 218(3.95)	[f]
H	246(4.12)[g]	273(4.07)[h]	285(4.12)[h]	297(4.21)[h]	283(4.30)[i]
		[f]	[f]	[f]	[f]
m-NO_2	257(3.87)[j]	268(4.30)[i]	294(4.27)	—	284(4.30)[i]
		[f]	210(4.20)	—	[f]
p-NO_2	268(4.02)[j]	343(4.10)	374(4.26)	392(4.28)[k]	328(4.20)[i]
		237(3.89)	246(4.01)	250(3.93)	[f]
p-CN	257(3.98)	306(4.31)	326(4.29)	—	303(4.47)
		226(3.96)	235(3.98)	—	218(4.14)
p-CH_3SO_2	243(3.96)	299(4.27)	320(4.39)	—	298(4.45)
		225(4.12)	227(3.96)	—	222(4.18)

[a] The solvent for the hydrazones was 95% ethanol; absolute ethanol was required to dissolve the semicarbazones. Figures in parentheses are values of log ϵ. [b] W. D. Kumler, *J. Am. Chem. Soc.*, **68**, 1184 (1946). [c] Log ϵ not determined. [d] R. A. Morton and A. L. Stubbs, *J. Chem. Soc.*, **1940**, 1347. [e] M. Ramart-Lucas and J. Klein, *Bull. soc. chim.*, [5], **16**, 454 (1949). [f] Portion of spectrum reported included only higher λ_{max}. [g] R. P. Mariella and R. R. Raube, *J. Am. Chem. Soc.*, **74**, 521 (1952). [h] D. Todd, *J. Am. Chem. Soc.*, **71**, 1353 (1949). [i] P. Grammaticakis, *Bull. Soc. chim.*, [5], **17**, 690 (1950). [j] P. Grammaticakis, *Bull. soc. chim.*, [5], **20**, 821 (1953). [k] For p-$NO_2C_6H_4CH{=}NN(CH_3)CH_2C_6H_5$ λ_{max} = 253,388 mμ; log ϵ = 4.04, 4.34 [R. L. Hinman, *J. Am. Chem. Soc.*, **78**, 2463 (1956)].

creased length of the resonating system causes both primary bands to be present when only the hydrazone group is on the ring (benzaldehyde hydrazone). No other nuclear substituent is necessary. Thus, the introduction of other electron-donating groups *para* to the hydrazone group causes only small displacements of the first primary band (λ) compared to that of the corresponding unsubstituted hydrazone. (Or, looking at it from the other end of the molecule, when an electron-donating group, such as methoxyl or dimethylamino is on the ring, increasing the electron-donating ability of the hydrazone group in the *para* position (by putting alkyl groups on the terminal nitrogen) causes but slight bathochromic shifts compared to the unmethylated hydrazone with the same nuclear substituent.) When electron-withdrawing groups are *para* to the hydrazone group, large bathochromic shifts are observed relative to benzaldehyde hydrazone, and the introduction of methyl groups on the terminal nitrogen causes large shifts toward the red.

These results are foreshadowed in the spectral changes which occur when the electron-withdrawing formyl group of the aldehyde is converted to the electron-donating hydrazone group. With electron-withdrawing groups on the ring, the conversion of aldehyde to hydrazone is accompanied by large bathochromic shifts of the first primary band. When electron-donating substituents are on the ring, however, the spectral changes are only slightly bathochromic (methoxyl), or actually hypsochromic (dimethylamino).[6]

(6) Similar effects are observed in the benzophenone series (ref. 3.)

The semicarbazones form an interesting class because the carbamyl group should withdraw electrons from the terminal nitrogen. It might be expected then that polarization of type B would be favored. If this were the case, however, it would be difficult to explain why the semicarbazones of aldehydes absorb at longer wave lengths than the aldehydes themselves, even when an electron-donating substituent (methoxyl) is in the *para* position. (The formyl group should withdraw electrons more effectively than the semicarbazone group.) These problems are not encountered if it is assumed that the semicarbazone group, like the hydrazone group, donates electrons, but less effectively than the latter.

An interesting parallel can be drawn between the hydrazone-semicarbazone pair and the aniline-acetanilide pair. The bathochromic shift and increased absorption of the high intensity band observed in passing from aniline to acetanilide has been ascribed to the extension of the conjugated system.[7] Similar spectral effects are observed when the terminal nitrogen of benzaldehyde hydrazone is substituted by a carbamyl group.[8] Conversion of p-methoxy-[7] or p-dimethylaminoaniline[9] to the corresponding acetanilide is also accompanied by bathochromic and hyperchromic displacements.

(7) H. E. Ungnade, *J. Am. Chem. Soc.*, **76**, 5133 (1954).

(8) Substitution of the terminal nitrogen by an acyl group effects a similar spectral change. Thus, for C_6H_5CH = NNHY, when Y = $CONH_2$, λ_{max} = 283 (log ϵ 4.30); when Y = $COCH_3$, λ_{max} = 280 (log ϵ 4.30); Y = COC_6H_5, λ_{max} = 295 (log ϵ 4.35) [P. Grammaticakis, *Bull. soc. chim.*, (5), **17**, 690 (1950)].

(9) P. Grammaticakis, *Bull. soc. chim.*, (5), **18**, 531 (1951).

Similar shifts occur in passing from the hydrazone to the semicarbazone of a correspondingly nuclear-substituted benzaldehyde. When aniline bears an electron-withdrawing group in the *para* position, it absorbs at longer wave lengths than the corresponding acetanilide, although the intensity of absorption of the anilide is frequently the larger of the two (e.g. *p*-aminobenzoic acid,[5] λ_{max} 284, ϵ 14000; *p*-*N*-acetylaminobenzoic acid,[7] λ_{max} 270, ϵ 21,200). These changes are paralleled closely by those in a hydrazone-semicarbazone pair, substituted by electron-withdrawing groups. It is concluded, therefore, that the semicarbazone group (or any *N*-acylhydrazone group) donates electrons, like the acetylamino group and, like the latter, has less tendency to do so than the corresponding unacylated amino form.

When both an acyl group and a methyl group are on the terminal nitrogen, the value of λ_{max} is that observed when the acyl group alone is present plus a small increment for the effect of the methyl group. Thus, with *p*-nitrobenzaldehyde the methylhydrazone has λ_{max} 374 mμ, the acetylhydrazone,[8] λ_{max} 320 mμ, and the *N*-methyl-*N*-acetylhydrazone,[10] λ_{max} 327 mμ. Ramart-Lucas has reported a similar effect of introducing an acyl group in compounds such as anisaldehyde phenylhydrazone and anisaldehyde 1-acetyl-1-phenylhydrazone.[11]

It is interesting that the parallel between the aniline-acetanilide and hydrazone-acylhydrazone pairs breaks down at this point, for introduction of a methyl group in acetanilide causes a drop in both λ_{max} and ϵ from 242 mμ (14,400) for acetanilide[7] to 228 mμ (6000) for *N*-methylacetanilide.[12] A similar effect is observed when *p*-chloroacetanilide is converted to the *N*-methyl derivative.[9] This decrease, which does not seem to have been commented upon, is probably due to steric inhibition of resonance. The acetyl group would be about equivalent to an isopropyl group, which together with the methyl, might cause some interference with planarity due to hindrance at the *o*-hydrogens. The presence of two large alkyl groups on the anilino nitrogen has been shown to have this sort of effect on the ultraviolet spectrum,[13] and additional evidence can be found in the base strengths of *N*,*N*-dialkylanilines. Hindrance to planarity is evident even in *N*,*N*-diethylanilines.[14] The suggestion that steric interference exists in the *N*-methylacetanilides is supported by the spectra of the closely related phenylcyanamides. Phenylcyanamide itself shows λ_{max} 232 mμ, while *N*-methylphenylcyanamide has λ_{max} 235 mμ[15]; *p*-nitrophenylcyanamide: λ_{max} 313 mμ; *N*-methyl-*p*-nitrophenylcyanamide: λ_{max} 313 mμ.[16] The cyanamide group undoubtedly donates electrons like the acetylamino group. However, as the cyano group is much smaller than the acetyl group the steric effects do not appear on introduction of an *N*-methyl group. In the hydrazone series the groups on the terminal nitrogen would be too far removed from the ring hydrogens to interfere with planarity.[17]

In the foregoing discussion it has been shown that the spectral features of the benzaldehyde and related hydrazones can be explained in terms of resonance structure A and *without* invoking formula B. It is also unnecessary to use formula B to explain the increase in basicity observed when benzophenone hydrazone is substituted by an electron-donating group such as methoxyl.[4] Rather, the methoxyl groups merely decrease the ability of the hydrazone group to donate electrons to the ring. *p*-Methoxyaniline is likewise considerably more basic than aniline.[18]

Implicit in the discussion is the idea that hydrazones are like vinylogs of aniline, in both of which the amino group is operating in the same way. The hydrazone group is therefore closely related to the vinylamine group, in which the amino function donates electrons in the same manner.[19]

Styrylamine would of course be a true vinylog of aniline. In this context the oximino group is also closely related, and the limited data available suggest that it probably donates electrons by a similar mechanism. As the ability of *p*-orbitals to overlap for bond formation decreases from nitrogen to oxygen, the oximes should absorb at shorter wave lengths than the hydrazones (just as phenol absorbs at a shorter wave length than aniline), which is in fact observed: benzophenone oxime, λ_{max} 253 mμ,[20] *p*-methoxybenzophenone oxime, λ_{max} 270 mμ,[20] and *p*-nitrobenzophenone oxime, λ_{max} 310 mμ.[21]

(10) R. L. Hinman and D. Fulton, *J. Am. Chem. Soc.*, 80, 1895 (1958).

(11) M. Ramart-Lucas and J. Klein, *Bull. soc. chim.* [5], 16, 454 (1949).

(12) P. L. Southwick, D. I. Sapper, and L. A. Pursglove, *J. Am. Chem. Soc.*, 72, 4940 (1950).

(13) P. Rumpf and G. Girault, *Compt. rend.*, 238, 1892 (1954).

(14) See the chapter by H. C. Brown, D. H. McDaniel, and O. Häfliger in E. A. Braude's *Determination of Organic Structures by Physical Methods*, Academic Press, New York, 1955.

(15) M. G. Seeley, R. E. Yates, and C. R. Noller, *J. Am. Chem. Soc.*, 73, 772 (1951).

(16) R. Huisgen and H. Koch, *Ann.*, 591, 200 (1955).

(17) Throughout the discussion the question of stereoisomerism of the hydrazone groups is ignored. It is assumed that all the compounds studied have the same configuration (presumably with the aldehyde hydrogen and the terminal nitrogen *cis*), not an unreasonable assumption in view of the common method of preparation.

(18) N. F. Hall and M. R. Sprinkle, *J. Am. Chem. Soc.*, 54, 3469 (1932).

(19) N. J. Leonard and V. Gash, *J. Am. Chem. Soc.*, 76, 2781 (1954), and subsequent papers.

(20) P. Grammaticakis, *Bull. soc. chim.*, [5], 8, 427 (1941).

(21) A. Meisenheimer, *Ann.*, 502, 162 (1933).

TABLE II

HYDRAZONES OF NUCLEAR SUBSTITUTED BENZALDEHYDES: X $C_6H_4CH{=}N{-}Y$

X	Y	M.P.	Formula	Calcd.			Found		
				C	H	N	C	H	N
p-$(CH_3)_2N$	$NHCH_3$	50–52°	$C_{10}H_{15}N_3$	67.74	8.53	—	67.41	8.69	—
p-$(CH_3)_2N$	$NHCONH_2$	224°(d)[a]	$C_{10}H_{11}N_4O$	59.10	5.46	—	59.22	5.41	—
p-CH_3O	$NHCH_3$	49–51°	$C_9H_{12}N_2O$	—	—	17.06	—	—	17.41
m-NO_2	$NHCH_3$	65–66°	$C_8H_9N_3O_2$	53.62	5.06	23.45	53.45	4.57	22.50
p-NO_2	$NHCH_3$	99–101°[b]	$C_8H_9N_3O_2$	53.61	5.06	23.43	53.74	5.10	23.65
p-CN	NH_2	66–67°	$C_8H_7N_3$	66.17	4.86	—	66.25	4.52	—
p-CN	$NHCH_3$	96–97°	$C_9H_9N_3$	67.90	4.53	—	67.74	5.03	—
p-CN	$NHCONH_2$	>250°	$C_9H_8N_4O$	57.44	4.28	—	57.36	4.19	—
p-CH_3SO_2	NH_2	149–150°	$C_8H_{10}N_2O_2S$	—	—	14.04	—	—	14.08
p-CH_3SO_2	$NHCH_3$	118–120°	$C_9H_{12}N_2O_2S$	50.94	5.70	—	51.35	5.66	—
p-CH_3SO_2	$NHCONH_2$	226–227°	$C_9H_{11}N_3O_3S$	44.80	4.60	—	45.13	4.38	—

[a] Reported m.p. 224° dec. (cor.) (F. Sachs and L. Sachs, *Ber.*, **38**, 525 (1905)). [b] Reported m.p. 93° (O. L. Brady and G. P. McHugh, *J. Chem. Soc.*, **121**, 1648 (1922).)

EXPERIMENTAL[22]

Hydrazones. With the exception of *p*-anisaldehyde hydrazone, these materials were prepared by the reaction of the aldehyde with a 10–20 fold molar excess of 85% hydrazine hydrate, according to the method of Curtius and Lublin.[23] *p*-Nitrobenzaldehyde hydrazone melted at 135–136° (lit.[23] m.p. 134°).

p-Anisaldehyde hydrazone, which could not be obtained by the above method, was prepared by the reaction of the corresponding azine with a 5-fold molar excess of 85% hydrazine hydrate. This method had been used previously[24] for the synthesis of *m*-methoxybenzaldehyde hydrazone. When the reaction was applied to anisaldehyde azine,[24] however, reaction appeared to take place, as evidenced by the gradual disappearance of the solid azine (and its characteristic yellow color), but after evaporation of the ether extracts of the reaction mixture, only azine was obtained. This experiment was repeated in the present work because it was felt that the azine obtained in the ether extract must have been formed from the desired hydrazone after extraction. The azine is relatively insoluble in ether. As traces of either acid or oxidizing agents will rapidly convert hydrazones of this type (see below under *Stability of Hydrazones*) to azines, the ether was washed with 10% sodium hydroxide, dried, and passed down an alumina column to remove peroxides. When this ether was used for extraction of the reaction mixture, a pale yellow liquid was obtained after evaporation of the solvent *in vacuo*. When exposed to air the product rapidly deposited *p*-anisaldehyde azine as a yellow powder. It was completely converted to the azine on attempted distillation. The spectrum was therefore determined without purification or analysis of the material. The general shape of the spectrum, as well as the mode of synthesis and facile conversion to the azine leave little doubt that the liquid product was anisaldehyde hydrazone. *p*-Dimethylaminobenzaldehyde hydrazone could not be obtained even by the latter method.

Methylhydrazones and dimethylhydrazones. These compounds were all prepared by the reaction of an ethanolic solution of the appropriate aldehyde with a molar excess of the hydrazine. A few drops of acetic acid were added, the mixture was heated to boiling, water was added until the solution became turbid, and the mixture was chilled. The crystals were filtered and recrystallized from ethanol-water mixtures. *p*-Dimethylaminobenzaldehyde dimethylhydrazone melted at 72–73° (lit.[25] m.p. 74–75°). *p*-Nitrobenzaldehyde dimethylhydrazone melted at 112–113° (lit.[25] m.p. 112°). *p*-Anisaldehyde dimethylhydrazone was distilled, b.p. 123–124° (2.4 mm.) (lit.[25] b.p. 120° (3 mm.).

Semicarbazones were prepared by a standard method.[26]

Stability of hydrazones. Hydrazones with electron-withdrawing groups in the *para* position were only slowly decomposed when exposed to moisture or air. Stability increased as methyl groups were introduced on the terminal nitrogen. The melting point and spectrum of *p*-nitrobenzaldehyde dimethylhydrazone were unchanged after standing overnight in an open beaker. The *p*-nitro derivatives were the most stable, as had been noted by Curtius and Lublin[23] for the simple hydrazones of *o*-, *m*-, and *p*-nitrobenzaldehyde. In 95% ethanol, λ_{max} of a 1.30×10^{-4} *M* solution of *p*-nitrobenzaldehyde hydrazone remained constant at 237 and 343 mμ during 12 hr., and the absorbancy at the higher peak decreased from 1.62 to 1.45. During the same interval, λ max of a 1.03×10^{-4} *M* solution of *p*-cyanobenzaldehyde hydrazone decreased from 306 to 302 and the second primary band at 226 mμ changed to a barely discernible shoulder; the absorbancy of the first primary band decreased from 2.08 to 1.90 during this period.

Hydrazones with electron-donating groups on the ring were extremely unstable, rapidly undergoing oxidation and/or hydrolysis when exposed to air. To save time in determining spectra, concentrations of the hydrazones and methylhydrazones were not determined. The dimethylhydrazones were more stable and their concentrations were determined.

Acknowledgment. The author expresses his appreciation to Dr. David Todd of the Worcester Foundation for Experimental Biology for permission to use his original data for the absorption spectra of the benzaldehyde hydrazones.[2]

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(22) Melting points and boiling points are uncorrected. Spectra were obtained with a Cary Model 11 recording spectrophotometer, using silica cells of 1 cm. light path. Properties and analyses of new compounds are listed in Table II.

(23) T. Curtius and A. Lublin, *Ber.*, **33**, 2460 (1900).

(24) H. Franzen and T. Eichler, *J. prakt. Chem.*, [2], **82**, 241 (1910).

(25) R. H. Wiley, S. C. Slaymaker, and H. Kraus, *J. Org. Chem.*, **22**, 204 (1957).

(26) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, Fourth Ed., John Wiley & Sons, Inc., New York, 1956, p. 218.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF NEW HAMPSHIRE]

Rotatory Dispersion Studies. I. Aralkylamines and Alcohols[1]

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The optical rotatory dispersion curves of compounds having an aromatic center attached to an asymmetric carbon bearing a hetero atom have been shown to exhibit Cotton effects. The investigation of this property with a number of aralkylamines and alcohols has led to correlations with the absolute configurations. The portion of the curve in the visible spectrum can be fitted to the Drude equation, and the slopes thus obtained are shown to be an intrinsic property of the asymmetric center and additive.

Compounds which possess a weakly absorbing chromophore, such as the carbonyl group, in the vicinity of an asymmetric center display anomalous variation of optical rotation with wavelength showing Cotton effects in the region of ultraviolet absorption. This property has provided a useful means of assigning relative and absolute configurations to ketonic steroids by Djerassi and co-workers.[3] Steroids such as equilenin[4] which contain one or more aromatic rings gave plain curves leading to the conclusion that the aromatic ring did not produce Cotton effects. In contrast to this, the rotatory dispersion of ergosterol which possesses no aromatic group but conjugated double bonds shows a Cotton effect of pronounced magnitude.[5] On the other hand, the $\Delta^{3,5}$-steroids,[6a] the $\Delta^{7,9(11)}$-steroids[6b] and $\Delta^{11,13(18)}$-and $\Delta^{12,18}$-terpenoids[6c] failed to reveal anomalous RD curves in the region examined.

It seemed likely that an aromatic ring in conjunction with an amino or hydroxyl function would produce optical rotatory dispersion curves exhibiting Cotton effects. The rotatory dispersion curves of relatively few alkaloids have been reported,[5,7,8]

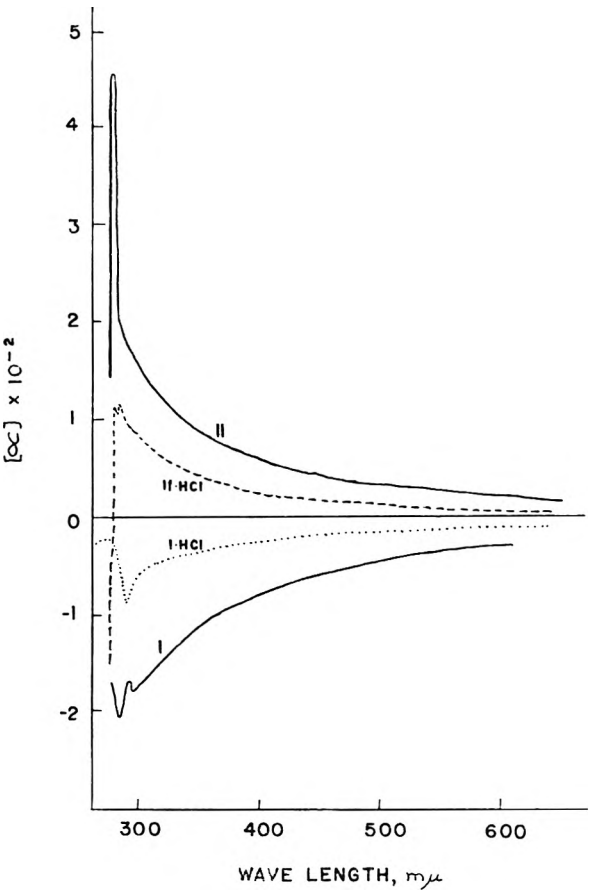


Fig. 1. Optical rotatory dispersion curves of (−)-α-methylbenzylamine (I), (+)-α,*p*-dimethylbenzylamine (II) and their hydrochlorides in ethanol

and in order to establish a basis for the correlation of configurations with the curves, a group of α-arylalkylkamines and α-arylalkanolamines was examined. When the aromatic ring was attached to an asymmetric center bearing a hydroxyl or amino function, the optical rotatory dispersion curves showed Cotton effects (one exception is discussed below).

The curve (Fig. 1) obtained for (S)-(−)-α-methylbenzylamine (I)[9,10] gave a negative Cotton

(1) Presented in part before the Organic Division of the American Chemical Society, 136th Meeting, Atlantic City, N. J., September, 1959, p. 71P.

(2) On leave from the University of New Hampshire, 1958–1959. Public Health Service Fellow, 1958–59. Work done at the Laboratory of the Chemistry of Natural Products, National Heart Institute, National Institutes of Health.

(3) C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry*, McGraw Hill, New York, 1960.

(4) E. W. Foltz, A. E. Lippman, and C. Djerassi, *J. Am. Chem. Soc.*, **77**, 4359 (1955).

(5) Private communication from Dr. U. Weiss.

(6) (a) A. K. Bose and W. A. Struck, *Chem. & Ind. (London)*, **1959**, 1628; (b) C. Djerassi, O. Halpern, V. Halpern, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 4001 (1958); (c) C. Djerassi, J. Osiecki, and W. Closson, *J. Am. Chem. Soc.*, **81**, 4587 (1959).

(7) T. M. Lowry, *Optical Rotatory Power*, Longmans, Green and Co., London, 1935, p. 326ff.

(8) (a) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956); (b) E. E. van Tamelen, P. E. Aldrich, and J. B. Hester, Jr., *J. Am. Chem. Soc.*, **81**, 6214 (1959); (c) J. M. Bobbitt, U. Weiss, and D. Hanessian, *J. Org. Chem.*, **24**, 1582 (1959); (d) W. Wildman and H. M. Fales, *J. Am. Chem. Soc.*, **80**, 6465 (1958); (e) H. G. Leemann and S. Fabbri, *Helv. Chim. Acta*, **42**, 2696 (1959).

(9) For nomenclature indicating absolute configurations, see R. Cahn, C. Ingold, and V. Prelog, *Experientia*, 12, 81 (1956).

(10) W. Leithe, *Chem. Ber.*, **64**, 2827 (1931).

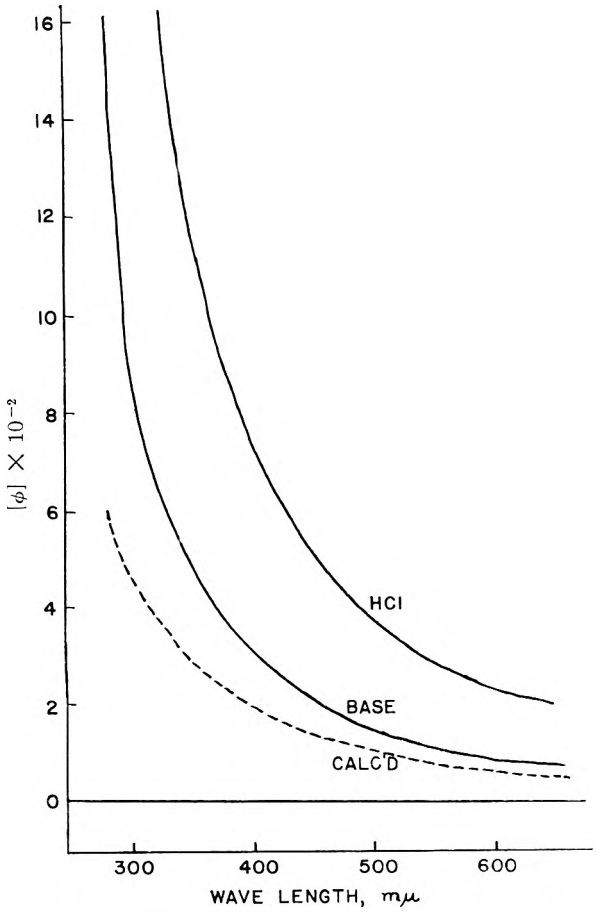


Fig. 2. Optical rotatory dispersion curves of (+)-1,2-diphenylethylamine (V) and its hydrochloride and (dotted line) the curve calculated for the base (see text)

effect, while the curve for (+)-α-*p*-dimethylbenzylamine (II) was essentially of mirror image shape. This suggests that the configurations of these amines are also enantiomeric, II having the (R)-configuration. Some β-arylalkylamines were also studied, and the simplest members of this group, (S)-(+)-amphetamine (III) and (S)-(+)-deoxyephedrine (IV), gave plain curves as the salts in water.[11] Both of these compounds gave anomalous curves, however, when their hydrochlorides were dissolved in ethanol. The shape of the curve was dependent upon the amount of water present in the alcoholic solution, the less the percentage of water, the more apparent the anomalous behavior.

A most interesting result was obtained when the open chain (+)-1,2-diphenylethylamine (V) was examined. The molecule may be considered the summation of (+)-I and (+)-III, as the relative positions of the two aromatic rings would cause the rotation of V to be intensely positive or negative. The curve showed no Cotton effect although V is an α-aralkyl amine. That this was reasonable was shown by calculating a curve for V based on the summation of the molecular rotation values for (+)-I and (+)-III. The two curves are shown in

(11) W. Leithe, *Chem. Ber.*, **65**, 660 (1932).

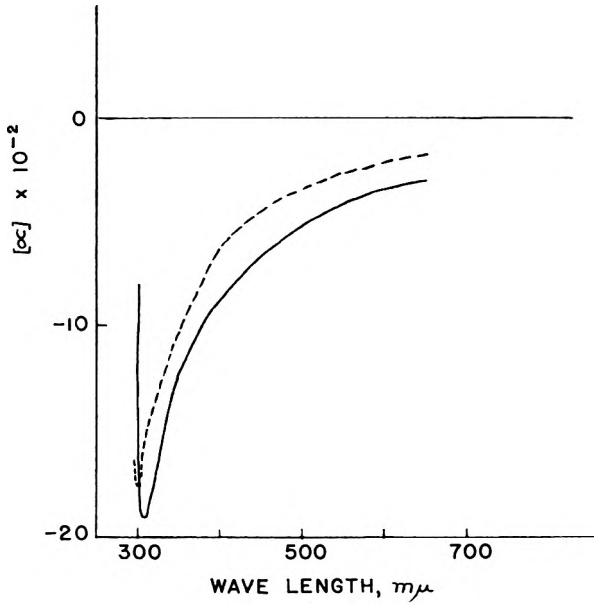
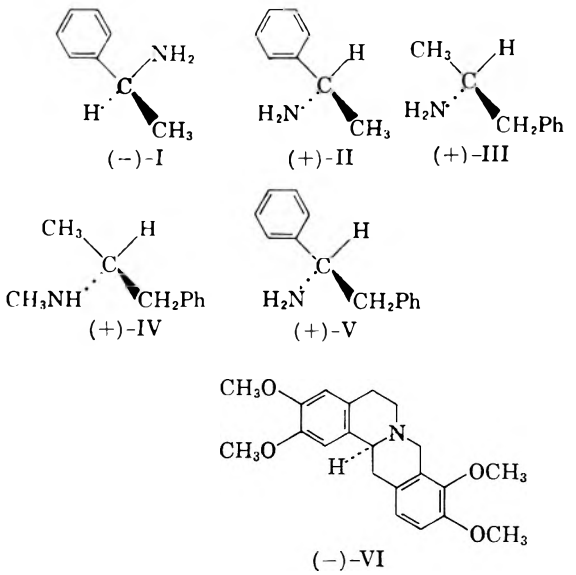


Fig. 3. Optical rotatory dispersion curves of (−)-tetrahydropalmatine (VI) (———) and its hydrochloride (———)

Fig. 2, and the calculated curve shows no Cotton effect in agreement with that found for V. Thus the effects of the phenyl groups appear to be additive even though they are interacting on a single asymmetric center. From these rotatory dispersion data, (+)-V may be assigned the (R)-configuration. Pratesi and co-workers[12] assigned the same configuration to this amine (V) from a relatively complex series of chemical reactions.

(−)-Tetrahydropalmatine (VI), one of the protoberberine alkaloids, has the amino function *alpha* to one aromatic ring and *beta* to the other and may be compared with (+)-1,2-diphenylethyl-



(12) P. Pratesi, A. LaManna, and L. Fontanella, *Il Farmaco (Pavia), Ed. sci.*, **10**, 673 (1955).

amine (V). In this case, however, the aromatic rings are not free to rotate and the confinement in a ring enhances the optical activity. This is in agreement with the discussion of similar open chain and cyclic compounds observed by Kauzmann, Walter, and Eyring.[13] The curve of VI showed a negative Cotton effect of large rotatory power (Fig. 3). The sign of the curve is compatible with its absolute configuration[14] which is enantiomeric to (+)-V and the same as (−)-I.

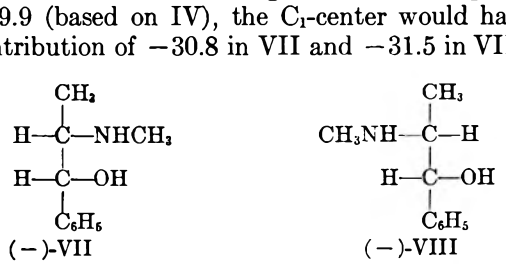
One property of these curves which has found limited application in recent studies is the conversion of the optical rotatory dispersion data to Drude equations.[15] For plain curves, a one-term Drude equation is usually adequate to describe the curve, but for Cotton effect curves, a more complex equation is necessary. In the visible region of the spectrum, however, almost all of the curves can be adequately described by a one-term Drude equation, *i.e.*, $[\phi] = A/(\lambda^2 - \lambda^2_0)$ where $[\phi]$ represents the molecular rotation at a given wave length[16] λ (expressed in microns), and A and λ_0 are characteristic constants of the compound. It is apparent that if a straight line is obtained by plotting $1/[\phi]$ (abscissa), *vs.* λ^2 (ordinate), the slope of this line is A and the intercept is λ_0. The compounds which are reported in this study had values for λ_0 in the far ultraviolet in most cases.

As the slope, A, seemed to be more characteristic of the compounds than the λ_0 values, this quantity was used to determine the configurations. Application of this concept to the amines described above revealed that the values of A for (−)-α-methylbenzylamine (I) and (+)-α,*p*-dimethylbenzylamine (II) were −10.5 and +9.0 respectively. The fact that the slopes are of similar magnitude but of opposite sign lends support to the assignment of configurations (*vide supra*). The substitution of methyl for hydrogen in the *para* position of the aromatic ring in II makes only a small contribution to the rotatory power in the visible region. Nerdel and co-workers[17] examined a group of *m*- and *p*-substituted hydratropic acid derivatives and a similar group of *m*- and *p*-substituted *N*-acetyl-α-methyl benzylamines at five wave lengths in the visible region. The curves of these compounds in alcohol solution were fitted to one-term Drude equations, the A-values of which did not vary with the position of the substituent. In addition, the plot of the A-values as ordinates against Hammett's *sigma* constant[18] as abscissas gave a straight line with a slope of 0. The lack of an electronic effect in similar systems permitted the determination of some absolute configurations (*vide infra*).

In the case of (+)-1,2-diphenylethylamine (V), the slope as determined from the Drude equation was +26.3. This value is in good agreement with that calculated from the A-values of the individual components whose curves were summed above. The A-values for (+)-I, +10.5, and (+)-III, +10.4, would predict a value of +20.9 for (+)-V. The hydrochlorides of amphetamine (III) and its *N*-methyl analog (IV) in aqueous solution gave values of close agreement, that of (+)-III hydrochloride being +10.1 and of (+)-IV hydrochloride being +9.9.

When a molecule possesses more than one asymmetric center, the rotation of the molecule has been assumed to be the summation of the rotations of each individual asymmetric center. Attempts to apply the Rule of Optical Superposition[19] to relatively complex molecules using the D-line rotations have met with limited success. The slope of the Drude equation reflects in a single value the rotations over a large number of wavelengths and may also be considered the rotation at a single wave length, one micron. This arises from the fact that if λ^2_0 is relatively small compared with λ^2, the former term may be ignored and the value, A, is approximately equal to the rotation of the molecule at one micron.[20] Application of this hypothesis to a group of alkanolamines indicated the feasibility of this approach.

Examination of two compounds of known absolute configuration,[10] (−)-ephedrine (VII) and (−)-ψ-ephedrine (VIII), showed that these alkaloids gave negative Cotton effect curves, the A-values being −20.9 and −41.4 for the salts of VII and VIII, respectively (Fig. 4). If the contribution of the carbon bearing the amine salt group is ±9.9 (based on IV), the C_1-center would have a contribution of −30.8 in VII and −31.5 in VIII.



Using the shapes of the curves with the presence or absence of Cotton effects as guides and the A-

(13) W. J. Kauzmann, J. E. Walter, and H. Eyring, *Chem. Rev.*, **26**, 339 (1940).

(14) H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, **39**, 889 (1956).

(15) See ref. 7, p. 120 *et seq.*

(16) Molecular rotation here is defined as in Lowry (ref. 7, p. 22) as one one hundredth of the specific rotation multiplied by the molecular weight. The symbol $[\phi]$ has been suggested by the late Dr. W. Moffitt and Dr. W. Klyne as an appropriate Greek letter to represent rotation rather than the symbol [M] used previously. This proposal is under consideration by the I. U. P. A. C. nomenclature committee.

(17) F. Nerdel and H. Härter, *Ann.*, **621**, 22 (1959); F. Nerdel and H. Würgan, *Ann.*, **621**, 34 (1959); F. Nerdel and H. Liebig, *Ann.*, **621**, 42 (1959).

(18) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, New York, 1940, p. 184ff.

(19) J. H. van't Hoff, *The Arrangement of Atoms in Space*, 2nd Ed., Longmans, Green and Co., London, 1898, p. 160; P. A. Guye and A. Gauthier, *Compt. rend.*, **119**, 740, 963 (1894).

(20) M. Betti, *Trans. Faraday Soc.*, **26**, 337 (1930).

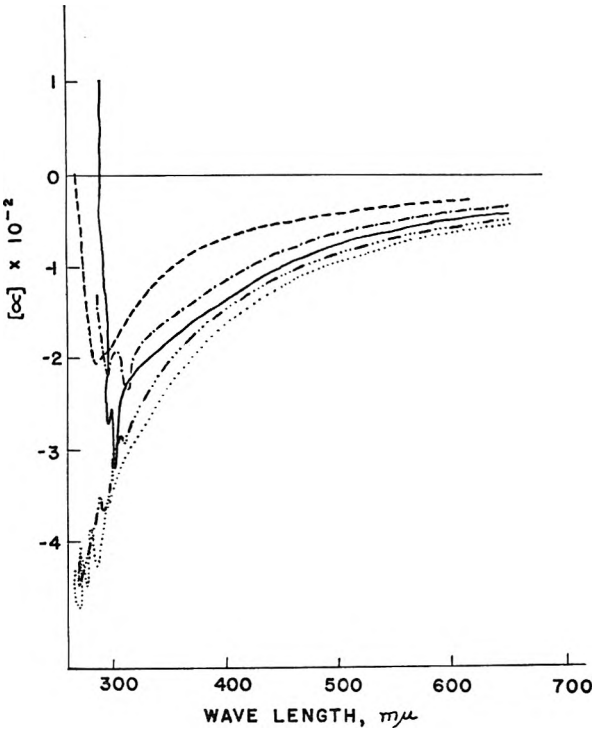


Fig. 4. Rotatory dispersion curves of (−)-ephedrine (VII) sulfate (———), (−)-ψ-ephedrine (VIII) hydrochloride (·····), (−)-halostachine (IX) hydrochloride (-·-·-), (−)-phenylephrine (X) hydrochloride (-··-··-), and (−)-epinephrine (XI) hydrochloride (———)

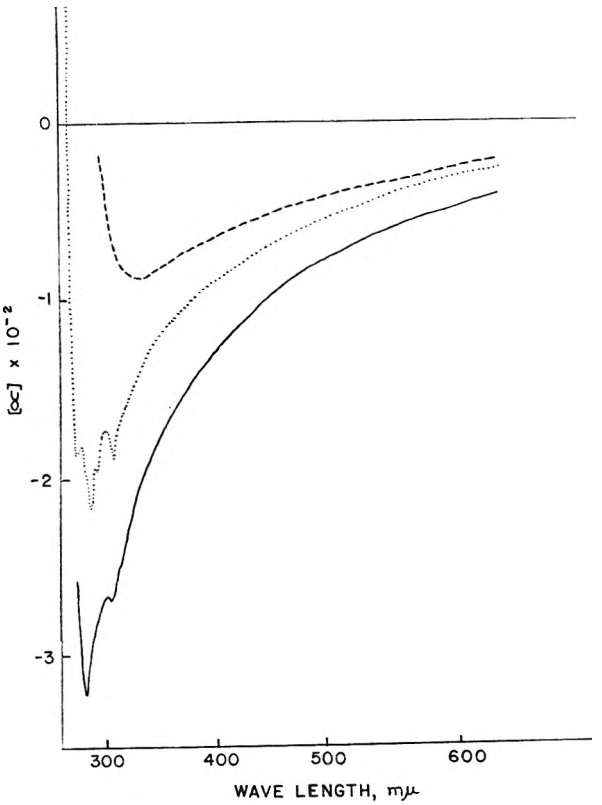
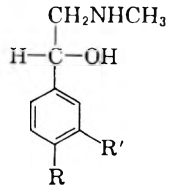


Fig. 5. Optical rotatory dispersion curves of (−)-ψ-ephedrine (VIII) (———), (−)-halostachine (IX) (·····), and (−)-phenylephrine (X) (———) in ethanol

values as significant confirmatory evidence, a group of α-arylalkanolamines was examined. One of the compounds failed to give adequate curves except as the salt because of racemization. The three compounds examined [halostachine (IX)[21] phenylephrine (X), and epinephrine (XI)] are all of physiological interest, the levorotatory isomer being the more active.[22,23] The absolute configuration of epinephrine (XI) has been assigned as (R) on the basis of unequivocal chemical correlations.[24] This configuration is the same as that of the C_1-center of (−)-ephedrine, a fact of significant physiological interest. The other two alkanolamines (IX and X) were of unknown configuration.



(−)-IX R=R'=H

(−)-X R=H; R'—OH

(−)-XI R=R'=OH

The optical rotatory dispersion curves of the salts of IX, X, and XI showed negative Cotton effects (Fig. 4). Of similar shape were the curves for the bases of IX and X (Fig. 5). Determination of the A-values for the salts of IX, X and XI gave, respectively, −34.9, −31.7, and −36.7 which are in good agreement with the calculated value of the C_1-center of ephedrine (VII) and ψ-ephedrine (VIII). The shapes of the curves and the A-values are strong evidence for assuming that all three of these compounds, IX, X, and XI, have the same absolute configuration, that is, the (R)-configuration.

Confirmation of the assignment (R) to (−)-halostachine (IX) was obtained unequivocally. The conversion of (R)-(−)-mandelic acid to the (−)-*N*-methylamide (XII) was effected through the acetonide with retention of activity. Attempts to form the amide from the ester gave a poor yield of XII with a large amount of racemization. Reduction of XII, of 34% optical purity, with an excess of lithium aluminum hydride in tetrahydrofuran gave (−)-halostachine (IX). The product was approximately 54% optically pure, the degree of purity being increased by the isolation procedure. The amine crystallized from the reaction mixture with only 15% activity, and the oil remaining possessed the greater activity. The infrared absorption spectra of pure (±)-amine and all fractions from the reduction were identical with that of pure (+)-IX, obtained by resolution of synthetic material. As the (−)-halostachine prepared from

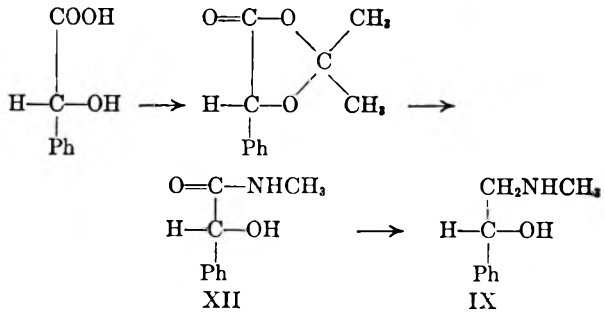
(21) G. P Men'shikov and M. M. Rubinshtein, *J. Gen. Chem. (USSR)*, 13, 801 (1943); *Chem. Abstr.*, 39, 1172 (1945).

(22) W. Osten, *Arzneimittel.-Forsch.*, 5, 84, 146 (1955).

(23) E. Voss, *Am. Profess. Pharmacist*, 19, 633, 719, 722, 751 (1953).

(24) P. Pratesi, A. LaManna, A. Campiglio, and V. Ghislandi, *J. Chem. Soc.*, 2069 (1958).

(−)-mandelic acid possessed the (R)-configuration, as XI does also, the absolute configuration of (−)-phenylephrine (X) must also be (R).



XII IX

EXPERIMENTAL

All measurements of rotations were made on a Rudolph spectropolarimeter equipped with a rocking polarizer using zirconium and xenon arcs. The concentrations were not varied over the region investigated, but the path length ranged from 0.5 cm. to 2.0 dcm. The solvent was ethanol or water in the proportions specified, and the temperature was essentially constant between 22 and 25°. Measurements of the blank solutions were made at every wave length read, except in a few cases when averages were obtained from readings at every 5 mμ.

(−)-*α-Methylbenzylamine* (I). R. D. (Fig. 1) in ethanol (*c*, 2.70): $[\alpha]_{610}$ −26.8°, $[\alpha]_{589}$ −29.3°, $[\alpha]_{295}$ −176°, $[\alpha]_{290}$ −167°, $[\alpha]_{284}$ −203°, $[\alpha]_{274}$ −163°. A = −10.5.

(−)-*α-Methylbenzylamine* (I) *hydrochloride*. R. D. (Fig. 1) in 87% ethanol-water (*c*, 2.13): $[\alpha]_{650}$ −4.18°, $[\alpha]_{589}$ −5.97°, $[\alpha]_{290}$ −82.7°, $[\alpha]_{276}$ −23.5°. A = −2.2.

(+)-*α,p-Dimethylbenzylamine* (II). R. D. (Fig. 1) in ethanol (*c*, 2.68): $[\alpha]_{650}$ 17.8°, $[\alpha]_{589}$ 22.7°, $[\alpha]_{278}$ 455°, $[\alpha]_{275}$ 144°. A = +9.0.

(+)-*α,p-Dimethylbenzylamine* (II) *hydrochloride*. R. D. (Fig. 1) in ethanol (*c*, 4.25): $[\alpha]_{650}$ 8.22°, $[\alpha]_{589}$ 10.1°, $[\alpha]_{286}$ 118°, $[\alpha]_{282}$ 106°, $[\alpha]_{281}$ 113°, $[\alpha]_{275}$ −150°. A = +5.1.

(+)-*Amphetamine* (III). R. D. in ethanol (*c*, 2.81): $[\alpha]_{650}$ 20.9°, $[\alpha]_{589}$ 26.3°, $[\alpha]_{275}$ 300°. A = +10.4.

(+)-*Amphetamine* (III) *hydrochloride*. R. D. in water (*c*, 0.785): $[\alpha]_{650}$ 16.5°, $[\alpha]_{589}$ 20.1°, $[\alpha]_{267}$ 293°. A = +10.1. R. D. in ethanol (*c*, 2.484): $[\alpha]_{589}$ −0.54°, $[\alpha]_{330}$ −4.67°, $[\alpha]_{280}$ 23.83°. R. D. in 50% ethanol-water (*c*, 1.241): $[\alpha]_{610}$ 3.86°, $[\alpha]_{589}$ 4.40°, $[\alpha]_{340}$ 20.06°.

(+)-*Deoxyephedrine* (IV). R. D. in ethanol (*c*, 1.956): $[\alpha]_{700}$ 12.4°, $[\alpha]_{589}$ 17.7°, $[\alpha]_{280}$ 138°. A = +8.9.

(+)-*Deoxyephedrine* (IV) *hydrochloride*. R. D. in water (*c*, 2.94): $[\alpha]_{650}$ 13.8°, $[\alpha]_{589}$ 17.1°, $[\alpha]_{310-304}$ 90° (sh,), $[\alpha]_{293-290}$ 108° (sh.), $[\alpha]_{278}$ 147°. A = +9.9. R. D. in ethanol (*c*, 2.26 to 400 mμ, *c*, 3.23, 400–276 mμ): $[\alpha]_{650}$ −4.98°, $[\alpha]_{589}$ −6.14°, $[\alpha]_{305}$ −32.7°, $[\alpha]_{300}$ −28.6°, $[\alpha]_{290}$ −32.3°, $[\alpha]_{276}$ −18.1°.

(+)-*1,2-Diphenylethylamine* (V). R. D. (Fig. 2) in ethanol (*c*, 2.68): $[\alpha]_{650}$ 37.5°, $[\alpha]_{589}$ 47.9°, $[\alpha]_{275}$ 795°. A = +26.3.

(+)-*1,2-Diphenylethylamine* (V) *hydrochloride*. R. D. (Fig. 2) in ethanol (*c*, 1.02): $[\alpha]_{650}$ 102°, $[\alpha]_{589}$ 128°, $[\alpha]_{275}$ 1720°. A = +86.7.

(−)-*Tetrahydropalmatine* (VI). R. D. (Fig. 3) in ethanol (*c*, 0.635): $[\alpha]_{650}$ −232°, $[\alpha]_{589}$ −290°, $[\alpha]_{305}$ −1920°, $[\alpha]_{298}$ −891°. A = −310.

(−)-*Tetrahydropalmatine* (VI) *hydrochloride*. R. D. (Fig. 3) in 95% ethanol (*c*, 0.412): $[\alpha]_{650}$ −183°, $[\alpha]_{589}$ −227°, $[\alpha]_{300}$ −1710°, $[\alpha]_{299}$ −1583°, $[\alpha]_{297}$ −1730°, $[\alpha]_{296.5}$ −1670°. A = −269.

(−)-*Ephedrine* (VII). R. D. in ethanol (*c*, 3.16): $[\alpha]_{650}$ −2.36°, $[\alpha]_{589}$ −2.65°, $[\alpha]_{460}$ −3.20° (broad trough), $[\alpha]_{330}$ 4.54°. This substance was not absolutely pure, containing some water of hydration.

(−)-*Ephedrine* (VII) *sulfate*. R. D. (Fig. 4) in 80% ethanol-water (*c*, 5.15): $[\alpha]_{610}$ −28.1°, $[\alpha]_{589}$ −30.4°, $[\alpha]_{290}$ −207° (broad trough), $[\alpha]_{272}$ −99°. A = −20.9.

(−)-*Pseudoephedrine* (VIII). R. D. (Fig. 5) in ethanol (*c*, 1.60): $[\alpha]_{650}$ −42.6°, $[\alpha]_{589}$ −52.5°, $[\alpha]_{305}$ −268° (sh), $[\alpha]_{280}$ −323°, $[\alpha]_{278}$ −256°. A = −27.5.

(−)-*Pseudoephedrine* (VIII) *hydrochloride*. R. D. (Fig. 4) in ethanol (*c*, 1.57): $[\alpha]_{650}$ −53.1°, $[\alpha]_{589}$ −65.6°, $[\alpha]_{290}$ −434°, $[\alpha]_{284}$ −381°, $[\alpha]_{278}$ −444°, $[\alpha]_{276}$ −415°, $[\alpha]_{274}$ −471°, $[\alpha]_{269}$ −414°. A = −41.4.

(−)-*Phenylephrine* (X). R. D. (Fig. 5) in ethanol (*c*, 0.276): $[\alpha]_{650}$ −22.8°, $[\alpha]_{589}$ −29.5°, $[\alpha]_{335}$ −88.4°, $[\alpha]_{298}$ −22.5°. A = −15.8.

(−)-*Phenylephrine* (X) *hydrochloride*. R. D. (Fig. 4) in ethanol (*c*, 1.22): $[\alpha]_{650}$ −39.3°, $[\alpha]_{589}$ −48.4°, $[\alpha]_{318}$ −232°, $[\alpha]_{315}$ −190°, $[\alpha]_{300}$ −220°, $[\alpha]_{290}$ −133°. A = −31.7.

(−)-*Epinephrine* (XI). R. D. (Fig. 4) in 0.5*N* hydrochloric acid (*c*, 1.20): $[\alpha]_{650}$ −43.7°, $[\alpha]_{589}$ −53.2°, $[\alpha]_{303}$ −325°, $[\alpha]_{299}$ −250°, $[\alpha]_{298}$ −273°, $[\alpha]_{290}$ 732°. A = −36.7.

(R)-(−)-*N-Methylmandelamide* (XII). A solution of 1.46 g. (0.0096 mole) of mandelic acid ($[\alpha]_D^{23}$ −60°, 37% optically pure) in 4.5 ml. of acetone was cooled to −10° in an ice-salt bath, and 1.0 g. of concd. sulfuric acid was added dropwise with stirring keeping the temperature below −5°. The solution was added slowly to an ice-cold solution of 2.1 g. of sodium carbonate in 20 ml. of water. The flocculent precipitate was separated by filtration, washed with ice water, and dried under reduced pressure over calcium sulfate. The acetonide which was contaminated with inorganic salts melted at 61–69°.

The crude acetonide was added in portions to a solution of 0.86 g. of methylamine in 8 ml. of methanol, and the mixture was allowed to stand at room temperature for 2 hr. The insoluble material was separated by filtration, washed with methanol, and discarded. The filtrate was concentrated yielding 0.85 g. (59.3%) of (−)-*N-methylmandelamide*, m.p. 86–94°, $[\alpha]_D^{23}$ −26.1° (acetone, *c*, 1.32). The pure (±)-amide, prepared in a similar manner, melted at 96–98° after recrystallization from benzene; lit.[25] m.p. of (+)-*N*-methylmandelamide, 94–95°, $[\alpha]_D$ not given. The infrared spectra in chloroform of the (±)-amide and the (−)-amide (XII) were identical, 3400 cm.$^{-1}$ (OH, NH), 1675 cm.$^{-1}$ (amide).

Anal. Calcd. for $C_9H_{11}NO_3$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.43; H, 6.51; N, 8.34.

(R)-(−)-*Halostachine* (XI). A suspension of 1.0 g. of lithium aluminum hydride in 20 ml. of tetrahydrofuran was mixed with a solution of 0.61 g. (0.004 mole) of (−)-*N*-methylmandelamide ($[\alpha]_D^{23}$ −26.1°) in 30 ml. of tetrahydrofuran, and the mixture was heated under reflux for 18 hr. The reaction mixture was decomposed with 5 drops of water, and an excess of 30% sodium hydroxide was added until the organic layer separated. The tetrahydrofuran solution was decanted and the inorganic residue was triturated twice with the same solvent. The combined organic solutions were concentrated and hexane was added to the residue. The precipitate (0.3 g.) was separated by filtration, m.p. 39–70°, and on recrystallization from hexane yielded 130 mg. of hexane-insoluble material whose infrared spectrum indicated unreduced amide and 91 mg. of hexane-soluble crystals, m.p. 70–76°, $[\alpha]_D^{23}$ −4.60° (ethanol, *c*, 1.50, 15% optically pure), lit.[26] m.p. 75–76° [(±)-α-methylaminomethylbenzyl alcohol].

The filtrate from the 0.3 g. precipitate deposited 16 mg. of the amino alcohol, $[\alpha]_D^{23}$ −10.9° (ethanol, *c*, 0.80, 28.9% active). Concentration of the filtrate gave 73 mg. of an oil which failed to crystallize but whose infrared spectrum in chloroform was identical with the two crystalline fractions

(25) I. Heilbron, *Dictionary of Organic Compounds*, Vol. III, Oxford University Press, New York, 1953, p. 211.

(26) G. P. Men'shikov and G. M. Borodina, *J. Gen. Chem. (USSR)*, 17, 1569 (1947); *Chem. Abstr.*, 42, 2245 (1948).

and with the optically pure amine (*vide infra*), 3300–3400 cm.$^{-1}$ (OH, NH), no carbonyl band, $[\alpha]_D^{23}$ −20.0° (ethanol, *c*, 2.48, 53.5% active). The total yield of amine was 30%; lit.[21,26] m.p. for halostachine, 43–45°, $[\alpha]_D$ −47.03° (no solvent given).

Resolution of (±)-halostachine. A solution of 2.3 g. of (±)-halostachine in acetone was added to an acetone solution containing 3.48 g. of (+)-10-camphorsulfonic acid (total volume = 60 cc.). On addition of ether, 3.64 g. of crystalline salt was obtained, m.p. 109–112°. $[\alpha]_D^{23}$ +28.21° (acetone, *c*, 1.74). Three recrystallizations from acetone-ether gave 0.65 g. of pure salt, m.p. 132–134°, $[\alpha]_D^{23}$ +49.41°.

The amine (IX) was obtained from the salt by passage over ethyl acetate-washed Merck alumina using chloroform as solvent and 10% ethanol-chloroform as eluent. From 650 mg. of salt 64.2 mg. of pure amine, $[\alpha]_D^{25}$ +37.43° (ethanol, c, 2.37), was obtained. R. D. (Fig. 5) in ethanol: $[\alpha]_{650}$ 30.21°, $[\alpha]_{589}$ 37.43°, $[\alpha]_{314}$ 172°, $[\alpha]_{306}$ 176°, $[\alpha]_{295}$ 203°, $[\alpha]_{292}$ 193°, $[\alpha]_{288}$ 219°, $[\alpha]_{280}$ 182°, $[\alpha]_{276}$ 187°, $[\alpha]_{271}$ 41°. A = +18.0. A total of 151 mg. (74%) of the base was recovered from the salt.

The hydrochloride of IX melted at 108–111°, $[\alpha]_D^{25}$ +53.20° (water, *c*, 0.750): lit.[26] m.p. 113–114°, $[\alpha]_D$ +52.46°. R. D. (Fig. 4) in ethanol (c, 1.57): $[\alpha]_{650}$ 48.6°, $[\alpha]_{589}$ 59.1°, $[\alpha]_{292}$ 362°, $[\alpha]_{290}$ 346°, $[\alpha]_{284}$ 392° (sh.), $[\alpha]_{274}$ 447°, $[\alpha]_{272}$ 411°. A = +34.9.

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DURHAM, N. H.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Intramolecular-Intermolecular Polymerizations of Some Phenyl Substituted Nonconjugated Diolefins[1]

C. S. MARVEL AND E. J. GALL

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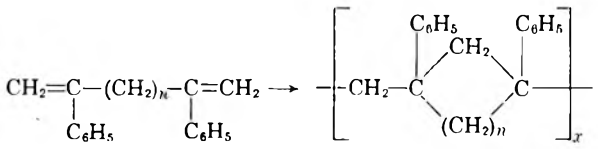
The three hydrocarbons 2,5-diphenylhexadiene-1,5, 2,6-diphenylheptadiene-1,6 and 2,7-diphenyloctadiene-1,7 have been synthesized and polymerized to yield polymers with cyclic recurring units. The evidence indicates that five- and seven-membered rings form less readily than does the six-membered ring in such polymerization reactions.

The work reported here was undertaken to determine whether phenyl substituted nonconjugated diolefins of the type shown in formula I would undergo the intramolecular-intermolecular polymerization reaction which has been successfully applied in a number of instances.[2] While the work



Ia. $n = 2$
Ib. $n = 3$
Ic. $n = 4$

IIa. $n = 2$
IIb. $n = 3$
IIc. $n = 4$

was in progress, we learned of the work of Field,[3] who has found that the heptadiene derivative (Ib) readily yields a polymer with a cyclic recurring unit (IIb) by all standard types of initiation. We have confirmed his experience.

The two homologous dienes (Ia and Ic) have been synthesized from the corresponding diketones by application of the Wittig reaction.[3,4] They polymerize to yield soluble, powdery solids which are rather low melting and have low inherent viscosities. These polymers show very little absorption in the infrared in the carbon-carbon double bond region. It seems obvious that these are low molecular weight polymers of the cyclic structures expected (IIa and IIc). It is quite evident however, that there is less tendency to yield five-or seven-membered recurring units than is the case for six-membered recurring units.

EXPERIMENTAL

Melting points are uncorrected.

Monomers: 2,6-Diphenylheptadiene-1,6 (Ib). This monomer was prepared according to the procedure reported by Field[3] and previously reported by us.[5]

2,7-Diphenyloctadiene-1,7 (Ic). 1,4-Dibenzoylbutane was prepared according to the procedure reported by Fuson and Walker.[6]

The conversion of 1,4-dibenzoylbutane to 2,7-diphenyloctadiene-1,7 (Ic) was similar to that described earlier for the preparation of 2,6-diphenylheptadiene-1,6 (Ib). Phenyllithium was prepared in the usual way from 86.4 g. (0.55 mole) of bromobenzene and 9.7 g. (1.4 g.-atoms) of lithium metal in dry diethyl ether in 94.5% yield. A solution of 0.455 mole of phenyl lithium was added to a slurry of 146 g.

(1) This work was carried out under the sponsorship of Contract AF-33(616)-5486 with the Materials Laboratory of Wright Air Development Center, Wright-Patterson Air Force Base, Ohio. This paper may be reproduced for any purpose of the United States Government.

(2) G. B. Butler and R. J. Angelo, *J. Am. Chem. Soc.*, **79**, 3128 (1957); C. S. Marvel and R. D. Vest, *J. Am. Chem. Soc.*, **79**, 5771 (1957); **81**, 984 (1959); C. S. Marvel and J. K. Stille, *J. Am. Chem. Soc.*, **80**, 1740 (1958); J. F. Jones, *J. Poly. Sci.*, **33**, 15 (1958) and others.

(3) N. D. Field, *J. Org. Chem.*, **25**, 1006(1960).

(4) G. Wittig and U. Schöllkopf, *Ber.*, **87**, 1318 (1954).

(5) C. S. Marvel and E. J. Gall, *J. Org. Chem.*, **24**, 1494 (1959).

(6) R. C. Fuson and J. T. Walker, *Org. Syntheses*, Coll. Vol. II, 169 (1943).

(0.414 mole) of methyltriphenylphosphonium bromide in 600 ml. of dry 1,2-dimethoxyethane. To the resulting yellow-brown solution was added a solution of 1,4-dibenzoylbutane (50 g.; 0.188 mole) in 450 ml. of dry 1,2-dimethoxyethane, and the mixture was stirred and heated under gentle reflux for 20 hr. After the usual work-up, the product isolated was a yellow-red colored solid. This solid was extracted with hot *n*-pentane, the insoluble material was isolated by filtration, and the pentane filtrate was evaporated to dryness. The yellow solid was recrystallized twice from ethanol to give 34.2 g. (71%) of a white, crystalline solid (shiny plates), m.p. 47.5–48.5°. The infrared spectrum (10% in chloroform) showed a small amount of absorption at 1685 cm.$^{-1}$, indicating a small amount of ketonic impurity. Consequently, the solid product was treated with Girard's T reagent, and recrystallized twice more from methanol. The crystalline material purified in this manner melted at 51.0–52.0°. The infrared spectrum[7] (10% in carbon tetrachloride) showed the following important absorption maxima: 700 cm.$^{-1}$ (C_6H_5—); 895 cm.$^{-1}$ ($CR_1R_2{=}CH_2$); 1025 cm.$^{-1}$ (C_6H_5—); 1625 cm.$^{-1}$ (C_6H_5— conjugated $\diagdown C{=}C \diagup$); 1800 cm.$^{-1}$ (overtone of 895 cm.$^{-1}$). The NMR spectrum[8] (20% in carbon tetrachloride) was consistent with the structure of the expected diene.

Anal.[9] Calcd. for $C_{20}H_{22}$: C, 91.55; H, 8.45. Found: C, 91.19; H, 8.82.

2,5-Diphenylhexadiene-1,5 (Ia). 1,2-Dibenzoylethane was prepared according to a procedure reported by Weygand and Meusel.[10]

Phenyllithium was prepared in the usual manner. From 70.7 g. (0.45 mole) of bromobenzene and 8.3 g. (1.2 g.-atoms) of lithium metal, there was obtained 320 ml. of 1.24*M* ethereal solution.

In a 2-l., three necked, round bottomed flask fitted with stirrer, dropping funnel, condenser, and nitrogen inlet tube was placed a slurry of 120.8 g. (0.338 mole) of methyltriphenylphosphonium bromide in 500 ml. of dry 1,2-dimethoxyethane. Over a period of about 45 min. a solution of 0.372 mole of phenyllithium in dry diethyl ether was added with stirring under nitrogen. As a considerable amount of the salt appeared not to have undergone reaction, the mixture was stirred and heated under gentle reflux overnight. A solution of 37.6 g. (0.158 mole) of 1,2-dibenzoylethane in 300 ml. of dry 1,2-dimethoxyethane was then added dropwise with stirring over a period of about 40 min. After stirring and heating under gentle reflux for an additional 20 hr., the solvents were removed to near dryness by distillation, and 1000 ml. of *n*-pentane was added to the oily red residue. The mixture was thoroughly shaken, the pentane solution was decanted, washed thoroughly with water, and dried over anhydrous sodium sulfate. The solvent was removed from the dried solution, leaving 12.0 g. of a mixture of red-colored liquid and yellow solid. Approximately 1000 ml. of water was added to the residue remaining after extraction with pentane, and the resulting aqueous solution was extracted three times with pentane. This pentane solution was treated as described above, and, after the solvent had been removed, there was obtained 2.7 g. of a mixture of red-colored liquid and yellow solid.

The two mixtures were combined, 100 ml. of dry *n*-pentane was added, and the solution obtained was purified by chromatography on a column prepared from 270 g. of silicic acid (B and A Reagent, Code 1169). The solid obtained was recrystallized three times from methanol to give 2.77 g. (7.9%) of a white, crystalline solid (shiny plates), m.p. 51.0–51.8°. The infrared spectrum (10% in carbon tetrachloride) showed the following important absorption maxima: 895 cm.$^{-1}$ ($CR_1R_2{=}CH_2$); 1495 cm.$^{-1}$, 1570 cm.$^{-1}$, 1600 cm.$^{-1}$ (C_6H_5—); 1625 cm.$^{-1}$ (C_6H_5— -conjugated $\diagdown C{=}C \diagup$); and 1795 cm.$^{-1}$ (overtone of 895 cm.$^{-1}$). There was no infrared absorption in the region 1675–1750 cm.$^{-1}$. The NMR spectrum was consistent with the structure of the expected diene.

Anal. Calcd. for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.08; H, 7.96.

Polymers. Polymer melting points were obtained by the capillary tube method. The lower temperature given is that at which the polymer begins to soften. The higher temperature is that at which the polymer is a clear, flowing liquid. Yields are based on the amount of monomer allowed to react. Inherent viscosities were obtained in reagent grade benzene solution at concentrations of *ca.* 0.25 g. of polymer per 100 ml. of solution. The amounts of residual unsaturation in the polymers were roughly determined by comparing the intensities of the absorption maxima at 895–900 cm.$^{-1}$ in the polymer and monomer infrared spectra, both measured in solution at the same concentrations. The spectra of all the polymers of each monomer were essentially alike. No attempts were made at quantitative infrared analysis.

Polymers of 2,6-diphenylheptadiene-1,6. (1) *Cationic initiation:boron trifluoride.* A solution of monomer (1.0 ml.) in 10 ml. of methylene chloride was placed in a 50-ml. flask equipped with a stirrer and gas inlet tube, and protected from moisture by a calcium chloride drying tube. The flask was cooled in a Dry Ice–acetone bath while the system was flushed well with nitrogen. While the solution was stirred, boron trifluoride gas was slowly bubbled in for about 2 min. The mixture under nitrogen was stirred at the cold temperature for 1 hr. more and was then slowly poured into methanol. The white solid obtained was reprecipitated twice more from benzene into methanol to give 0.67 g. (67%) of a white, amorphous solid, m.p. 240–270°, $[\eta]_{\text{inherent}} = 0.145$. The presence of a small amount of residual unsaturation (3–5%) was shown by infrared absorption at 900 cm.$^{-1}$. There was no absorption at 1625 cm.$^{-1}$.

Anal. Calcd. for $(C_{19}H_{20})_x$: C, 91.88; H, 8.12. Found: C, 91.55; H, 8.37.

(2) *Cationic initiation:titanium tetrachloride.* In the dry box, in an atmosphere of nitrogen, a small amount of titanium chloride (0.12 g.; 0.00063 mole) was dissolved in 3 ml. of anhydrous, purified *n*-heptane, contained in a 2-ounce bottle. The monomer (5.0 ml.) was added to this solution, and the mixture was thoroughly shaken. An almost immediate reaction took place, as heat was liberated, the mixture turned dark brown and became very viscous. After the stoppered bottle had stood at room temperature for 78 hr., 30 ml. of methanol was added to precipitate the polymer and decompose the catalyst. The solid obtained was reprecipitated from benzene into methanol to give 2.6 g. (52%) of a powdery solid, m.p. 115–130°; $[\eta]_{\text{inherent}} = 0.051$. Infrared analysis indicated a small amount of residual unsaturation; approximately 5–10% of that of the monomer.

(3) *Anionic initiation:phenyl lithium.* The diene (2.0 g.) was dissolved in 1,2-dimethoxyethane (6.0 g.) in a 2-ounce bottle. The solution was flushed well with dry nitrogen, and the bottle was stoppered with a serum cap. While the solution was cooled in powdered Dry Ice (−40° to −50°), a solution of phenyllithium in diethyl ether (1 ml. of 0.99*N* solution; 0.99 mmole) was added by means of a hypodermic syringe, and, after thorough shaking, the mixture was cooled for an additional 3.5 hr. At the end of this time, there

(7) The infrared spectra were obtained from a Perkin-Elmer model 21 spectrophotometer by Mr. P. E. McMahon, Mrs. M. Verkade, Miss C. Luebke, Mr. R. Johnson, and Mr. W. Dalton, University of Illinois.

(8) The NMR spectra were obtained from a Varian 4300-B spectrometer by Mr. B. Shoulders and Mr. O. Norton, University of Illinois.

(9) The microanalyses were performed by Mr. J. Nemeth, Mrs. F. Ju, Miss C. Higham, Miss J. Liu, and Mrs. A. S. Bay, University of Illinois.

(10) C. Weygand and W. Meusel, *Ber.*, **76**, 498 (1943).

was no apparent change in viscosity of the solution. After standing at room temperature for 18 hr., however, the entire mixture had solidified. Methanol (100 ml.) was added, and the white solid (1.9 g.) was isolated by filtration on a Büchner funnel. This solid was completely dissolved in 40 ml. of benzene, and was reprecipitated by filtration into 400 ml. of methanol. There was obtained 1.7 g. (85%) of a white, powdery solid, m.p. 275–290°; $[\eta]_{inherent}$ = 0.26. Residual unsaturation: 5–10%.

(4) *Free radical initiation:cumene hydroperoxide.* The monomer (1.0 ml.) containing approximately 40 mg. of cumene hydroperoxide was sealed off under nitrogen in a small test tube, and was kept in boiling water for 5 days. The polymer obtained was an opaque, nonflowing plastic, which was, however, soft, not brittle, and could easily be scratched. The softening point of this plastic material, taken on a hot stage, was 85°. It was completely soluble in benzene; precipitation into methanol gave 0.56 g. (56%) of a white powder, m.p. 240–270°; $[\eta]_{inherent}$ = 0.128. Residual unsaturation: approximately 3%.

(5) *Thermal polymerization.* The monomer (1.0 ml.) was sealed under nitrogen in a small test tube, and was kept in *o*-dichlorobenzene, heated to its reflux temperature, for 5 days. The polymer obtained was a clear, nonflowing plastic, which, however, was soft and could easily be scratched. Its softening point, taken on a hot stage, was 90°. This plastic solid was completely dissolved in benzene, and was precipitated into methanol to give 0.54 g. (54%) of a white powdery solid, m.p. 260–290°; $[\eta]_{inherent}$ = 0.154. Residual unsaturation: approximately 3%.

(6) *Ziegler-type polymerization.* The catalyst was prepared in a dry box in an atmosphere of nitrogen by adding titanium tetrachloride (0.12 g.; 0.00063 mole) to a solution of aluminum triisobutyl (0.1 g.; 0.0005 mole) in dry *n*-heptane (2.05 g.). The monomer (5.0 g.) was added, and the mixture was allowed to stand under nitrogen in a stoppered bottle at room temperature for 72 hr. After precipitation into methanol, there was obtained 2.79 g. (56%) of a white powdery solid, m.p. 185–200°, $[\eta]_{inherent}$ = 0.041. Residual unsaturation: 5–10%.

Polymers of 2,7-diphenyloctadiene-1,7. (1) *Cationic initiation:boron trifluoride.* The procedure used was the same as that described above for the boron trifluoride–initiated polymerization of 2,6-diphenylheptadiene-1,6. From 1.0 g. of monomer there was obtained 0.06 g. (6%) of solid polymer after two precipitations from benzene into methanol. Polymer m.p. 115–150°; no residual unsaturation (no infrared absorption at 900 or 1625 cm.$^{-1}$); $[\eta]_{inherent}$ = 0.021.

Anal. Calcd. for $(C_{20}H_{22})_x$: C, 91.55; H, 8.45. Found: C, 91.10; H, 8.51.

(2) *Cationic initiation titanium tetrachloride.* Under conditions like those described above for the titanium tetrachloride–initiated polymerization of 2,6-diphenylheptadiene-1,6, this monomer (1.5 g.) was allowed to react with the catalyst (0.12 g.; 0.07 ml.) in 5.5 ml. of purified *n*-heptane for 40 hr. at room temperature. At the end of this time, the reaction was quenched by the addition of 10 ml. of methanol. There was obtained an oily, viscous liquid, insoluble in the solvent. The solvent was carefully decanted, the oil was dissolved completely in benzene, and precipitated into methanol to give 0.70 g. (47%) of a tan-colored powder, m.p. 87–128°; $[\eta]_{inherent}$ = 0.039. Residual unsaturation: approximately 2–5%.

(3) *Ziegler-type polymerization.* The catalyst was prepared as described above. From 2.0 g. of monomer there was obtained 1.5 g. of a white, powdery solid, m.p. 95–157°; $[\eta]_{inherent}$ = 0.040. This polymer possessed no residual unsaturation.

Polymers of 2,5-diphenylhexadiene-1,5. (1) *Cationic initiation:boron trifluoride.* The procedure used was the same as that described above for the boron trifluoride–initiated polymerization of 2,6-diphenylheptadiene-1,6. From 0.4 g. of monomer there was obtained 0.33 g. (83%) of a white powdery solid, m.p. 185–210°; $[\eta]_{inherent}$ = 0.083, after three precipitations from benzene into methanol. Residual unsaturation: 5–10%.

Anal. Calcd. for $(C_{18}H_{18})_x$: C, 92.26; H, 7.74. Found: C, 91.35; H, 7.41.

(2) *Free radical initiation:cumene hydroperoxide.* The monomer (0.50 g.) containing approximately 25 mg. of cumene hydroperoxide was sealed off under nitrogen in a small test tube and was kept in boiling water for 5 days. The tube was then opened, and the contents were poured into 100 ml. of methanol. The white, insoluble solid was isolated and reprecipitated from benzene into methanol to give a very small amount (11 mg.) of white, powdery solid, m.p. 150–170°. The amount isolated was not sufficient for a viscosity measurement. Residual unsaturation: <5%.

(3) *Ziegler-type polymerization.* The catalyst was again prepared by using aluminum triisobutyl and titanium tetrachloride in a mole ratio of 0.8. From 0.5 g. of monomer there was obtained 0.29 g. (58%) of a white, powdery solid, m.p. 157–177°; $[\eta]_{inherent}$ = 0.072. Residual unsaturation: 3–5%.

URBANA, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF SOUTH CAROLINA]

The Reaction of Free Radicals with Non-benzenoid Aromatic Hydrocarbons. II. 6-Alkylfulvenes and Benzofulvenes

JOHN L. KICE[1] AND FATEMEH TAYMOORIAN

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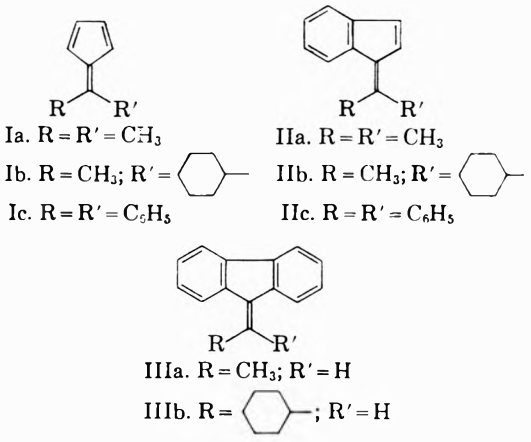
Kinetic studies of the reactivity of a series of 6,6-dialkylfulvenes and benzofulvenes toward free radicals have provided fairly definite evidence that these substances like their phenyl substituted counterparts undergo radical attack at one of the ring positions and not at the external 6-position. The experimental evidence seems to favor the 2-position as the site of radical attack.

The reactivity of various phenyl substituted fulvenes and benzofulvenes toward free radicals and the site of radical attack on these molecules were the subjects of a previous paper.[2] That study

(1) To whom inquiries should be sent: Department of Chemistry, Oregon State College, Corvallis, Ore.

(2) J. L. Kice and F. M. Parham, *J. Am. Chem. Soc.*, 80, 3792 (1958).

provided convincing evidence that 6,6-diphenylfulvene (Ic) and 6,6-diphenylbenzofulvene (IIc) are attacked by radicals at the ring positions and not at the external 6-position. For several reasons we felt that this result did not ensure that 6,6-



dialkylfulvenes and benzofulvenes would also react in similar fashion, and we therefore thought it desirable to carry out experiments which would elucidate the site of radical attack on such alkyl substituted fulvenes and benzofulvenes.

Regrettably, the most direct approach, the examination of the products produced when a radical source is decomposed in benzene solutions of dimethylfulvene or dimethylbenzofulvene, has in our hands proved unsatisfactory. The products of the reaction of 2-cyano-2-propyl radicals with either compound were intractable gums and viscous oils.[3] Although the physical properties and chemical behavior of these materials afford some qualitatively useful information, we felt that kinetic studies of the reactivity of certain alkyl fulvenes and benzofulvenes would provide more conclusive results.

In the dibenzofulvenes (III), where radical attack certainly occurs at the external 6-position, replacement of the methyl group in 6-methyldibenzofulvene (IIIa) with a cyclohexyl group (IIIb) leads to a 2000 fold decrease in the reactivity of the double bond toward methyl methacrylate radicals.[4] This is undoubtedly due to increased steric hindrance to radical attack at the 6-position.[4,5] Similarly, one would expect, if radical attack on 6,6-dimethylfulvene (Ia) took place at the 6-position, that replacement of one of the methyl groups by a cyclohexyl, as in 6-methyl-6-cyclohexylfulvene (Ib), would lead to a drastic decrease in reactivity toward methacrylate radicals. On the other hand, if radical attack occurs at one of the ring positions, the steric consequences of the replacement of methyl by cyclohexyl will be much less and the reactivity of Ib should not differ greatly from that of dimethylfulvene. Similar arguments apply to the benzofulvenes IIa and IIb.

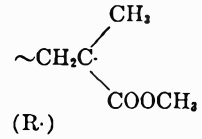
(3) We have not studied other radical sources since we learned that Dr. W. B. Smith of Ohio University plans work in this area.

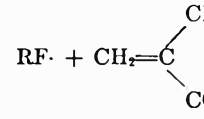
(4) J. L. Kice, *J. Am. Chem. Soc.*, **80**, 348 (1958).

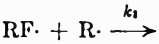
(5) M. Szwarc and F. Leavitt, *J. Am. Chem. Soc.*, **78**, 3590 (1956).

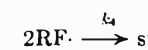
RESULTS AND DISCUSSION

Ia and IIa were prepared by published procedures,[6,7] and the new compounds Ib and IIb were synthesized by analogous methods. The reactivity of the four compounds toward methyl methacrylate radicals (Equation 1) was determined by the retardation-of-polymerization method.[4] The results are shown in Table I as values of k_1, together with values for the ratio k_2/k_3, which can also be obtained from the kinetic data.







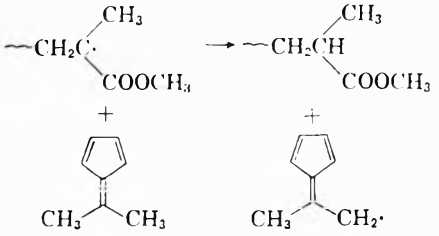


The results show that substitution of a cyclohexyl for a methyl causes no marked decrease in reactivity either with the fulvenes or the benzofulvenes. This would therefore seem to be convincing evidence that the site of radical attack on 6,6-dialkylfulvenes and benzofulvenes is at the ring positions and not at the external 6-position.[8]

(6) J. Thiele and K. Merck, *Ann.*, **415**, 257 (1918).

(7) J. Thiele, *Ber.*, **33**, 666 (1900).

(8) The possibility that the observed retardation occurs through chain transfer of one of the alkyl group hydrogens to the methacrylate radical (Equation 5) seems very unlikely for the following reasons: (i) The rate of such a reaction as Equation 5 should probably be about the same for dimethylfulvene, dimethylbenzofulvene, and dimethyldibenzofulvene. For the latter compound previous kinetic studies[3] have shown that the rate of Equation 5 cannot be more than 1/100th the reactivity of Ia or IIa and may actually be much less. (ii) Szwarc[9] has shown that with methyl radicals the rate of hydrogen-atom transfer from dimethyldibenzofulvene is much lower than the rate of addition to the external double bond, a fact which also indicates a rather low reactivity for these hydrogens in homolytic transfer reactions.



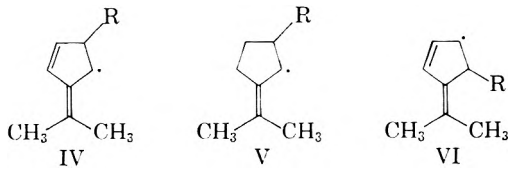
(9) F. Carnock and M. Szwarc, *J. Am. Chem. Soc.*, **81**, 4138 (1959).

TABLE I

RATE CONSTANTS FOR REACTION OF METHACRYLATE RADICALS WITH ALKYLFULVENES

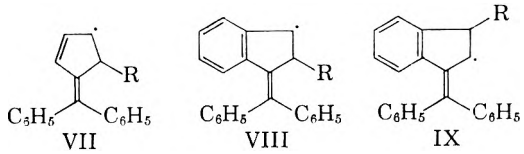
Compound	$k_1 \times 10^{-2}$ (L./mol.$^{-1}$/ Sec.$^{-1}$)	$(k_2/k_3) \times 10^{10}$
Ia	1.8	50
Ib	0.85	17
IIa	0.23	9
IIb	0.65	2

Although the k_1 values clearly indicate that radical attack on the dialkylfulvenes and benzofulvenes occurs at the ring positions, they do not tell us whether the reaction responsible for the observed retardation involves attack on the 2- or the 3-position. We are inclined, however, to believe it is the 2-position for the following reasons: The (k_2/k_3) values for all four of the compounds are much smaller than that observed in the same system for the styryl radical[1] $[(k_2/k_3) \times 10^{10} = 10^4]$. As we doubt that the internal double bond of radical IV would provide much stabilization, we would expect that IV, if formed, would behave in



a fashion similar to V and would show a (k_2/k_3) of the same order of magnitude as the styryl radical. On the other hand, VI, resulting from attack at the 2-position, should have considerable additional stabilization and a considerably smaller k_2/k_3 value, reflecting its lower reactivity. The results in Table I are thus in much better accord with attack at the 2-position for all four of the fulvenes and benzofulvenes studied, although before attaching too much significance to this conclusion, one should recall that one recent experience[10] has shown k_2/k_3 is not always a reliable measure of the resonance stabilization of a radical.

It is of interest to compare the behavior of the 6,6-dialkylfulvenes and benzofulvenes with their phenyl substituted counterparts.[2] In both cases going from the fulvene to the benzofulvene produces no large change in reactivity (k_1). However, going from 6,6-diphenylfulvene to diphenylbenzofulvene causes a 400 fold increase in k_2/k_3 while with the alkyl substituted compounds the k_2/k_3 values of the benzofulvenes are actually somewhat smaller than those of the fulvenes. In the phenyl substituted series the large increase in k_2/k_3 on going from fulvene to benzofulvene was attributed to a change from the 2- to the 3-position as the site of radical attack leading to retardation. One must consequently inquire why such a change is not also observed in the alkyl substituted case. We believe the reason is as follows. For maximum stabilization of the radicals VII and VIII (which would result from attack at the 2-position of the diphenyl compounds) it is necessary that at least one of the phenyl groups be able to be approxi-



mately coplanar with the 5-membered ring. This is possible for VII (from diphenylfulvene), but it is not possible for VIII, where the bulky R-group on one side and the aromatic ring on the other prevent either 6-phenyl group from even approaching coplanarity. Consequently radical VIII is not stabilized to the same extent as VII. As a result, VIII and the radical resulting from attack at the 3-position (IX), where one phenyl can still achieve approximate coplanarity, become of comparable stability. As the 3-position probably offers somewhat less steric hindrance to radical attack, it is the reaction at this site which predominates for diphenylbenzofulvene. On the other hand, in the alkyl fulvenes the radicals resulting from attack at the 2-position are approximately equally stabilized for both fulvenes and benzofulvenes, with the result that the k_2/k_3 values do not differ very greatly, and the site of radical attack responsible for retardation remains the same.

Exponents of the use of free valence as a means of predicting the preferred position for radical attack would expect that with the fulvenes the 6-position should intrinsically be the most reactive.[11] Our finding that dialkylfulvenes undergo radical attack at the ring positions does not, however, constitute evidence contradicting the correctness of predictions based on free valence, as one would expect that steric hindrance from the alkyl 6-substituents would bring about an enormous decrease in the rate of reaction at the 6-position, as witness our previous observation that 6,6-dimethylbenzofulvene is at least 10^6 times less reactive toward methacrylate radicals than dibenzofulvene itself. Under such circumstances the less hindered ring positions might easily become more reactive than the 6-position. We had hoped to be able to investigate this point more fully through study of fulvene itself, but unfortunately despite numerous careful attempts we were unable to to repeat the recent reported preparation of this compound.[12a] Angus and Bryce-Smith[12b] have

(10) J. L. Kice and F. Taymoorian, *J. Am. Chem. Soc.*, 81, 3405 (1959).

(11) E. D. Bergmann, "The Fulvenes," Chap. 3 in *Progress in Organic Chemistry*, V. 3, Academic Press, New York, N. Y., 1955; *cf.* pp. 90–6.

(12) (a) J. Thiec and J. Wiemann, *Bull. soc. chim. Fr.*, [5], 23, 177 (1956). (b) H. J. F. Angus and D. Bryce-Smith, *J. Chem. Soc.*, 1409 (1960).

also recently reported inability to repeat Thiec and Wiemann's work.

EXPERIMENTAL

Preparation of fulvenes. Dimethylfulvene (Ia). This was prepared by the method described by Thiele.[7] After purification by fractional distillation, the center cut, b.p. 43–44°/10 mm., was degassed on the vacuum line and distilled into a number of small ampoules which were then sealed and stored in the dark at −20°. Ia melts slightly above 0° and when stored as described shows no evidence of dimer or polymer formation even on relatively prolonged storage.

Dimethylbenzofulvene (IIa). The preparative procedure of Thiele and Merck[6] was followed with the additional precaution that the reaction mixture was kept under a nitrogen atmosphere. The reaction mixture was poured into water and the organic layer was taken up in benzene. The benzene layer was washed repeatedly with water, dried over sodium sulfate, and the benzene removed under reduced pressure. The residue was fractionally distilled through a short Vigreux column, and IIa was collected as a yellow oil, b.p. 89–93°/2 mm. Confirmation of the purity of IIa was provided by comparison of its ultraviolet absorption spectrum with that previously reported.[13] Purified IIa was stored under nitrogen at 0° until used.

Methylcyclohexylfulvene (Ib). Methyl cyclohexyl ketone was prepared by the method described by van Woerden.[14] A mixture consisting of 25.2 g. (0.2 mole) of the ketone and 13.2 g. (0.2 mole) of freshly distilled cyclopentadiene was added with stirring to a solution of 5 g. of sodium in 75 ml. of ethanol. The solution was stirred at room temperature for 3 hr. under nitrogen, at the end of which time it was poured into 250 ml. of water. The fulvene which separated was taken up in methylene chloride; the methylene chloride solution was washed with water, dried over sodium sulfate, and the methylene chloride removed under reduced pressure. The crude fulvene was purified by two fractional distillations under reduced pressure through a Vigreux column. There was obtained 8.0 g. (23%) of pure 6-methyl-6-cyclohexylfulvene, b.p. 72–73°/0.5 mm. Ultraviolet absorption spectrum in isooctane λ_{max}, 360 mμ (log ε, 2.5).

In view of the considerable sensitivity of fulvenes to oxygen, Ib was converted for analysis to its hexahydro derivative, 1-cyclopentyl-1-cyclohexylethane. Six grams of Ib was hydrogenated over platinum oxide in ethanol at 25° and 15 p.s.i. After 3.5 hr. the catalyst was removed by filtration, the solvent evaporated, and the residue distilled. There was obtained 3.5 g. (56%) of 1-cyclopentyl-1-cyclohexylethane, b.p. 103–104°/7 mm.

Anal. Calcd. for $C_{13}H_{24}$: C, 86.58; H, 13.42. Found: C, 86.12; H, 13.04.

6-Methyl-6-cyclohexylbenzofulvene (IIb). To 4 g. of sodium in 200 ml. of ethanol was added 16.7 g. (0.132 mole) of methyl cyclohexyl ketone and 20 g. (0.17 mole) of freshly distilled indene. The solution was refluxed under nitrogen for 8 hr. It was then poured into water and the organic layer was taken up in methylene chloride. The methylene chloride solution was washed and dried and the solvent removed under reduced pressure. The crude product was chromatographed on alumina using hexane as eluant and 100 g. of alumina for each 10 g. of crude product. The hexane was removed and the residues containing the benzofulvene were heated at 60–65° at 12–14 mm. pressure in order to remove unchanged indene. The residue from this treatment was then distilled in a molecular still (bath temp., 140°; pressure, 0.05 mm.) giving 6.0 g. (20%) of IIb. Ultraviolet absorption spectrum in isooctane: λ_{max}, 322 mμ (log ε, 3.79); 309 mμ (log ε, 3.86).

Four grams of IIb was hydrogenated over palladium-charcoal in ethanol solution for 4 hr. at room temperature and 15 p.s.i. The catalyst was removed by filtration, and the solvent was evaporated. The residue was distilled under reduced pressure giving 3.0 g. (74%) of 1-(1-cyclohexyl-1-ethyl-)indane, b.p. 143–145°/3 mm.

Anal. Calcd. for $C_{17}H_{24}$: C, 89.41; H, 10.59. Found: C, 89.57; H, 10.81.

Methyl methacrylate and *2,2'-azobisisobutyronitrile* were purified as previously described.[15]

Procedure for kinetic runs. For all of the compounds the procedure was the same as that previously used for dibenzofulvene.[4]

The results of the individual runs are given in Table II. The method of obtaining the k_1 and k_2/k_3 values from these data has been described.[4] In the present work the best plots were obtained in the various cases as follows: Ia and Ib, c = 0.075; IIa, c = any value less than 0.1; IIb, c = any value less than 0.01.

TABLE II

RESULTS OF INDIVIDUAL KINETIC RUNS AT 50° IN METHYL METHACRYLATE

Compound	(AIBN) × 10^3 (moles/l.)	(Fulvene) × 10^3 (moles/l.)	$\phi \times 10^{2a}$
Ia	5.41	67.0	23.8
	4.58	39.2	30.6
	9.62	50.1	28.0
	2.72	59.1	25.2
	2.91	37.9	32.1
	12.7	47.3	29.1
	6.17	40.3	31.5
Ib	4.93	42.0	28.5
	2.75	34.4	29.7
	10.4	52.4	26.6
	10.7	47.0	28.8
	3.84	24.3	36.6
	5.69	103	15.8
IIa	5.57	20.9	64.5
	5.34	46.3	44.7
	5.37	81.3	31.8
	2.46	45.6	40.1
	10.7	46.1	49.5
IIb	5.74	38.8	20.2
	6.08	109	8.30
	6.18	49.3	16.8
	10.4	59.6	15.3
	2.82	57.4	13.7

[a] $\phi = R/R_0$, where R = rate of polymerization in the presence of the fulvene and R_0 equals the rate in the absence of the fulvene at the same initiator concentration; $R_0 = 1.36 \times 10^{-4}(AIBN)^{1/2}$.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Intramolecular Radical Reactions. Decomposition of *o*-Methyl-, o-Benzyl-, and *o*-Phenylbenzoyl Peroxide

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Decompositions of *o*-methyl-, *o*-benzyl-, and *o*-phenylbenzoyl peroxides have been studied in carbon tetrachloride in the presence and absence of iodine and iodine plus water (Tables I–IV). In carbon tetrachloride alone, for the *o*-methyl compound the ratio of decarboxylation to intramolecular hydrogen transfer is 2.5 to 1. The radical derived from hydrogen transfer undergoes cross-termination with the trichloromethyl radical and like-termination. In the *o*-benzyl compound intramolecular hydrogen transfer occurs to the exclusion of decarboxylation or attack on the adjacent ring. In the *o*-phenyl compound decarboxylation occurs to the extent of 26% and, in confirmation of previous reports,[3,4] intramolecular aromatic substitution is an important process (38% yield of 3,4-benzcoumarin, IX). Decompositions of the peroxides in carbon tetrachloride in the presence of iodine and water result in substantial increases in yields of the corresponding acids, suggestive of the ability of the scavenger to compete with the intramolecular reactions.

Of the many detailed investigations of diacyl peroxides[1] little attention has been directed toward the *ortho*-substituted benzoyl peroxides.[2–4] The possibilities of intramolecular reaction that members of this class offer and the information that might be obtained thereby with respect to competition between intra- and intermolecular processes has prompted the present study of the decomposition of *o*-methyl-, *o*-benzyl-, and *o*-phenylbenzoyl peroxide.

RESULTS

The *o*-substituted benzoyl peroxides employed in this study were subjected to thermal decomposition principally under three sets of conditions: a) in carbon tetrachloride; b) in carbon tetrachloride containing iodine; c) in carbon tetrachloride, iodine and water. The data are summarized in Tables I–III. The assignment of structure to *o*-(β,β,β-trichloroethyl)benzoic acid (Table I) is based on conversion to homophthalic acid by hydrolysis under strongly acidic conditions and dehydrochlorination with base to give a compound of the expected analysis and ultraviolet absorption spectrum for *o*-(β,β-dichlorovinyl)benzoic acid. The characterization of the high melting acid frac-

TABLE I

PRODUCTS OF DECOMPOSITION OF *o*-TOLUOYL PEROXIDE AT 80°

Products	Yield in Moles per Mole of Peroxide: Carbon tetrachloride[a]	Carbon tetrachloride,[a] iodine[b]	Carbon tetrachloride,[a] iodine and water
Carbon dioxide	1.2[c]		
Hexachloroethane	.67		
o-Chlorotoluene	1.1		
o-Iodotoluene		.98	.07
o-Cresyl *o*-toluate	.04	.02	.02
Phthalide	.1	.2	.08
o-Toluic acid		.48	1.7
o-(β,β,β-Trichloroethyl)-benzoic acid	.44		
1,2-Di-*o*-carboxyphenyl-ethane	.04		

[a] Initial peroxide concn., 0.055*M*. [b] Initial iodine concn., 0.25*M*. [c] Average of three determinations: 1.14, 1.19, 1.38.

TABLE II

PRODUCTS OF DECOMPOSITION OF *o*-BENZYLBENZOYL PEROXIDE AT 80°

Product	Yield in Moles per Mole of Peroxide: Benzene[a]	Carbon tetrachloride[a]	Carbon tetrachloride[a] and iodine[b]	Carbon tetrachloride,[a] iodine[b] and water
o-Benzylbenzoic acid	0.63	0.64	0.99	1.2
3-Phenylphthalide	.62	.66	.89	.75
1,2-Di-*o*-carboxyphenyl-1,2-diphenylethane[c]	.35	.34		

[a] Initial peroxide concn., 0.036*M*. [b] Initial iodine concn., 0.35*M*. [c] Mixture of *meso* and *dl* material.

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(3) G. W. Kenner, M. A. Murray, and C. M. B. Tylor, *Tetrahedron*, **1**, 259 (1957).

(4) D. B. Denney and P. P. Klemchuk, *J. Am. Chem. Soc.*, **80**, 3289 (1958).

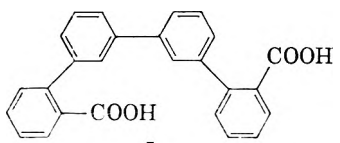
TABLE III

PRODUCTS OF DECOMPOSITION OF o-PHENYLBENZOYL PEROXIDE AT 80°[a]

Products	Yield in Moles per Mole of Peroxide: Carbon tetrachloride	Carbon tetrachloride, iodine, and water
Carbon dioxide	0.53	
o-Chlorobiphenyl	0.39	
3,4-Benzcoumarin	0.77 (0.49[b])	0.88
o-Phenylbenzoic acid	0.18 (0.31[b])	0.84
"Dimeric acid"	0.05	
Fractions A, B, and C	(0.2)	

[a] Initial peroxide concn., 0.017*M*. [b] Data of Kenner, Murray and Tylor, ref. 3.

tion from *o*-benzylbenzoyl peroxide as a mixture of *meso*- and *dl*-1,2-di-*o*-carboxyphenyl-1,2-diphenylethane (Table II) is based on the conversion of the mixture to the corresponding *meso*- and *dl*-dimethyl esters, separation of the esters into the two pure components (possessing markedly similar infrared spectra but differing in melting point), and establishment of the identity of the higher melting diester with the major product obtained from the decomposition of di-*t*-butyl peroxide in the presence of methyl *o*-benzylbenzoate by the Kharasch coupling reaction.[5] The major product of the decomposition of *o*-phenylbenzoyl peroxide, 3,4-benzcoumarin, has been reported by two groups[3,4] since the start of this work. The materials referred to in Table III as dimeric acid and Fractions A, B and C were not obtained in pure form. The principal component of the dimeric acid is considered to be 3,3′-(di-*o*-carboxyphenyl)biphenyl (I) on the basis of the marked similarity in infrared spectrum to *o*-phenylbenzoic acid, the probable mode of formation, and de-



I

carboxylation to a material exhibiting a prominent mass spectral peak at mass number 306, the expected parent peak for a quaterphenyl. Fractions A, B, and C are halogen-containing mixtures showing absorption in the infrared characteristic of acids (Fraction A) and of lactones of the 3,4-benzocoumarin type (Fractions B and C). A search for hexachloroethane in the products of decomposition of *o*-phenylbenzoyl peroxide failed to reveal any of this material. Vapor phase chromatographic control experiments showed that it would have been detected if present at a level above 0.02 mole per mole of peroxide. Vapor phase chromatography likewise failed to reveal the presence of biphenyl.

(5) M. S. Kharasch, H. C. McBay, and W. H. Urry, *J. Org. Chem.*, 10, 401 (1945).

The negligible amount of carbon dioxide from the decomposition of *o*-benzylbenzoyl peroxide prompted the examination of the extent of decarboxylation in the decomposition of *p*-benzylbenzoyl peroxide. Decomposition in carbon tetrachloride at 80° afforded carbon dioxide (1.06 moles per mole of peroxide), hexachloroethane, *p*-chlorodiphenylmethane (0.98 mole per mole of peroxide), *p*-benzylbenzoic acid (0.2 mole per mole of peroxide), and two unidentified fractions. Vapor phase chromatographic analysis failed to reveal diphenylmethane in the *p*-chlorodiphenylmethane fraction.

The rates of decomposition of the peroxides in carbon tetrachloride were measured at concentrations approximating those of the product studies, both in the presence and absence of styrene.[6] The data are summarized in Table IV. The rates

TABLE IV

DECOMPOSITION OF SUBSTITUTED BENZOYL PEROXIDES IN CARBON TETRACHLORIDE AT 80°

Substituent	Initial Concn., *M*	Styrene Concn., *M*	Carbon Dioxide Evolution, %[a]	$k_1 \times 10^4$, Sec.$^{-1}$
Hydrogen	0.017	[b]	90[c]	0.30[b]
o-Methyl	0.055	0	~60	1.15
	0.049	1.0		1.0
o-Benzyl	0.033	0	trace	1.34
	0.010	0		1.31
	0.037	1.0		1.34
p-Benzyl	0.007	0	53	2.9
	0.014	0.2		2.4
o-Phenyl	0.019			2.1
	0.017		26	2.0
	0.016	1.0		2.5
	0.015	1.0		2.6

[a] Based on two moles per mole of peroxide. [b] Ref. 6, rate measured in the presence of 3,4-dichlorostyrene. [c] Ref. 8.

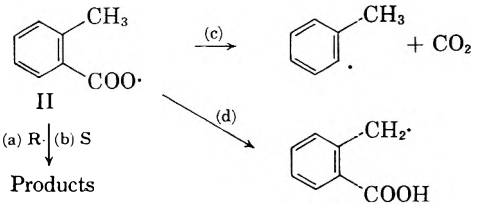
of the *ortho*-substituted peroxides are within a factor of three and all are several-fold faster than benzoyl peroxide. Of the benzoyl peroxides reported by Blomquist and Buselli substitution in the *ortho*-position (*o*-methoxy, *o*-nitro, *o*-phenoxy, *o*-chloro, and *o*-methyl) resulted in an increase in rate of decomposition, measured in acetophenone solution. Substitution in the *meta*- and *para*-positions in general produces a smaller effect on rate[2b,6] (ρ of -0.38 in dioxane at 80°).[6] Comparison of the rates in the presence and absence of styrene in this study is suggestive of the absence of induced decomposition in the isolation experiments employing *o*-benzyl- and *o*-phenylbenzoyl peroxide and of 15–20% induced decomposition in the experiments with *o*-phenylbenzoyl peroxide and of 15–20% induced decomposition in the experiments with *o*-methyl- and *p*-benzylbenzoyl peroxide.

(6) C. G. Swain, W. H. Stockmayer, and J. T. Clarke, *J. Am. Chem. Soc.*, 72, 5426 (1950).

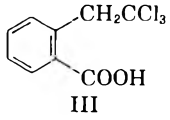
DISCUSSION

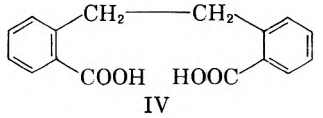
The rate-determining step in the thermal decomposition of benzoyl peroxide has been shown to be homolytic fission of the oxygen-oxygen bond[7] since decomposition in carbon tetrachloride in the presence of iodine and water (proceeding at the same rate as in carbon tetrachloride alone) afforded a high yield of benzoic acid, *i.e.*, capture of carboxylate radical by iodine followed by hydrolysis of the acyl hypoiodite to acid. DeTar and Lamb recently have confirmed this result[8] and have extended the technique to the problem of determination of multiple bond cleavage in the rate-determining step of decomposition of δ-phenylvaleroyl peroxide. The high yields of acid obtained by subjection of the *ortho*-substituted peroxides of this study to the conditions of Hammond and Soffer may be interpreted in the same way, *viz.* oxygen-oxygen fission in the rate-determining step, assuming that here also the rates of decomposition are independent of the iodine and water.

Following rate-determining fission of the oxygen-oxygen bond in *o*-toluoyl peroxide, four possibilities are open to the radical II: a) termination reactions, b) reactions with scavengers, c) decarboxylation, and d) hydrogen transfer to afford the *o*-carboxybenzyl radical. From the decomposition in carbon tetrachloride in the presence of



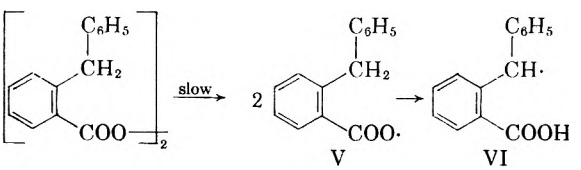
iodine and water *o*-toluic acid was obtained in 85% yield. The capture of II by iodine of initial concentration 0.25*M* indicates that this process is occurring at a time later than that required for primary[9] (cage) reaction, and thus indicates that the decarboxylation and hydrogen transfer observed in the absence of scavengers must occur principally after separation of the original radical partners. The phthalide isolated from the iodine-water experiments sets an upper limit of 4% on the extent of hydrogen transfer within the solvent cage. In the absence of added scavengers, decarboxylation and hydrogen transfer account for 90% of radical II, with the former process proceeding approximately two and one-half times faster than the latter. In comparison, decomposition of benzoyl peroxide in *toluene* at 84° results in 74–77% decarboxylation and in benzene at 80° in 80–86% decarboxylation.[8] If one attributes the 8% decrease in decarboxylation in toluene *vs.* benzene to abstraction of benzyl hydrogen by benzoate, one obtains a ratio of rate of decarboxylation to hydrogen transfer (intermolecular analog of path d) of ten to one, suggestive of a small (several-fold) advantage for the intramolecular reaction over the intermolecular counterpart. That the advantage is not larger may be associated with the geometry of the transition state for the intramolecular hydrogen transfer which would appear to be unfavorable for stabilization by the ring π electrons of the developing benzyl radical, a restriction that obviously does not apply to the intermolecular case. The principal fate of the *o*-methylphenyl radical, formed by loss of carbon dioxide from II, is chain transfer with the solvent to give *o*-chlorotoluene and the trichloromethyl radical. The correspondence in yield of *o*-chlorotoluene with yield of carbon dioxide indicates that intramolecular hydrogen transfer within the *o*-methylphenyl radical to give the benzyl radical, if operative at all, is unimportant. The *o*-carboxybenzyl radical derived from hydrogen transfer in II appears to be of sufficient stability to achieve statistical distribution and is ultimately consumed by cross-termination with the trichloromethyl radical giving *o*-(β,β,β-trichloroethyl)benzoic acid(III) and like-termination giving 1,2-di-*o*-carboxyphenylethane (IV). In the presence





of iodine the *o*-chlorotoluene is replaced by a comparable amount of *o*-iodotoluene, and some *o*-toluic acid is formed. The latter may be attributed to hydrolysis of acyl hypoiodite by adventitious moisture. Under all of the conditions of Table I a constant, small amount (2–4%) of *o*-cresyl *o*-toluate is obtained, attributed to cyclic ester formation or cage reaction.

The principal feature of the decomposition of *o*-benzylbenzoyl peroxide (Table II) is the cleanness of the reaction. The increased lability of the benzhydryl hydrogen (over benzyl hydrogen, compare Tables I and II) results in hydrogen transfer to the exclusion of decarboxylation. The four products obtained in this decomposition, accounting for over 95% of the peroxide, are easily derivable from termination reactions of radical VI: disproportionation to give equal amounts of 3-phenylphthalide and *o*-benzylbenzoic acid; recombination to give *meso*- and *dl*-1,2-di-*o*-carboxy-



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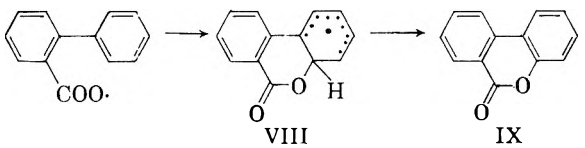
(8) D. F. DeTar and R. C. Lamb, *J. Am. Chem. Soc.*, 81, 122 (1959).

(9) R. M. Noyes, *J. Am. Chem. Soc.*, 77, 2042 (1955).

phenyl-1,2-diphenylethane.[10] The increase in yield of *o*-benzylbenzoic acid from decomposition of the peroxide in carbon tetrachloride in the presence of iodine and water indicates that efficient scavengers can compete with the hydrogen transfer reaction and points to capture of a minimum of 60% of V by iodine. (The 37% of 3-phenylphthalide from this experiment probably is derived from capture of VI by iodine followed by conversion to the lactone although conceivably some of the lactone might arise from the acyl hypoiodite of V.) The increase in yield of acid under these conditions may be interpreted in terms of hydrogen transfer occurring later than the time required for a cage reaction and indicates that the hydrogen transfer is intramolecular rather than intermolecular. Further evidence in favor of intramolecular hydrogen transfer within radical V, the inherently more attractive path, is found in the greatly reduced importance of hydrogen transfer in the decomposition of *p*-benzylbenzoyl peroxide in which substantial amounts of carbon dioxide are evolved in spite of the availability to intermolecular abstraction processes of benzhydryl hydrogen.

The product data for *o*-benzylbenzoyl peroxide indicate abstraction of hydrogen in preference to attack on the neighboring aromatic ring. *o*-Phenylbenzoyl peroxide[3,4] represents a case in which the principal choices available to the carboxylate radical are attacked on the adjacent aromatic ring or decarboxylation. The importance of the former path is reflected in the isolation of 3,4-benzcoumarin (IX) in 36% yield, in confirmation of the results of Kenner, Murray, and Tylor,[3] and of Denney and Klemchuk,[4] and in the decreased extent of decarboxylation in this system. The obser-



VIII IX

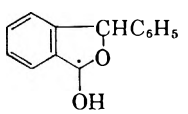
vation of 80–86% decarboxylation of benzoyl peroxide in *benzene*[8] *vs.* 26% decarboxylation of *o*-phenylbenzoyl peroxide in carbon tetrachloride indicates an advantage for the intramolecular process over the intermolecular counterpart. The absence of hexachloroethane from the product mixture and the complexity of this mixture are suggestive that radical VIII or, alternatively, the *pi* complex related to VIII is formed to an important extent and is of moderate stability, ultimately disappearing by disproportionation (formation of 3,4-benzcoumarin), by cross-termination reactions with trichloromethyl radical (Fractions A, B, C) generated in the formation of the *o*-chlorobiphenyl and by like termination reactions leading to a large number of possible products (including dimeric acid I). Of the 2-biphenylyl radicals derived from decarboxylation of *o*-phenylbenzoate radicals, two-thirds are converted to *o*-chlorobiphenyl by chain transfer with the solvent, leaving a maximum of one third that may be consumed *via* an intramolecularly complexed species. Decomposition of the peroxide in carbon tetrachloride in the presence of iodine and water affords a small increase in yield of 3,4-benzcoumarin (44% *vs.* 36%) and a large increase in yield of *o*-phenylbenzoic acid (42% *vs.* 9% in carbon tetrachloride alone) indicative of the occurrence in the absence of added scavengers of decarboxylation after separation of the original radical partners, in agreement with the other *o*-substituted cases of this study.

The possible formation of VIII to the extent of 74% (based on the observation of 26% decarboxylation) and destruction by paths in addition to the one leading to formation of lactone IX (36%) further complicates interpretation of the isotope effect, k_H/k_D, of 1.32 observed in the conversion of 2-(2-deuterophenyl)benzoyl peroxide[4] to the (partially) deuterium-labeled 3,4-benzcoumarin and consideration of the related question of reversibility in the formation of VIII from the carboxylate radical.

The decomposition of *o*-phenoxybenzoyl peroxide to yield phenyl salicylate[2c] may represent a case exhibiting the further possibility of association of carboxylate radical with the aryl carbon attached to the oxygen, resulting in over-all phenyl migration, a process that also appears to be operative in the conversion of silver 3,3,3-triphenylpropionate to phenyl 2,2-diphenylacrylate by the action of bromine in carbon tetrachloride.[11]

It is of interest to compare the data of the diaroyl peroxides of this study with the diacyl peroxides, δ-phenylvaleroyl peroxide,[12,8] and ε-phenylcaproyl peroxide.[13] In these cases a substantial percentage of the products appears to arise from cage (and/or cyclic) reactions. The carboxylate radicals that escape cage reaction undergo decarboxylation.[14] Although intramolecular hy-

(10) Conversion of VI to VII is a further possibility but such a formulation is neither required by the data nor able to account as satisfactorily for the formation of the coupling product of VI.



VII

A comparison at equal radical concentrations of the efficiency toward polymerization of styrene of *o*-benzylbenzoyl peroxide *vs.* benzoyl peroxide indicates that the former is about half as efficient as the latter.

(11) J. W. Wilt and D. D. Outhoudt, *J. Org. Chem.*, **23**, 218 (1958).

(12) D. F. DeTar and C. Weis, *J. Am. Chem. Soc.*, **78**, 4296 (1956).

(13) C. A. Grob and H. Kammüller, *Helv. Chim. Acta*, **40**, 2139 (1957).

(14) For thermochemical evidence on the greater exothermicity of carbon dioxide loss from alkylcarboxylate than from arylcarboxylate, see L. Jaffe, E. J. Prosen, and M. Szwarc, *J. Chem. Phys.*, **27**, 416 (1957).

drogen transfer apparently cannot compete with decarboxylation in these cases, intramolecular reactions may occur within the resulting primary carbon radicals, as seen in the isolation of tetralin in 30% yield from the decomposition of δ-phenylvaleroyl peroxide in benzene[12] and of 5,6-diphenyldecane in 14% yield from the decomposition of ε-phenylcaproyl peroxide.[13,15]

EXPERIMENTAL

o-Toluic acid was prepared by carbonation of the Grignard reagent derived from *o*-bromotoluene (Eastman white label). Recrystallization from benzene-hexane afforded material, m.p. 104–105° (lit. m.p. 104–105°).

o-Toluoyl peroxide was prepared by the general method[16] of Price and Krebs utilizing ether instead of toluene as solvent for the *o*-toluoyl chloride (prepared from the acid and thionyl chloride and distilled before use). Recrystallization of the crude product from ethanol afforded *o*-toluoyl peroxide as colorless needles, m.p. 54.5–55° (lit.,[2b] m.p. 52.5–53.5°) in a yield of 78%.

o-Cresyl o-toluate was prepared by reaction of *o*-toluoyl chloride and *o*-cresol in ethyl ether containing an equivalent of pyridine. After 16 hr. at 25° the mixture was filtered, the ether was washed three times with dilute hydrochloric acid, three times with dilute sodium hydroxide solution, with water and dried over magnesium sulfate. Filtration, removal of the ether, and distillation of the residue afforded the ester, b.p. 135–136° at 1 mm., n_D^{27} 1.5651.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.80; H, 6.40.

Decomposition of o-toluoyl peroxide (*See* Table I). A. *In carbon tetrachloride.* A 6.0-g. sample (22 mmoles) of the peroxide in 400 ml. of carbon tetrachloride was placed in a flask equipped with a gas inlet tube and condenser. The top of the condenser was connected to a trap and this in turn to a gas washing bottle, protected from the atmosphere by an Ascarite-filled tube, containing a standardized barium hydroxide solution. The peroxide solution was swept with nitrogen for 1 hr. with the barium hydroxide bottle disconnected. The bottle then was connected, the nitrogen flow was decreased, and the peroxide solution was heated at reflux for 20 hr. Carbon dioxide yield, determined by titration of the excess hydroxide in the barium hydroxide solution by standard perchloric acid, was 26.1, 25.1, 30.4 mmoles in three decompositions.

One half of the carbon tetrachloride solution was reduced to dryness through a 20-inch Vigreux column. The residue was treated with pentane, filtered from a small amount of 1,2-di-*o*-carboxyphenylethane (see below), and chromatographed on a silica gel column in pentane. The first compound eluted by pentane was hexachloroethane, 1.05 g. Recrystallization from ligroin afforded material, m.p. 188–189° (sealed tube); mixed melting point showed no depression. The second component eluted by pentane was *o*-chlorotoluene, 0.64 g., n_D^{20} 1.5247 (lit. n_D^{20} 1.5247) of identical infrared spectrum with an authentic sample. From a control experiment with hexachloroethane and *o*-chlorotoluene, 60% of the former and 33% of the latter were reisolated in pure form by the above procedure. Elution with pentane-ether (10:1) afforded 0.11 g. of *o*-cresyl *o*-toluate, identical in infrared spectrum with that of the authentic sample. Elution with pentane-ether (5:1) yielded 1.2 g. of an acid, *o*-(β,β,β,-trichloroethyl)benzoic acid contaminated with a small amount of phthalide. Recrystallization from ligroin afforded the pure acid, m.p. 113–114°.

Anal. Calcd. $C_9H_7O_2Cl_3$: C, 42.64; H, 2.78; Cl, 41.97; neut. equiv. 254. Found: C, 42.44, 42.70; H, 2.80, 3.19; Cl, 41.42, 41.93; neut. equiv., 251.

A 350-mg. sample of this acid was added to 1 ml. of concd. sulfuric acid and heated on a steam bath for 1 hr. Six milliliters of water was added and heating was continued for 1 hr. The solution was cooled to room temperature and extracted with benzene. Upon cooling the aqueous solution to 0°, crystals separated. One recrystallization from water afforded 200 mg. of homophthalic acid, m.p. 175° (lit.,[17] m.p. 175°). The infrared spectrum was identical in all respects with an authentic sample of homophthalic acid prepared from indene.

Elution of the silica gel column with pentane-ether (1:1) afforded 0.12 g. of 1,2-di-*o*-carboxyphenylethane. Recrystallization from 95% ethanol gave material, m.p. 228–230° (lit.,[18] m.p. 231°). The diacid was esterified with diazomethane and the dimethyl ester was recrystallized from methanol yielding material, m.p. 99–100° (lit.,[18] m.p. 100°).

The second half of the original carbon tetrachloride solution of the peroxide decomposition was heated under reduced pressure to remove solvent and the bulk of the hexachloroethane and *o*-chlorotoluene. Treatment of the residue with petroleum ether (b.p. 30–60°) afforded 0.11 g. of a colorless solid, crude 1,2-di-*o*-carboxyphenylethane, m.p. 180–220°, raised to m.p. 225–229° by recrystallization from ethanol. The petroleum ether filtrate was chromatographed on alumina. Elution with benzene-ether (7:1) afforded 0.16 g. of phthalide, m.p. 73–74° after recrystallization from ligroin (b.p. 90–100°); mixture melting point with an authentic sample gave no depression and infrared spectra were identical.

B. *In benzene.* Analysis was made only for 1,2-di-*o*-carboxyphenylethane. A 2.2-g. sample of *o*-toluoyl peroxide in 40 ml. of benzene was heated at reflux for 24 hr. during which time a small amount of precipitate appeared. The mixture was cooled, filtered, giving a residue of 109 mg. of 1,2-di-*o*-carboxyphenylethane, m.p. 231–232°.

C. *In carbon tetrachloride containing iodine.* A solution of 6 g. of *o*-toluoyl peroxide and 25 g. of iodine in 400 ml. of carbon tetrachloride was heated at reflux for 17 hr. The solution was cooled and the supernatant liquid was decanted from the precipitated iodine. Excess iodine was destroyed by extraction of the cooled solution with sodium bisulfite solution. The dried carbon tetrachloride layer was reduced to a small volume, diluted with petroleum ether (b.p. 30–60°) and chromatographed on silica gel. Elution with petroleum ether afforded 3.59 g. of *o*-iodotoluene, n_D^{20} 1.6030 (lit. n_D^{20} 1.6085), identical in infrared spectrum with authentic material. A control experiment identical in procedure to the actual product isolation indicated 80% recovery of *o*-iodotoluene. Elution with petroleum ether–ether (100:1) afforded 0.1 g. of *o*-cresyl *o*-toluate. Elution with petroleum-ether–ether (10:1) afforded 1.3 g. of *o*-toluic acid, m.p. 104–105°, mixed m.p. 104–105°. Elution with pet. ether-ether (5:1) afforded 0.28 g. of a compound, m.p. 122–128°, that was not identified. (Sublimation afforded material, m.p. 135–136°.) Elution with petroleum ether–ether (4:1) afforded 0.62 g. of phthalide, m.p. 72–73°; mixed melting point showed no depression.

D. *In carbon tetrachloride containing iodine and water.* A mixture of 3 g. of *o*-toluoyl peroxide, 27 g. of iodine, 75 ml. of water, and 200 ml. of carbon tetrachloride was heated at reflux for 20 hr. Excess iodine was destroyed by extraction with bisulfite solution. The bisulfite solution was extracted with ether and the combined ether–carbon tetrachloride

(15) For examples of related intramolecular aromatic substitution reactions, see S. Winstein, R. Heck, S. Lapporte, and R. Baird, *Experientia*, 12, 138 (1956); see also D. B. Denney and P. P. Klemchuk (ref. 4).

(16) C. C. Price and E. Krebs, *Org. Syntheses*, Coll. Vol. III, 649 (1955).

(17) O. Grummitt, R. Egan, and A. Buck, *Org. Syntheses*, Coll. Vol. III, 449 (1955).

(18) C. Fischer and R. Wolffenstein, *Chem. Ber.*, 37, 3219 (1904).

phases were extracted with sodium hydroxide solution. Acidification with hydrochloric acid, extraction of the aqueous phase with ether, drying of the ether phase over magnesium sulfate, filtration, and removal of the ether afforded 2.6 g. of *o*-toluic acid, m.p. 103–104°; mixture melting point showed no depression.

o-(β,β-Dichlorovinyl)benzoic acid. A 400-mg. sample of *o*-(β,β,β-trichloroethyl)benzoic acid, 1 g. of potassium hydroxide, and 30 ml. of 95% ethanol was heated on a steam bath for 0.5 hr. Dilution with water and acidification with hydrochloric acid gave a solid. Recrystallization from isooctane afforded 200 mg., m.p. 117–118°, λ_{max}^{250} in ethanol (ϵ = 8,040), λ^{290} (ϵ = 2,250).

Anal. Calcd. for $C_9H_6O_2Cl_2$: C, 49.81; H, 2.78; Cl, 32.66. Found: C, 50.03; H, 2.63; Cl, 32.95.

o-Benzylbenzoic acid was prepared by the reduction of *o*-benzoylbenzoic acid according to the procedure of Barnett, Cook, and Nixon,[19] m.p. 115–117° (lit.,[19] m.p. 118°).

o-Benzylbenzoyl peroxide. To a solution of 30 g. of *o*-benzylbenzoic acid in 100 ml. of anhydrous ethyl ether was added 6 ml. of pyridine followed by the slow addition of 15 ml. of thionyl chloride with stirring (magnetically). The mixture was stirred for 3 hr. at room temperature and filtered to remove the pyridine hydrochloride. Removal of the ether under reduced pressure afforded a light yellow oil, *o*-benzylbenzoyl chloride. This liquid was dissolved in 150 ml. of petroleum ether, (b.p. 30–60°). After standing at room temperature for 30 min. the solution was filtered to remove a small amount of insoluble matter and cooled to −80°, resulting in the separation of the acid chloride as a semi-solid mass. When the acid chloride was needed, the petroleum ether layer was decanted and the acid chloride was dissolved in 120 ml. of ether. To this ether solution was added 6 g. of sodium peroxide and 10 drops of water. The mixture was stirred for 6 hr. at 0° during which time 1 ml. of water was added. The mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The colorless residue was dissolved in 50 ml. of chloroform and poured into 250 ml. of methanol with stirring, resulting in the slow precipitation of needles, 18 g. The 18-g. sample was dissolved in 20 ml. of chloroform, added to 100 ml. of methanol and cooled, yielding 16 g. (53% yield based on acid), m.p. 72.5–73°.

Anal. Calcd. for $C_{28}H_{22}O_4$: C, 79.60; H, 5.25. Found: C, 79.41; H, 5.07. Iodometric analysis indicated a purity of 99 ± 1%.

Decomposition of o-benzylbenzoyl peroxide (*see* Table II). Description of decomposition in carbon tetrachloride is reported in detail. Data on decomposition in benzene, in carbon tetrachloride and iodine, in carbon tetrachloride in the presence of iodine and water are summarized in Table II. Product isolations were made by the procedure described below and those described under *o*-toluoyl peroxide.

In carbon tetrachloride. A 12-g. sample of *o*-benzylbenzoyl peroxide in 800 ml. of carbon tetrachloride was decomposed at reflux temperature under slow nitrogen flow for 20 hr. as described above for *o*-toluoyl peroxide. A white precipitate appeared in the carbon tetrachloride solution as the reaction progressed. The yield of carbon dioxide was negligible. The carbon tetrachloride reaction mixture was cooled and filtered affording a residue of 4.2 g. This material was dissolved in sodium carbonate solution and reprecipitated by hydrochloric acid, 4.1 g. dec. p. 270–290°, insoluble in methanol or benzene, fairly soluble in acetone. The acid gave analyses corresponding to 1,2-di(*o*-carboxyphenyl)-1,2-diphenylethane, a mixture of the *meso* and *dl* modifications.

Anal. Calcd. for $C_{28}H_{22}O_4$: C, 79.60; H, 5.25; neut. eq., 211. Found: C, 79.32; H, 5.29; neut. eq., 222.

A 2.0-g. sample of the acid was esterified with diazomethane. Repeated recrystallizations from methanol-benzene gave a dimethyl ester, m.p. 207–207.5°.

Anal. Calcd. for $C_{30}H_{26}O_4$: C, 79.98; H, 5.82. Found: C, 80.01; H, 5.96.

The infrared spectrum of this material was identical with the material prepared by use of the Kharasch coupling reaction[5] on methyl *o*-benzylbenzoate (see below). From the mother liquors a second isomer was obtained, m.p. 143–145°, markedly similar in infrared spectrum to the 207° compound.

Anal. Calcd. for $C_{30}H_{26}O_4$: C, 79.98; H, 5.82. Found: C, 79.77; H, 6.00.

One half of the original carbon tetrachloride filtrate from the peroxide decomposition was reduced to dryness under reduced pressure, dissolved in ether, and extracted with aqueous sodium hydroxide solution. Acidification afforded 2.0 g. of crude *o*-benzylbenzoic acid, identical in infrared spectrum to authentic material. Reprecipitation and recrystallization from acetic acid gave material, m.p. 114–117°, mixed melting point with authentic sample 115–117°. The ether solution from which the *o*-benzylbenzoic acid had been extracted was dried over magnesium sulfate, filtered, and evaporated leaving 1.95 g., m.p. 110–115°, of crude 3-phenylphthalide of identical infrared spectrum with authentic material. Recrystallization from 95% ethanol gave material, m.p. 114–115°; mixture melting point with an authentic sample of 3-phenylphthalide[20] gave no depression.

Subjection of a portion of the original decomposition solution (after removal of the dimeric acid by filtration) to chromatography on silica gel afforded only the same two products reported above, *o*-benzylbenzoic acid and 3-phenylphthalide.

1,2-Di(o-carbomethoxyphenyl)-1,2-diphenylethane. A solution of 8.6 g. of methyl *o*-benzylbenzoate (b.p. 167–170° at 10 mm., lit.,[19] b.p. 320° at 760 mm., prepared by Fischer esterification of the corresponding acid) and 6.0 g. of di-*t*-butyl peroxide was heated at 125° for 52 hr. Repeated recrystallizations of the residue from acetone afforded 3.5 g. (40% yield) of material, m.p. 204–205°, identical in infrared spectrum with the diester derived from the diacid isolated from the peroxide decomposition above, mixture m.p. 204–206°.

Reaction of silver o-benzylbenzoate with iodine. A 175-ml. portion of carbon tetrachloride was distilled from phosphorus pentoxide into a flask containing 10 g. of silver *o*-benzylbenzoate (prepared by the usual procedure—addition of aqueous silver nitrate solution to an aqueous solution of the acid at *p*H of 9, followed by filtration, washing, and rigorous drying of the silver salt). An 8-g. sample of iodine was added and the mixture was heated at reflux for 17 hr. The mixture was filtered and excess iodine was destroyed by extraction of the filtrate by sodium bisulfite solution. From the filtrate was isolated 1.0 g. of 3-phenylphthalide and 3.3 g. of *o*-benzylbenzoic acid by the procedure described above.

Effectiveness of o-benzylbenzoyl peroxide in polymerization of styrene. A 0.044-g. sample of the peroxide was dissolved in 25 ml. of freshly distilled styrene. To a second 25-ml. portion of styrene was added 0.145 g. of benzoyl peroxide. To a third flask was added 25 ml. of styrene alone. The solutions were heated for 1 hr. at 80°, cooled, and poured into 200 ml. of methanol. The polystyrene (softening point 125–165°) obtained from the sample of pure styrene, the benzoyl peroxide–initiated sample and the *o*-benzylbenzoyl peroxide–initiated sample amounted to 0.1 g., 4.6 g., and 2.1 g., respectively. In conjunction with the first order rate constants for decomposition of these two peroxides (see Table IV), the polystyrene yields indicate that *o*-benzylbenzoyl peroxide is approximately half as effective as benzoyl peroxide in initiating the polymerization of styrene.

o-Phenylbenzoic acid was prepared from fluorenone by

(19) E. de B. Barnett, J. W. Cook, and I. G. Nixon, *J. Chem. Soc.*, 508 (1927).

(20) F. Ullmann, *Ann.*, 291, 23 (1896).

the procedure of Gutsche and Johnson,[21] m.p. 112–113° (lit.[21] m.p. 110–113°).

o-Phenylbenzoyl chloride was prepared by the action of thionyl chloride on the acid. Distillation afforded material, b.p. 99.5–101° at 0.3 mm. (lit.,[22] b.p. 169° at 16 mm.). Some closure to fluorenone occurs during distillation (weak carbonyl absorption in the infrared at 1728 cm.$^{-1}$).

o-Phenylbenzoyl peroxide was prepared by the general procedure of Price and Krebs.[16] The toluene solution of product was taken to a residual oil under reduced pressure. The oil solidified on treatment with pentane. Recrystallization from benzene–petroleum ether (b.p. 30–60°) afforded material of dec. p. 101.5–102.5° (lit.,[3,4] dec. p. 107–108°).

Anal. Calcd. for $C_{26}H_{18}O_4$: C, 79.17; H, 4.60. Found: C, 79.27; H, 4.65.

Decomposition of o-phenylbenzoyl peroxide in carbon tetrachloride (Table III). A 1-g. sample of the peroxide in 150 ml. of carbon tetrachloride was decomposed under slow nitrogen flow for 21 hr. at reflux temperature as described above for *o*-toluoyl peroxide. Carbon dioxide yield amounted to 0.53 mole per mole of peroxide. (A duplicate run gave the same value: 0.53 mole.) Concentration of the carbon tetrachloride solution through a 20-inch Vigreux column to a small volume and cooling afforded 0.05 g. of base-soluble material, referred to below as dimeric acid, dec. p. 282–286°. Extraction of the carbon tetrachloride solution with sodium bicarbonate and acidification with hydrochloric acid afforded 0.09 g. of crude *o*-phenylbenzoic acid. Two reprecipitations from an alkaline solution by acid yielded material, m.p. 110–113°, mixed m.p. 110–113°. The carbon tetrachloride solution of the remaining products of decomposition of the peroxide was chromatographed on 25 g. of acid-washed alumina eluting with carbon tetrachloride. The first fraction solidified on standing, 0.15 g. *o*-chlorobiphenyl. Recrystallization from petroleum ether (b.p. 30–60°) gave material, m.p. 33–34°, mixed melting point with authentic material 33–34° (lit., m.p. 32°). Vapor phase chromatography of a portion of the crude material gave a small peak (carbon tetrachloride) and a large peak (*o*-chlorobiphenyl). No bands ascribable to hexachloroethane or to biphenyl were present. The second fraction, eluted with carbon tetrachloride–ether (50 to 1), was 0.29 g. of crude 3,4-benzeoumarin. Three recrystallizations from petroleum ether afforded material (prepared by the procedure of Graebe and Schestakow, lit.,[23] m.p. 92.5°), m.p. 92–94°.

From a parallel experiment employing 10 g. of peroxide were obtained three additional fractions (A, B and C) corresponding to 17% of the peroxide by weight. Extraction of the carbon tetrachloride solution with bicarbonate afforded a third layer at the interface which was separated, dissolved in methanol-water, and acidified affording 0.9 g. of precipitate, Fraction A. Repeated recrystallizations failed to give a pure material: broad decomposition range, 143–147°; poorly defined infrared spectrum with broad absorption at 1710 cm.$^{-1}$.

Anal. Found: C, 67.05; H, 4.01; Cl, 14.82. Chromatography of the dried carbon tetrachloride solution afforded, in addition to the fractions described above, Fraction B, 0.57 g., eluted with ether and Fraction C, 0.3 g. eluted with ether-methanol (10:1). Repeated recrystallizations of Fractions B and C afforded samples of dec. p. 140–144° and 161–164° respectively, poorly defined infrared spectra with broad absorption at 1725 cm.$^{-1}$ (Fraction B) and 1730 cm.$^{-1}$ (Fraction C).

Anal. of Fraction C. Found: C, 60.65; H, 3.62; Cl, 21.71.

Control experiments. A solution of 30.8 mg. of hexachloroethane in 150 ml. of carbon tetrachloride was treated exactly like the solution of peroxide decomposition products. The yield from the chromatogram was 19.1 mg. (62% recovery), m.p. 183–186° (sealed tube). Mixtures of hexachloroethane and *o*-chlorobiphenyl were easily separated and distinguished by vapor phase chromatography on a silicone-firebrick column.

Chromatography on alumina of a synthetic mixture of 0.106 g. of *o*-chlorobiphenyl and 0.045 g. of 3,4-benzcoumarin afforded 0.087 g. of the former, m.p. 31–33° (82% recovery) and 0.035 g. of the latter, m.p. 91–93° (78% recovery).

Decarboxylation of "dimeric acid" from o-phenylbenzoyl peroxide. A mixture of 0.039 g. of the material, dec. p. 282–286°, 0.064 g. of copper chromite and 5.5 ml. of quinoline was heated at reflux for 2 hr. After cooling, 20 ml. of ether was added and the mixture was poured into 50 ml. of 10% hydrochloric acid. The mixture was filtered and the filtrate was extracted with ether. The ether layer was washed with 10% hydrochloric acid, with water, dried over magnesium sulfate, and the solvent removed. The residue was dissolved in benzene and chromatographed on a column consisting of an upper layer of 1 g. of alumina and a lower layer of 3 g. of silica gel. Elution with benzene afforded 8 mg. of tan solid. Sublimation at 155° and 0.3 mm. gave slightly tan material, m.p. 79–93° (lit.,[24] m.p. of 1,3-(diphenyl)biphenyl 84.5–85°). Mass spectral analysis showed a major peak at mass 306 (calcd. mol. wt., 306).

Decomposition of o-phenylbenzoyl peroxide in the presence of iodine and water (Table III). A mixture of 1.31 g. of the peroxide, 4.55 g. of iodine, 3.64 ml. of water, and 100 ml. of carbon tetrachloride was heated at reflux for 10 hr. and worked up by the above procedure and that described in the corresponding experiment with *o*-toluoyl peroxide.

p-Benzylbenzoic acid was prepared by the reaction of oxalyl chloride and diphenylmethane according to the procedure of Liebermann.[25] Recrystallization from benzene afforded material, m.p. 161–162° (lit., m.p. 155–156°).

p-Benzylbenzoyl peroxide was prepared by the method described above for *o*-benzylbenzoyl peroxide. Recrystallization from carbon tetrachloride-methanol afforded the peroxide, m.p. 87–88°. Iodometric analysis indicated a purity of 99 ± 1%.

Anal. Calcd. for $C_{28}H_{22}O_4$: C, 79.60; H, 5.25. Found: C, 79.49; H, 5.30.

p-Chlorodiphenylmethane was prepared by Wolff-Kishner reduction of *p*-chlorobenzophenone, affording material, b.p. 118° (1 mm.), n_D^{27} 1.5840 (lit.,[26] b.p. 298° at 743 mm.).

p-Benzylphenyl p-benzylbenzoate was prepared by the reaction of *p*-benzylbenzoyl chloride (crude, from 2 g. of acid by the action of thionyl chloride) and 2 g. of *p*-benzylphenol in 20 ml. of pyridine. After 15 hr. at 25° the mixture was poured into water and the precipitate was recrystallized from hexane, 1.4 g., m.p. 70–71°.

Anal. Calcd. for $C_{29}H_{22}O_2$: C, 85.68; H, 5.86. Found: C, 85.87; H, 6.06.

Decomposition of p-benzylbenzoyl peroxide in carbon tetrachloride. A 6.37-g. sample (15.1 mmoles) of the peroxide in 1500 ml. of carbon tetrachloride was decomposed under slow nitrogen flow for 60 hr. as described above for *o*-methylbenzoyl peroxide. Yield of carbon dioxide was 15.9 mmoles. The carbon tetrachloride was removed through a 24-inch Vigreux column. The residue was dissolved in ether and extracted fifteen times with 50-ml. portions of 5% sodium bicarbonate solution. The bicarbonate solution was acidified and extracted with ether; the ether was dried over magnesium sulfate, filtered, and evaporated giving 0.63 g. of crude *p*-benzylbenzoic acid, m.p. 118–123°. Recrystallization from petroleum ether (b.p. 70–90°) afforded material, m.p. 153–155°, mixed m.p. 154–156°. The original ether layer containing the neutral products of the peroxide decomposition was evaporated, dissolved in petroleum ether, filtered

(21) C. D. Gutsche and W. S. Johnson, *J. Am. Chem. Soc.*, **68**, 2239 (1946).

(22) W. Schlenk and E. Bergmann, *Ann.*, **464**, 33 (1928).

(23) C. Graebe and P. Schestakow, *Ann.*, **284**, 317 (1895).

(24) G. F. Woods and F. T. Reed, *J. Am. Chem. Soc.*, **71**, 1348 (1949).

(25) C. Liebermann, *Chem. Ber.*, **45**, 1207 (1912).

(26) P. J. Montagne, *Rec. trav. chim.*, **26**, 267 (1907).

from a small amount of insoluble matter, and chromatographed on 30 g. of acid-washed alumina. The first fraction was hexachloroethane, 0.63 g.

The second fraction, 3.0 g. of a colorless liquid, n_D^{27} 1.5842 was identified as *p*-chlorodiphenylmethane by identity of infrared spectrum with that of authentic material and by chromic acid oxidation in acetic acid to *p*-chlorobenzophenone, m.p. 73–74° after recrystallization from ethanol, mixture m.p. 73–74°. The *p*-chlorodiphenylmethane fraction gave a single peak on gas phase chromatography on a firebrick-silicone column with no peak at the position shown by an authentic sample of diphenylmethane. The third fraction, eluted from the alumina by ether, was a semisolid which resisted attempts at purification. The infrared spectrum was similar to but not identical with that of *p*-benzylphenyl *p*-benzylbenzoate.

Kinetic determinations were made in carbon tetrachloride at 80°, following the peroxide concentration by iodometric analysis.[27] Initial concentrations closely approximated the conditions of the product studies. The data are summarized in Table IV.

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(27) F. D. Greene, *J. Am. Chem. Soc.*, **78**, 2254 (1956).

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Cleavage of Tetrahydrofuran during Reductions with Lithium Aluminum Hydride[1]

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A mixture of aluminum chloride and lithium aluminum hydride was shown to cleave tetrahydrofuran to *n*-butyl alcohol. There appears to be a direct relationship between the maximum amount of *n*-butyl alcohol produced under extended reflux and the theoretical amount of aluminum hydride produced. Although the reduction of most compounds with lithium aluminum hydride in tetrahydrofuran does not result in cleavage, the reduction of alkyl halides and benzylphosphonium halides under these conditions gave *n*-butyl alcohol and hydrocarbon in nearly equivalent amounts. Dioxane, diethoxyethane and di-*n*-butyl ether were cleaved with the mixed reagent, but at a much slower rate than was tetrahydrofuran.

Because of its unique solvent properties tetrahydrofuran has found extensive and successful use as a solvent for reductions with lithium aluminum hydride. However, during an investigation of the reductive cleavage of benzylphosphonium compounds[3] with lithium aluminum hydride in tetrahydrofuran, it was found that an excess of hydride was required for high yields and *n*-butyl alcohol was formed as a by-product by the reductive cleavage of the solvent. Therefore, a research program was undertaken in order to investigate this unusual reductive cleavage.

In general, the ether bond is resistant to attack by lithium aluminum hydride and other complex hydrides at temperatures to 80–100°.[4,5] When the oxygen is part of a ring possessing strain, such as ethylene oxide and thebain, or containing the N—C—O— grouping, cleavage takes place, but ordinary cyclic ethers, such as tetrahydrofuran, tetrahydropyran, and dioxane, are reported to be stable. Of course, activated ethers, such as allyl ethers and cyclohexyloxyacetic acid,[6] are known to be cleaved under vigorous conditions. It has been reported[7] that during the reduction of active carbon dioxide at 0° or active acetyl chloride at −78° in diethyl carbitol 4 to 7% of inactive ethanol was formed. In addition, Karrer *et al.*,[8] showed that lithium aluminum hydride in the presence of cobaltous chloride would cleave phenyl benzyl and phenyl allyl ethers in refluxing ethyl ether.

More recently, a mixture of lithium aluminum hydride and aluminum chloride has been suggested as a more specific reducing agent.[9] Eliel *et al.*[10] recently have applied this reagent to the reduction

(1) This work was done in fulfillment of a contract with the Army Chemical Corps.

(2) Army Chemical Corps Postdoctoral Fellow, 1957–59.

(3) W. J. Bailey, S. A. Buckler, and F. Marktscheffel, *J. Org. Chem.*, in press.

(4) P. Karrer, *Angew. Chem.*, **62**, 334 (1950).

(5) N. G. Gaylord, *Reductions with Complex Metal Hydrides*, Interscience Publishers, Inc., New York, N.Y., 1956.

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(8) P. Karrer and A. Chatterjee, *Helv. Chim. Acta*, **33**, 802 (1950); P. Karrer and O. Rütner, *Helv. Chim. Acta*, **33**, 812 (1950).

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TABLE I

CLEAVAGE OF TETRAHYDROFURAN

Experiment No.	$LiAlH_4$,[a] Mole	$AlCl_3$,[b] Mole	Tetrahydrofuran, Ml.	Temp., °C.	Time of Heating, Hr.	Method of Addition of Reactants[c]	Isolation Procedure[d]	Yield of *n*-Butyl Alcohol, G.	Yield Based on AlH_3, %
1[e]	0.166	0.0395[f]	350	Reflux	11	M	A	12.1	103
2[g]	0.216	0.052[h]	700	Reflux	25.5	M	A	24.0	156
3[g]	0.19	0.048[h]	1150	Reflux	20	M	A	20.7	146
4	0.1	0.15	414	Reflux	13.8	N	B	11.7	119
5	0.1	0.1	364	Reflux	12	O	B	10.2	104
6	0.1	0.033	264	Reflux	13.8	N	B	11.5	117
7	0.05	0.005	132	Reflux	13.8	N	B	0.18	12
8A	0.075	0.0228	200	30	3	N	C	0.29	4
8B	0.075	0.0228	200	30	71	N	C	1.55	21
9A	0.04	0.0133	106	105–110	1	N	D	0.67	17
9B	0.04	0.0133	106	105–110	3	N	D	1.66	42
9C	0.04	0.0133	106	105–110	16	N	D	3.32	84
10A	0.04	0.0133	106	105–110	16	N	D	3.67	93
10B	0.04	0.0133	106	105–110	24	N	D	3.83	97
11	0.04	0.0133	106	105–110	26	N	D	3.95	100
12	0.04	0.0133[i]	100	81	17.5	N	D	1.93	49
13A	0.04	0.0133[i]	100	80	73	N	D	2.29	58
13B	0.04	0.0133[i]	100	80	145	N	D	2.61	66
14	0.04	0.0133[i]	100	100	24	N	D	3.39	86
15A	0.04	0.0133[i]	100	100	72	N	E	3.27	83
15B	0.04	0.0133[i]	100	100	144	N	E	3.32	84
16	0.107	0.033	170[j]	Reflux	9	P	F	3.78	96
17	0.04	0.0133[i]	100	100	24	N	D	2.52	64

[a] Added as a standard solution in tetrahydrofuran unless otherwise specified. [b] Commercial grade unless otherwise specified. [c] Method M involved the formation of aluminum chloride or aluminum hydride during the reaction by reduction of a halogen compound. Method N involved the addition of a solution of aluminum chloride in tetrahydrofuran to the solution of lithium aluminum hydride. Method O involved the addition of a solution of lithium aluminum hydride in tetrahydrofuran to a solution of aluminum chloride. Method P involved the addition of a lithium aluminum hydride solution to a benzene solution of aluminum chloride. [d] Method A involved the decomposition of the reaction mixture with a 20% sodium potassium tartrate solution, followed by extraction with ether and subsequent concentration of products. Method B involved removal of 70–85% of the tetrahydrofuran by distillation at atmospheric pressure, followed by decomposition of the residue with cold dilute sulfuric acid. Method C involved the removal of the tetrahydrofuran under reduced pressure over a 1-hr. period and treatment of the residue as in method B. Method D involved the removal of the tetrahydrofuran from the cold reaction mixture under 30–35 mm. pressure, followed by treatment of the residue as in method B. Method E involved the cooling of the reaction mixture with ice for 15 min. before treatment as in method D. Method F involved the direct decomposition of the reaction mixture with dilute sulfuric acid. [e] Reduction of benzyl chloride. [f] No aluminum chloride added; maximum amount theoretically produced from reduction of the benzyl chloride. [g] Reduction of methylethylpentylphosphonium iodide. [h] No aluminum chloride added; maximum amount theoretically produced from reduction of methylethylpentylphosphonium iodide. [i] Sublimed aluminum chloride. [j] Plus 60 ml. of benzene.

of acetals and ketals to the corresponding ethers and of cyclic acetals and cyclic hemithioacetals to the corresponding hydroxyethers and thioethers. A similar reagent, hydrogen chloride or bromide plus lithium aluminum hydride or sodium borohydride, has been used to cleave the acetal ring of spirostanols or spirostenols of sapogenins.[11] The use of *p*-toluenesulfonic acid or hydrogen sulfide in place of the hydrogen chloride was ineffective.

Although the electrophilic cleavage of tetrahydrofuran, such as polymerization with boron trifluoride[12] and formation of δ-chlorobutyl acetate with acetyl chloride and zinc chloride,[13] is known, the reductive cleavage has not been reported. By use of vapor-phase chromatography we have verified that, in contrast to the reduction of the benzylphosphonium compounds which produced an equivalent amount of *n*-butyl alcohol,[3] the reduction of acetone in tetrahydrofuran or treatment of tetrahydrofuran alone with an excess of lithium aluminum hydride produced no detectable amount of *n*-butyl alcohol. Similarly, the addition of sodium chloride or lithium chloride had no effect. However, when benzyl chloride was reduced with an excess of lithium aluminum hydride, toluene plus nearly an equimolar amount of *n*-butyl alcohol were formed. Similarly, when aluminum chloride was added to tetrahydrofuran plus lithium aluminum hydride, *n*-butyl alcohol was produced. A reasonably comprehensive study was conducted on the reduction with the aluminum chloride–lithium aluminum hydride mixture, and the results are listed in Table I. Because of the difficulty in the determination of small quantities of *n*-butyl alcohol in a relatively large volume of tetrahydrofuran, the experiments were carried out on a large scale. Even so, the values are probably accurate only

(11) H. M. Doukas and T. D. Fontaine, *J. Am. Chem. Soc.*, **73**, 5917 (1951); **75**, 5355 (1953).

(12) H. Meerwein, *Angew. Chem.*, **59**, 168 (1947).

(13) I. H. Helberger and H. Lautermann, *Ann.*, **586**, 158 (1954).

TABLE II

CLEAVAGE OF OTHER ETHERS

Solvent	Volume, Ml.	$LiAlH_4$,[a] Mole	$AlCl_3$,[b] Mole	Temp., °	Time of Heating, Hr.	Method of Addition of Reactants[c]	Isolation Procedure[d]	Product	Yield, G.
Di-*n*-butyl ether	340	0.1	0.033	Reflux	26.5	N	F	*n*-Butyl alcohol	0.45
Dioxane	720	0.1	0.033	Reflux	31	N	F	2-Ethoxyethanol	0.91
Dioxane	720	0.1	0.033	Reflux	24	N	F	2-Ethoxyethanol	0.87
1,2-Diethoxyethane	400	0.198	0.0606	95–105	24	N	F	2-Ethoxyethanol	4.16

[a–d] See footnotes for Table I.

within ±10%. Nevertheless, the total number of experiments allows several definite conclusions: (1) The amount of *n*-butyl alcohol produced does not appear to depend on the order of addition of the three components. (2) The amount of *n*-butyl alcohol increases with increasing temperatures and time of reaction, reaching a maximum value after the mixture is heated under reflux from ten to twenty hours. (3) Although a variation in the ratio of aluminum chloride to lithium aluminum hydride from 1:0.68 to 1:3 did not appreciably affect the amount of *n*-butyl alcohol produced, there did appear to be a relationship between the amount of aluminum hydride that could be produced and the amount of alcohol obtained. If it is assumed that the equation[5]

$$AlCl_3 + 3LiAlH_4 \longrightarrow 4AlH_3 + 3LiCl$$

is applicable to these conditions, a fair agreement is obtained between the maximum amount of *n*-butyl alcohol produced and the maximum amount of aluminum hydride present, as indicated in the last column of Table I. Although this relationship holds quite well for the reduction of benzyl chloride with lithium aluminum hydride, more butyl alcohol is produced during the reduction of the benzylphosphonium salts than this relationship would predict. Since it has been shown that the reduction of alkyl halides takes place in two steps with the first step quite rapid,[14] one would expect that with an excess of hydride the reaction would proceed as follows:

$$C_6H_5CH_2Cl + LiAlH_4 \longrightarrow C_6H_5CH_3 + LiCl + AlH_3$$

The reduction of the benzylphosphonium salts may be more complex. Although Wiberg and Gösele[15] reported that no reductive cleavage of tetrahydrofuran occurred with aluminum hydride, an apparent duplication of their experimental conditions in our laboratory produced *n*-butyl alcohol[16] but in a lower yield than obtained in the other reductions with lithium aluminum hydride. Since it has been shown that aluminum hydride and tetrahydrofuran form a 1:1 complex and that the strength of the complex actually increases the reducing power of lithium aluminum hydride by aiding in the removal of a hydride ion,[17] it seems probable that this complex is involved in the reductive cleavage. The function of the aluminum complex apparently is to weaken the carbon-oxygen bond so that a rearrangement or an attack by a hydride reagent can proceed. Much more extensive data are required before an exact mechanism can be formulated with any certainty.

Since extensive cleavage took place with tetrahydrofuran, a study with other solvents that have been used for reductions with either lithium aluminum hydride alone or in mixtures with aluminum chloride was undertaken and the results are summarized in Table II. Thus at 105–110° 1,2-diethoxyethane and dioxane gave 19 and 8% yields, respectively, of 2-ethoxyethanol based on aluminum hydride, while di-*n*-butyl ether gave a 5% yield of *n*-butyl alcohol. The yield of the cleavage product appears to increase with the stability of the π-complex with aluminum hydride.

It can be concluded that tetrahydrofuran is not a good solvent for reductions with the lithium aluminum hydride–aluminum chloride reagent unless the reduction proceeds extremely rapidly. If a long period of reflux is required, a solvent with a much lower complexing power should be selected.

EXPERIMENTAL

All solvents were freshly distilled from lithium aluminum hydride before use. The amounts of each product of the reaction were determined by vapor-phase chromatography on a Perkin-Elmer Vapor Fractometer, Model 154-B. An internal standard of benzene or toluene was used with the "C" column (silicone grease on Celite). All heating under reflux was carried out with a heating mantle unless specified. When part of the solvent was removed by distillation at atmospheric pressure before further treatment of the residue, this time is included in the indicated reaction time. The reductions of acetone, benzyl chloride, and phosphonium

(14) J. E. Johnson, R. H. Blizzard, and H. W. Carhart, *J. Am. Chem. Soc.*, 70, 3664 (1948).

(15) E. Wiberg and W. Gösele, *Z. Naturforsch.*, 11b, 485 (1956).

(16) In a private communication Dozent Dr. W. Zeil, Phys. Chem. Inst., Technische Hochschule, Karlsruhe, Germany, reported spectroscopic evidence for the cleavage of tetrahydrofuran by aluminum hydride.

(17) L. W. Trevoy and W. G. Brown, *J. Am. Chem. Soc.*, 71, 1675 (1949); N. L. Paddock, *Nature*, 167, 1070 (1951).

salts were carried out in a three-necked flask equipped with a mechanical stirrer. All other reductions were carried out by heating under reflux without stirring.

The standard solutions of lithium aluminum hydride in tetrahydrofuran were prepared as follows: A mixture of 62 g. of hydride in 2 l. of solvent was heated under reflux for 6 hr., cooled overnight and then filtered through glass wool under nitrogen. The concentration of lithium aluminum hydride was determined by the addition of an excess of 0.1*N* hydrochloric acid, followed by back-titration with standard 0.1*N* sodium hydroxide solution and by the addition of an excess of a standard solution of iodine in benzene, followed by back-titration with a standard sodium thiosulfate solution.[18]

Reduction of benzyl chloride in tetrahydrofuran. To a stirred solution of 6.3 g. (0.166 mole) of lithium aluminum hydride in 300 ml. of tetrahydrofuran, heated under reflux, was added a solution of 20.0 g. (0.158 mole) of benzyl chloride in 50 ml. of tetrahydrofuran over a 30-min. period. After the solution had been heated under reflux for an additional 5.6 hr., 270 ml. of tetrahydrofuran was removed by distillation through an 18-inch, helix-packed column over a 5-hr. period. The residue was diluted with 300 ml. of ether and cooled in an ice bath while 400 ml. of a 20% sodium potassium tartrate solution was added. After the aqueous layer was extracted with two 75-ml. portions of ether, the combined ether layers were dried over magnesium sulfate. The solvents were removed by distillation through a 10-inch, helix-packed column to yield 25.3 g. of a residue which was shown by vapor-phase chromatographic analysis to contain 12.1 g. (0.163 mole) of *n*-butyl alcohol and 12.5 g. (86%) of toluene as well as 0.7 g. of tetrahydrofuran.

A similar experiment with acetone in place of benzyl chloride gave no amount of *n*-butyl alcohol detectable by vapor-phase analysis, as described above.

Cleavage of tetrahydrofuran with a lithium aluminum hydride–aluminum chloride mixture. To a standard solution containing 1.52 g. (0.04 mole) of lithium aluminum hydride in 66 ml. of tetrahydrofuran was added as rapidly as possible with shaking a mixture of 1.78 g. (0.0133 mole) of aluminum chloride in 40 ml. of tetrahydrofuran. During the addition the solution became warm and a white fog (not hydrogen chloride) was produced. After the mixture had been heated under mild reflux for 26 hr. in an oil bath (105–110°),[19] most of the tetrahydrofuran was removed by distillation under reduced pressure (15 mm.) at room temperature over a 30-min. period. The residue was added to dilute sulfuric acid (prepared from 15 ml. of concd. sulfuric acid, 60 g. of ice and 86 ml. of water), and the resulting solution was extracted with three 50-ml. portions of ether. The ether extracts were then extracted with 40 ml. of a 5% sodium bicarbonate solution and two 20-ml. portions of water. The combined aqueous extracts were neutralized and extracted with 30 ml. of ether. After the combined ether layers had been dried over magnesium sulfate, the ether plus some tetrahydrofuran was removed by distillation through a 10-inch, helix-packed column. An analysis of the residue by vapor-phase chromatography showed the presence of 3.96 g. (0.0535 mole) of *n*-butyl alcohol. (In a similar vapor-phase analysis of the distillates, no additional *n*-butyl alcohol was detected.) If it is assumed that 1.78 g. (0.0133 mole) of aluminum chloride can yield 1.6 g. (0.0532 mole) of aluminum hydride and that 1 mole of *n*-butyl alcohol is produced for every mole of aluminum hydride present, 3.95 g. (0.0532 mole) of *n*-butyl alcohol is expected. On this basis, the actual amount of *n*-butyl alcohol obtained was 100.3% of the theoretical amount.

Cleavage of tetrahydrofuran with aluminum hydride. A solution of 1.72 g. (0.04 mole) of lithium aluminum hydride in 100 ml. of dry ether was heated under reflux for 5 hr. and then transferred through a fritted-glass filter into a solution of 1.72 g. (0.0133 mole) of freshly sublimated aluminum chloride in 200 ml. of dry ether. After the mixture had been allowed to stand for 10 min., it was filtered and the ether was removed from the filtrate by distillation under reduced pressure at 0°. To the dry residue was added 100 ml. of tetrahydrofuran, and the resulting solution was heated for 24 hr. at 100°. (The solution then contained a small amount of a gray precipitate.) When the solution was worked up as described above, the vapor-phase chromatographic analysis showed the presence of 2.52 g. (0.034 mole) of *n*-butyl alcohol. With the stated assumptions, this corresponds to a 64% yield.

COLLEGE PARK, MD.

(18) H. Felkin, *Bull. soc. chim. France*, [5] 18, 347 (1951).

(19) After the mixture had been heated for about 2 hr., there was observed a gray voluminous precipitate which was not dissolved by the dilute sulfuric acid during decomposition of the mixture. Wiberg and Gösele[15] observed a similar precipitate from the heating of a solution of aluminum hydride in tetrahydrofuran.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

Polymers. III. Synthesis of Optically Active Stereoregular Polyolefins[1-3]

WILLIAM J. BAILEY AND EDWIN T. YATES[4]

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Polymerization of optically active 3-methyl-1-pentene, $[\alpha]_D^{25}$ +33.49°, with a Ziegler catalyst gave a low melting atactic fraction, $[\alpha]_D^{23}$ + 94.9°, and a high melting isotactic fraction, $[\alpha]_D^{25}$ − 257°. The high melting fraction, m.p. 271–278°, was insoluble in boiling xylene but soluble in boiling 1,1-ditolylethane and was almost entirely crystalline. In contrast, the polymer from *dl*-3-methyl-1-pentene melted at 229–237°, was soluble in boiling 1,1-diphenylethane, and was composed of equal parts of amorphous and crystalline phases. Copolymerization of a mixture containing 40% *d*-3-methyl-1-pentene and 60% 4-methyl-1-pentene gave a copolymer with $[\alpha]_D^{26}$ +112.4°.

In a program to determine the correlation of chemical structure with physical properties of polymers, the effect of symmetry on the crystallinity of polymers has been of particular interest. Earlier

(1) Previous paper in this series, *J. Org. Chem.*, 24, 545 (1959).

(2) Presented before the Division of Polymer Chemistry at the 137th Meeting of the American Chemical Society, Cleveland, Ohio, April 1960.

(3) This work was supported in part by a grant from the National Science Foundation.

(4) Office of Naval Research Fellow, 1955–57; Goodyear Tire and Rubber Co. Fellow, 1957; Dunlop Research Fellow, 1957–58.

work[5] has shown that the symmetrical poly-1,2-dimethylenecyclohexane was a highly crystalline material melting at 165°. However, the introduction of a methyl group in an asymmetric manner in the 4-position, even though it decreased the extent of crystallinity, did not appreciably affect the melting point.[6] It was of interest, therefore, to determine how asymmetry in the side chain affects the crystallinity of polymers. In addition to these derivatives of the cyclic dienes, the crystalline polyolefins were an interesting series for the study of the relationship. Natta, *et al.*,[7] have shown that by the use of stereospecific catalysts a series of highly crystalline isotactic polymers from *alpha* olefins could be prepared. It was shown by x-ray studies that these isotactic polymers contained long sequences, if not the entire chain, of similar configurations of the asymmetric carbon atoms. When the side chain was increased from methyl to *n*-butyl, the melting point of the isotactic polymer decreased from 160° to below room temperature. Also, the effect of a branched side chain was quite large; the change of the side group from *n*-propyl to isopropyl increased the melting point of the isotactic polymer from 80 to 240°. A very curious phenomenon occurred with the introduction of a second asymmetric center in the side chain of an isotactic polyolefin. For example, the stereoregular polymer derived from *d,l*-4-methyl-1-hexene melts at 188, while the polymer from the related 5-methyl-1-hexene, which is symmetrical, melts at 130°. At first glance this high melting point would be difficult to explain unless there was some order of the asymmetric centers in the side chains as well as in the main chain. However, Natta[8] feels that, on the basis of relatively high solubility and inferior sharpness of the x-ray photographs, the side chains have a random distribution of *d* and *l* configurations.

In order to determine just what effect this asymmetry in the side chain had on the physical properties of the polymers, it was necessary to prepare the polymers from both a racemic and an optically active olefin. The simplest optically active olefin for this purpose appeared to be 3-methyl-1-pentene. This olefin seemed to be an excellent candidate for study, as it would produce an optically active polymer with the asymmetric center in the side chain immediately adjacent to the asymmetric center in the main chain to produce a notable effect on the properties.

A preliminary study of the method of preparation of the Ziegler catalyst from triisobutylaluminum and titanium tetrachloride showed that aging the catalyst at an elevated temperature gave a very active catalyst for the production of a stereoregular polymer. With such a catalyst a polypropylene that consisted of 95% of ether-insoluble isotactic material was produced. In a similar manner, polymers were obtained from 1-octene and a mixture of isomeric hexenes and *d,l*-3-methyl-1-pentene. When pure *d,l*-3-methyl-1-pentene,[9] which had been treated with sodium, was used, a 12% yield of solid polymer was obtained. This material was separated into four fractions by successive extractions with cold benzene, hot xylene, hot *p*-cymene, and hot 1,1-diphenylethane. The major fraction that was soluble in refluxing 1,1-diphenylethane was shown to melt at 229–237°[10] with the aid of a polarizing microscope. X-ray studies indicated that this polymer was composed of about equal portions of a crystalline phase and an amorphous phase. Even though the exact configuration of this fraction is not known, it appears not to be an isotactic polymer with a random distribution of the asymmetric carbons in the side chains as reported by Natta for poly-5-methyl-1-hexene.[8] The relatively low solubility and high melting point indicate that this fraction probably is an isotactic polymer with at least long sequences of regularity of configuration of the asymmetric centers in the side chain. The more soluble fractions of this racemic polymer probably contain some crystalline isotactic polymer with a random distribution of configurations in the side chain.

In order to determine the effect on the rotation of the incorporation of an optically active olefin into a polymer, the copolymerization of *d*-3-methyl-1-pentene and 4-methyl-1-pentene was studied. As a mixture of isoamyl and active amyl alcohols was more readily available than the pure active amyl alcohol, a mixture containing 40% *d*-3-methyl-1-pentene and 60% 4-methyl-1-pentene was prepared in a series of model reactions for the preparation of the pure optically active olefin.[9] Thus, the mixture of alcohols was treated with thionyl chloride to give a mixture of the corresponding chlorides, which was converted to the Grignard reagents. Treatment of the Grignard reagents with formaldehyde, followed by esterification with butyric anhydride, gave a mixture of *d*-3-methylamyl and 4-methylamyl *n*-butyrates. Pyrolysis of this mixture of esters gave the mixture of olefins. Copolymerization with an aged catalyst gave a 5% yield of a benzene-soluble copolymer, $[\alpha]_D^{26}$ +112.4°.

(5) W. J. Bailey and H. R. Golden, *J. Am. Chem. Soc.*, 76, 5418 (1954).

(6) W. J. Bailey, Proceedings of Joint Army-Navy-Air Force Elastomer Research and Development Conference, Washington, D. C., 1954, p. 113.

(7) G. Natta, P. Pino, P. Corradini, F. Danusso, E. Mantica, G. Mazzanti, and G. Moraglio, *J. Am. Chem. Soc.*, 77, 1708 (1955).

(8) G. Natta, *Stereospecific Catalysis and Isotactic Polymers* (English translation of a review article), Milan, Italy, 1957.

(9) W. J. Bailey and E. T. Yates, *J. Org. Chem.*, in press.

(10) Gaylord and Mark (N. G. Gaylor and H. F. Mark, *Linear and Stereoregular Addition Polymers: Polymerization with Controlled Propagation*, Interscience Publishers, Inc., New York, N. Y., 1959, p. 321) list the specific gravity for poly-3-methyl-1-pentene as 0.83 but give no other data.

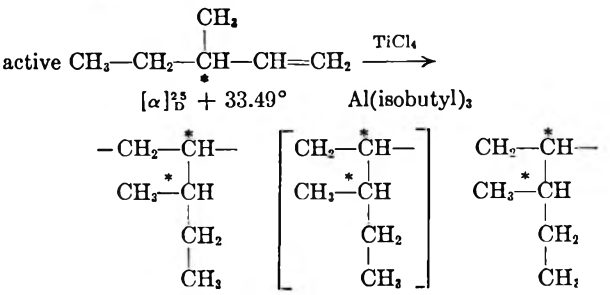
An infrared study indicated that the copolymer was composed of about equal portions of the two monomeric units. It is interesting that polymerization causes such a significant increase in rotation. One cannot be sure whether part of this change is due to asymmetric induction in the polymer chain or to the change of the groups around the active center, but at least part of it must be due to the retention of a helical conformation of the polymer chain in solution.

When a sample of *d*-3-methyl-1-pentene, which was estimated from vapor-phase chromatography and rotational values to be at least 96% pure,[9] was polymerized with an aged catalyst, an 11% yield of polymer was obtained. Extraction of this material with xylene produced a small amount of a fraction, $[\alpha]_D^{23}$ +94.9, that was only partially crystalline. As its properties were quite similar to those of the copolymer described, it was assumed that this fraction was mostly atactic. The major portion, m.p. 271–278°, was soluble in refluxing 1,1-ditolylethane. It was shown by x-ray studies as well as by observations with the polarizing microscope that the xylene-insoluble fraction was almost entirely crystalline; in fact, it was so crystalline that it was completely soluble in 1,1-ditolylethane only at temperatures above its melting point. This limited solubility made it extremely difficult to determine the optical rotation with any degree of accuracy with the instruments available. However, when a hot solution of this fraction was cooled, a small portion remained in solution and had an $[\alpha]_D^{25}$ −257°. Because the amount that remained in solution was small, it was not possible to determine whether this soluble portion is representative of the crystalline fraction or is only a minor component. However, x-ray studies indicate that the xylene-insoluble fraction is almost entirely crystalline and the crystalline phase present is different from the crystalline phase of the poly *d,l*-3-methyl-1-pentene. (Of course, different crystalline structures are possible even if the structures of the polymers are related.)

Of the possible configurations of the crystalline phase, three isotactic systems are considered to be the most likely, with the same configurations in the side chain in every monomer unit but different end groups—all *d* configurations in the main polymer chain, all *l* configurations, and a block copolymer of the two. As two of the isotactic polymers are diastereoisomers, they have different rotations and solubilities and should be separable. Of course, the presence of an asymmetric center in the monomer will favor the formation of one of the configurations in the polymer chain so that one of the diastereo forms will predominate. If the crystalline fraction can be separated into two or more different polymer forms, an insight into the structure of isotactic polymers could be obtained. From the high crystallinity of the xylene-insoluble fraction one would conclude that it is probably not a block copolymer of equal portions of the two diastereo forms. Of course, asymmetric induction would favor a block copolymer containing predominantly one form or the other.

Thus the presence of the asymmetric atom in the monomer had considerable influence on the formation of the asymmetric centers in the polymer chain, and accordingly had a profound influence on the properties of the final polymer.

It is interesting that, although the molecular weights of these polymers are not known with any accuracy, the molecular rotation of these materials must be extremely high.



EXPERIMENTAL[11]

Polymerization procedure. Triisobutylaluminum was removed from a rubber-capped bottle with hypodermic syringe. A medicine dropper was used to handle titanium tetrachloride. Reasonable care was taken to keep all air and moisture from the polymerization flask. The materials were tested by the polymerization of propylene, 1-octene, and a mixture of isomeric hexenes. To a 200-ml. flask were added 100 ml. of dry xylene, 2.0 ml. of triisobutylaluminum, and 10 drops of titanium tetrachloride. The flask was swept with nitrogen and then stoppered and heated in an oil bath at 59–62° for 30 min. Propylene, dried by passage through a column of activated alumina, was bubbled through the mixture for 1.5 hr. while the temperature was kept at 60–65°. The reaction mixture was cooled and poured into 100 ml. of a 50:50 acetone-concd. hydrochloric acid solution. The crude polymer was removed by filtration and extracted with boiling methanol. The yield was 2.0 g. of isotactic polypropylene, m.p. 156–161° (reported[12] m.p. 158–160°).

Freshly distilled 1-octene (10.6 g.) was heated under reflux with sodium for 1 hr. and polymerized in a manner similar to that described above. The polymerization was carried out with stirring in a stoppered flask heated at 93–96° for 27 hr. To remove the catalyst, the cooled reaction mixture was poured into 100 ml. of a 50:50 acetone-concd. hydrochloric acid solution. When the xylene layer was added to methanol cooled in an ice bath, a gummy polymer coagulated. The polymer was extracted with boiling methanol and then placed in a vacuum desiccator to remove the last trace of solvent. The yield of polymer was 1.4 g. (13%). The approximate molecular weight, determined by the Rast method, was 1400.

A mixture of olefins, shown by vapor-phase chromatography to be a four-component mixture containing 4-methyl-

(11) The authors are grateful to Dr. E. R. Lippincott, C. E. White, and W. R. Fearheller for the infrared spectra and aid in their interpretation. The spectra were obtained on a Beckman IR-4 spectrometer.

(12) G. Natta, *A New Class of Polymers from Alpha-Olefins Having an Exceptional Regularity of Structure*, paper presented in Rome, Italy, December 11, 1954.

1-pentene, *n*-1-hexene, 3-methyl-1-pentene, and 2-methyl-1-pentene, was treated in a similar manner. In an 8-ounce, screw-capped bottle were placed 50 ml. of dry xylene, 2 ml. of triisobutylaluminum, and 25 drops of titanium tetrachloride. After the bottle was swept with nitrogen, it was stoppered and heated in an oil bath at 100–111° for 1 hr. The mixture was cooled to room temperature, and 5.22 g. of the mixed olefins, which had been treated with freshly cut sodium for 2 hr., was added. The bottle again was swept with nitrogen, and the cap was replaced and sealed with paraffin. The reaction mixture was stirred with a magnetic stirrer and heated at 110–120° for 50 hr. When the reaction mixture was poured into a large volume of methanol, a white polymer precipitated. The copolymer, which was removed by filtration, amounted to 0.85 g. (16%).

Polymerization of d,l-3-methyl-1-pentene. In an 8-ounce, screw-capped bottle were placed 50 ml. of dry xylene, 1.6 ml. of triisobutylaluminum, and 25 drops of titanium tetrachloride. After the bottle was swept with nitrogen, it was capped and heated in an oil bath at 115–126° for 1 hr. The catalyst mixture was cooled to room temperature and 4.85 g. of *d,l*-3-methyl-1-pentene,[9] which had been treated with freshly cut sodium for 2 hr., was added. After the bottle again was swept with nitrogen, the cap was replaced and sealed with paraffin. The mixture was stirred with a magnetic stirrer and heated at 120–132° for 7 days. After the cooled reaction mixture was poured into a large volume of methanol, 0.60 g. (12%) of a white polymer was removed by filtration. Fractionation of the polymer resulted in the following fractions: benzene-soluble, 0.09 g.; xylene-soluble, 0.05 g.; hot *p*-cymene-soluble, 0.03 g.; and refluxing 1,1-diphenylethane-soluble, 0.12 g. The fraction of polymer which was soluble in refluxing 1,1-diphenylethane appeared to be highly crystalline and melted at 229–237°.

Polymerization of d-3-methyl-1-pentene. The procedure was similar to that described for the polymerization of the corresponding racemic olefin. Dry nitrogen was bubbled through 50 ml. of dry xylene in an 8-ounce, screw-capped bottle for 1 hr., followed by the addition of 1.6 ml. of triisobutylaluminum and 25 drops of titanium tetrachloride. The bottle was swept with nitrogen, capped, and stirred at 112–118° for 1 hr. The catalyst mixture was cooled to room temperature and 6.28 g. of *d*-3-methyl-1-pentene,[9] which had been treated with freshly cut sodium for 1 hr., was added. The bottle was swept with nitrogen, capped, and sealed. The reaction mixture was stirred while it was heated on an oil bath at 125–130° for 7 days. When the cooled mixture was added dropwise to a large volume of stirred methanol, a white polymer precipitated and was removed by filtration. The yield of crude polymer was 0.69 g. (11%). Fractionation yielded 0.08 g. of xylene-soluble polymer and 0.45 g. of a xylene-insoluble, crystalline polymer. The specific rotation of the xylene-soluble polymer, as determined in xylene, was $[\alpha]_D^{23}$ +94.9°. The xylene-insoluble polymer, m.p. 271–278°, was soluble in hot 1,1-ditolylethane. When a solution of this polymer in hot 1,1-ditolylethane was allowed to cool to room temperature, most of the polymer precipitated and was removed by filtration with the aid of Celite. The filtrate had a negative optical rotation. Evaporation of the solvent and weighing of the residual polymer led to calculation of an apparent specific rotation of $[\alpha]_D^{26}$ −257.2°.

Synthesis of a mixture of d-2-methyl-n-amyl n-butyrate and 4-methyl-n-amyl n-butyrate. By use of the procedure of McKenzie and Clough,[13] 201.2 g. (2.29 moles) of a mixture of about 60% *d*-amyl alcohol and 40% isoamyl alcohol (α_D^{25} −2.98°, 1:1.0) in 300 ml. of anhydrous ether was allowed to react with 286 g. (2.40 moles) of thionyl chloride in the presence of 5 ml. of pyridine. Distillation of the reaction products yielded 180.9 g. (74%) of the corresponding amyl chlorides, b.p. 97–99°, $[\alpha]_D^{25}$ +0.86° (1:1.0).

By the use of the procedure described previously,[9] the Grignard reagent from 123.6 g. (1.15 moles) of a mixture of *d*-2-methyl-*n*-butyl chloride and isoamyl chloride (α_D^{25} +0.77°, 1:1.0) was treated with formaldehyde. Distillation of the reaction products through a 6-inch, helix-packed column yielded 56.7 g. (48%) of a mixture of the corresponding hexyl alcohols, b.p. 147–154°, α_D^{26} +3.61° (1:1.0). This mixture of isomeric hexyl alcohols was esterified with 130 ml. of chloroform, 73.9 g. (0.94 mole) of pyridine, and 95.9 g. (0.90 mole) of butyryl chloride. The reaction mixture was treated as described previously.[9] Distillation of the residue yielded 95.0 g. (94%) of a mixture of about 60% *d*-3-methyl-*n*-amyl *n*-butyrate and 40% 4-methyl-*n*-amyl *n*-butyrate, b.p. 86–91° (18–23 mm.), α_D^{24} +3.89° (1:1.0).

Pyrolysis of a mixture of d-3-methyl-n-amyl n-butyrate and 4-methyl-n-amyl n-butyrate. Five separate pyrolyses were run on 53.0 g. (0.31 mole) of the mixture of esters (α_D^{24} +3.89°, 1:1.0) by essentially the same method that was employed in the pyrolyses of the *d,l*- and the *d*-3-methyl-*n*-amyl *n*-butyrates[9] at 515–530°, with an addition rate of 20 drops per minute. Distillation of a washed and dried *n*-butyl ether solution of the combined pyrolysates through a 6-inch, helix-packed column yielded 8.0 g. (31%) of a mixture of *d*-3-methyl-1-pentene and 4-methyl-1-pentene, b.p. 51–53°, α_D^{25} +13.15° (1:1.0); and 13.0 g. (25% recovery) of unpyrolyzed starting material. The yield of olefin, based on unrecovered butyrate, was 44%. On the basis of the observed optical rotation of the mixture of olefins relative to that of pure *d*-3-methyl-1-pentene,[9] the composition was approximately 40% *d*-3-methyl-1-pentene and 60% 4-methyl-1-pentene.

Copolymerization of d-3-methyl-1-pentene and 4-methyl-1-pentene. To 50 ml. of dry xylene in an 8-ounce, screw-capped bottle were added 1.6 ml. of triisobutylaluminum and 25 drops of titanium tetrachloride; a brown precipitate formed. The catalyst mixture was activated by heating at 119–129° for 75 min. To the mixture was added 2.55 g. of the previously described mixture of olefins which had been treated for 1 hr. with freshly cut sodium. After it was stirred at 130–137° for 7 days, the reaction mixture was poured into a large volume of methanol and 0.13 g. (5%) of precipitated copolymer was removed by filtration. The crude product was purified by solution in boiling xylene and reprecipitation with methanol to yield 0.11 g. of white polymer. A melting point determination on a hot-stage microscope with crossed Nicol prisms showed that the copolymer started to shrink at 68° and was melted at 193°. The copolymer was completely soluble in benzene; the specific rotation, as determined in benzene solution, was $[\alpha]_D^{26}$ +112.4°. The copolymer was melted on a salt plate and the infrared spectrum of the film was determined. Bands at 1360 and 1380 cm.$^{-1}$ indicated the presence of isopropyl groups contributed by 4-methyl-1-pentene units in the polymer. The infrared spectrum of a film of the xylene-soluble fraction of the polymer of *d*-3-methyl-1-pentene[9] had one band at 1380 cm.$^{-1}$ but otherwise was similar to that of the copolymer.

X-ray diffraction studies.[14] Attempts to pull fibers from the xylene-insoluble fraction of poly-*d*-3-methyl-1-pentene failed because of the high melting point; apparently, decomposition occurs at these elevated temperatures. For these reasons, powder patterns were run on both the active polymer and the corresponding racemic polymer. The crystalline phases of the two polymers were not the same but the amorphous regions of each appeared quite similar. Dr. Ashby reports: "The *d,l* polymer has both crystalline and noncrystalline phases present in about equal proportions. The optically active polymer also has both crystalline and

(13) A. McKenzie and G. W. Clough, *J. Chem. Soc.*, 699 (1913).

(14) The authors are grateful to Dr. George Ashby and Dr. Frank X. Werber of the Washington Research Center, W. R. Grace and Co., for the X-ray studies as well as their interpretation.

noncrystalline material present, but in this case most of the sample is crystalline. In both samples the noncrystalline phases have the same interchain distance, suggesting that these phases are very similar. Because of the magnitude of the interchain distance (9.4 Å) large pendant groups are probably on the polymer chain."

COLLEGE PARK, MD.

[CONTRIBUTION FROM THE MIDWEST RESEARCH INSTITUTE]

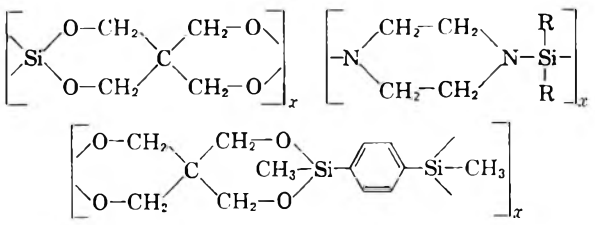
Reactions of Silanes with Pentaerythritol and Piperazine[1]

L. W. BREED, WILLIAM J. HAGGERTY, JR., AND JOHN HARVEY

Received January 7, 1960

Possible reactions for the preparation of linear polymers containing the alternate silane-pentaerythritol and silane-piperazine groups were investigated. Although prototype compounds were prepared by several procedures, attempted polymerization reactions failed to yield the desired polymers.

In the search for new polymer systems with good thermal stability, certain condensation products of silanes with pentaerythritol or piperazine could provide linear, rigid chains. For example:



Several U. S. patents[2-4] report that the addition of pentaerythritol in varying amounts to silicone resins as a cross-linking agent gives resins which are superior to the unmodified resins, but no evidence was found that pentaerythritol has been used as an integral part of a silane polymer. In such a polymer, the absence of a β-hydrogen, as well as the rigidity of the chain, may contribute to thermal stability. No piperazine polymers containing silicon have been reported. The silicon-nitrogen bond is known to be very thermally stable if no hydrogen is attached to the nitrogen atom.[5] Polymers containing silicon-nitrogen bondings have been described by Cheronis.[6,7,8]

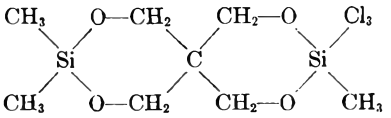
We obtained the prototype compound, 3,3,9,9-tetramethyl-2,4,8,10-tetraoxa-3,9-disilaspiro[5.5]-undecane by three procedures.

Procedure No. 1 was previously described by Davydova.[9] None of these syntheses is a high yield reaction likely to produce high molecular weight materials during polymerization.

1. $C(CH_2OH)_4 + 2(CH_3)_2Si(OAc)_2 \xrightarrow{61.5\%}$

2. $C(CH_2OAc)_4 + 2(CH_3)_2Si(OC_2H_5)_2 \xrightarrow[Al(OisoPr)_3]{40.4\%}$

3. $C(CH_2OH)_4 + 2(CH_3)_2Si(OC_2H_5)_2 \xrightarrow[p\text{-toluene-sulfonic acid}]{\text{low yield}}$



A fourth method used in the attempted preparation of dioxasilacyclohexane ring structure gave only a polymer. It is reported that chlorotrimethylsilane and pentaerythritol, in the presence of pyridine, gave a 90% yield of the tetrakistrimethylsilyl derivative.[10] However, when we treated pentaerythritol and dichloromethylphenylsilane in the presence of pyridine, a polymer rather than the bicyclic compound, 3,9-dimethyl-3,9-diphenyl-2,-4,8,10-tetraoxa-3,9-disilaspiro[5.5]undecane was obtained.

A portion of the polymer that flowed at 170° had a molecular weight of about 2000. The largest part, however, was benzene insoluble and could be drawn into fibers. The ratio of elements calculated from elementary analyses indicated that the amount of cyclization in the polymer was low.

Polymerization reactions generally resulted in the formation of insoluble and infusible products containing unchanged functional groups. The properties of the polymers suggest that a highly crosslinked structure is formed in preference to the

(1) This research was supported in whole or in part by the United States Air Force under Contract AF 33(616)-3675, monitored by the Materials Laboratory, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio.

(2) J. E. Dereich, U. S. Patent 2,684,354 (July 29, 1954).

(3) J. T. Goodwin, Jr., U. S. Patent 2,686,740 (Aug. 17, 1954).

(4) J. L. Speier, U. S. Patent 2,576,486 (Nov. 27, 1951).

(5) R. R. McGregor, *Silicones and Their Uses*, McGraw-Hill Book Co., Inc., New York, 1954, p. 228.

(6) N. D. Cheronis, U. S. Patent 2,579,416 (Dec. 18, 1951).

(7) N. D. Cheronis, U. S. Patent 2,579,417 (Dec. 18, 1951).

(8) N. D. Cheronis, U. S. Patent 2,579,418 (Dec. 18, 1951).

(9) V. P. Davydova, and M. G. Voronkov, *Zhur. Obschei Khim.*, 28, 1879 (1958).

(10) M. M. Sprung, *J. Org. Chem.*, 23, 58 (1958).

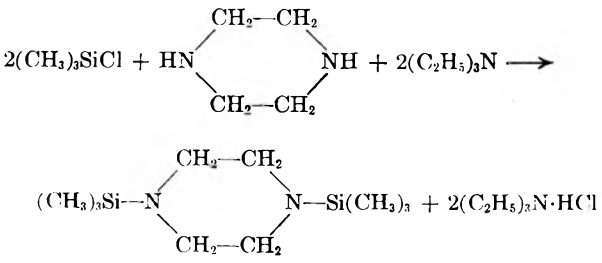
linear structure that would result if the reaction had produced a series of rings.

When ethyl orthosilicate and pentaerythritol tetraacetate were heated in cyclohexane in the presence of aluminum isopropylate, about 56% ethyl acetate was recovered in the distillate. A toluene soluble resin was obtained which formed a transparent brittle film on curing. Heated, the material gave visual evidence of decomposition between 250° and 320°. Elemental analyses indicated that the postulated polymer backbone had not been obtained and showed that the material contained a ratio of about two pentaerythritol groups per silicon atom.

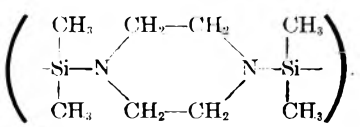
Treating pentaerythritol with silicon tetraacetate gave only a small amount of the expected acetic acid. The product, however, was insoluble in aromatic solvents.

When pentaerythritol tetraacetate and *p*-phenylenebis(diethoxymethylsilane) were condensed in the presence of a Lewis acid, only a 24% recovery of the theoretical ethyl acetate was obtained, but the resulting polymer was infusible and insoluble in benzene, toluene, and diethyl ether.

In studying the piperazine-silane system, no difficulty was encountered in the preparation of the prototype compound, *N*,*N*-bis(trimethylsilyl)-piperazine, by the dehydrohalogenation of the piperazine-chlorotrimethylsilane adduct with triethylamine, although the yield of the product was somewhat low (34%).



Attempts to prepare a polymer from piperazine and dichlorodimethylsilane gave a product containing distillable materials. The results of analyses for elements on the distillates from two experiments approximated the ratio of elements that would indicate a structure with two silane units for each piperazine unit. Although the properties of the two distillates were not identical—probably because of the different degree of hydration of the starting piperazine samples—the over-all degree of polymerization was low. The basic unit obtained by the reaction of equimolar quantities of dichlorodimethylsilane and piperazine had the structure:



EXPERIMENTAL[11]

3,3,9,9-Tetramethyl-2,4,8,10-tetraoxa-3,9-disilaspiro[5.5]-undecane. A 100-ml. round bottom flask equipped for distillation through a short Vigreux column was charged with 14.8 g. (0.1 mole) of diethoxydimethylsilane, 15.2 g. (0.05 mole) of pentaerythritol tetraacetate, 0.2 g. (0.001 mole) of aluminum isopropoxide, and 25 ml. of cyclohexane. While 75 ml. of the cyclohexane–ethyl acetate azeotrope was distilled from the mixture, constant volume was maintained by the addition of cyclohexane. When an insoluble material formed in the reaction flask and no more ethyl acetate was found in the distillate as determined by vapor phase chromatography, 50 ml. of toluene was added. The distillation was continued with the collection of additional ethyl acetate (total recovery—about 100%). The residue was distilled at atmospheric pressure and 5.0 g. (40.4%) of the product was obtained boiling 230–240°, m.p. 135° (reported,[9] m.p. 136°).

Anal. Calcd. for $C_9H_{20}O_4Si_2$: C, 43.50; H, 8.12. Found: C, 43.36; H, 8.17.

With Davydova's procedure, 0.30 mole of diacetoxydimethylsilane and 0.15 mole of pentaerythritol gave 61.5% of the same product boiling 243–260° (mostly between 243–245°).

When 17 g. (0.12 mole) of pentaerythritol, 34.0 g. (0.26 mole) of diethoxydimethylsilane, and 1 g. of *p*-toluenesulfonic acid were heated, ethanol distilled from the mixture. Distillation of the product, a viscous white mass, gave a small amount of the same material, melting at 130–132°.

Pentaerythritol and diethoxymethylphenylsilane. After a mixture of 17 g. (0.13 mole) pentaerythritol, 54.7 g. (0.26 mole) of diethoxymethylphenylsilane, and 1 g. of *p*-toluenesulfonic acid was heated at reflux for 3 hr., unchanged pentaerythritol was removed by filtration and a portion of the filtrate was heated at 110° for 72 hr. A flexible, elastic film was obtained.

Pentaerythritol and dichloromethylphenylsilane. To a stirred mixture of 27.2 g. (0.20 mole) of pentaerythritol and 126 g. (1.6 mole) of pyridine was added 76.4 g. (0.40 mole) of dichloromethylphenylsilane dropwise over a 1-hr. period with no attempt to control the temperature. In order to maintain stirring throughout the addition, several portions of anhydrous ether were added. When the product had cooled to room temperature, it was filtered and the filtrate was washed with several portions of ether. The combined filtrate and ether washings were concentrated by downward distillation to yield a soft, tacky residue. This residue was redissolved in ether and benzene, the solution was washed with water, and the solvents were again removed by distillation. After devolatilizing the residue for 3 hr. at 0.5 mm. and 140°, 56 g. of a tacky material remained which could be drawn into long fibers. Qualitative tests for nitrogen and chlorine were negative. The product was divided into two fractions by collecting the material which flowed through a hole in the bottom of an aluminum evaporating dish heated at 170°. The less fluid, benzene insoluble fraction, which constituted the major portion of the material, was labelled "A"; the other fraction, "B." The molecular weight of fraction B determined cryoscopically in benzene was 2,215 and 2,180. Empirical formulas, calculated from analysis for elements, are tabulated below.

Sample	C	H	Si	Empirical Formula
A	57.41	6.96	13.59	$C_{10.0}H_{14.4}O_{2.7}Si$
B	59.51	6.36	15.70	$C_{8.8}H_{11.3}O_{2.0}Si$

(11) All melting points and boiling points are uncorrected. Vapor phase chromatography was performed with a Perkin-Elmer 154B Vapor Fractometer. Elemental analyses were performed by Spang Microanalytical Labs., Ann Arbor, Mich.

Reaction of pentaerythritol and silicon tetraacetate. After 13.2 g. (0.05 mole) of silicon tetraacetate and 6.8 (0.05 mole) of pentaerythritol were heated at 120° for 2 hr., the acetic acid was distilled from the reaction mixture. Residual acetic acid was removed at room temperature with water aspirator vacuum. The weight loss was 5.5 g. (theory 12.0 g.) and only part of the residue toluene soluble. Evaporation of the solution of the soluble portion gave an oil which did not cure to a solid at 130°.

Reaction of pentaerythritol tetraacetate and ethyl orthosilicate. A mixture of 10.4 g. (0.05 mole) of redistilled ethyl orthosilicate, 15.2 g. (0.05 mole) of pentaerythritol tetraacetate, 0.2 g. of aluminum isopropylate, and 25 ml. of cyclohexane was heated to reflux and the cyclohexane–ethyl acetate azeotrope was removed at 73° until vapor phase chromatography indicated no more ester was being distilled. Toluene was added to the mixture and the distillation was continued; however only 56% of the theoretical ethyl acetate could be obtained. A film, formed by the evaporation of the solvent from the resin solution, was cured at 130° for several days and gave a transparent brittle solid which exhibited visual evidence of decomposition at 250–320°.

Anal. Calcd. for $C_5H_8O_4Si$ (the theoretical polymer): C, 37.48; H, 5.03; Si, 17.53. Found: C, 42.86; H, 5.95; Si, 8.50.

After 8-months' storage, the resin solution had gelled and additional ethylacetate had formed as indicated by odor.

Pentaerythritol tetraacetate and p-phenylenebis(diethoxymethylsilane). A mixture was prepared from 7.6 g. (0.025 mole) of pentaerythritol tetraacetate, 8.7 g. (0.024 mole) of *p*-phenylenebis(diethoxymethylsilane),[12] and 0.1 g. of ferric chloride. When this mixture was heated 20 hr. from 115° to 165°, the volatile products were collected in a Dry Ice trap. Vapor phase chromatographic analysis indicated that only 2.08 g. of ethyl acetate (23.5%) had been recovered. The polymer was infusible and insoluble in benzene, toluene, and diethyl ether.

N,N-bis(trimethylsilyl)piperazine. A stirred solution of 5 g. (0.06 mole) piperazine in 200 ml. of anhydrous ether was heated to reflux to dissolve the piperazine and then 12.6 g. (0.12 mole) of chlorotrimethylsilane was added dropwise. After the chlorosilane was added, 11.7 g. (0.12 mole) triethylamine was introduced. Filtration gave triethylamine hydrochloride (m.p. 254°) and a solution that was fractionally distilled to give 4.7 g. (34%) of *N,N*-bis(trimethylsilyl)-piperazine boiling at 210–216°.

Anal. Calcd. for $C_{10}H_{26}N_2Si_2$: C, 52.11; H, 11.37; N, 12.15; Si, 24.37. Found: C, 52.63; H, 10.85; N, 12 21; Si, 24.31.

Piperazine and dichlorodimethylsilane. Two attempts were made to prepare a polymer by the reaction of equimolar quantities of piperazine and dichlorodimethylsilane. Freshly distilled dichlorodimethylsilane and fresh anhydrous piperazine (Eastman, practical) were used.

After a stirred mixture of 20 g. (0.23 mole) of piperazine, 47 g. (0.46 mole) of triethylamine, and 750 ml. of anhydrous ether was heated to reflux, a solution of 30 g. (0.23 mole) of dichlorodimethylsilane in 200 ml. of anhydrous ether was added dropwise during 4 hr. Heating and stirring were continued for an additional 3 hr., and then the cooled mixture was filtered and the residue was washed with ether. The combined filtrate and washings were evaporated *in vacuo* yielding 39 g. of a reddish solid still containing some solvents. A portion of the product was purified by short path distillation, and about half the material was obtained as a white crystalline, moisture sensitive product boiling between 120–150° at 2–4 mm.

In a second experiment using a fresh lot of piperazine, a total of 84 g. of ether-insoluble solids separated. Evaporation of the ether gave 7.0 g. of a white solid, melting 105–115°, which distilled in a short path column mostly between 200–250° at 0.07 mm.

Anal. Calcd. for $C_8H_{20}Cl_2N_2Si_2$ (*N,N*-bis(chlorodimethylsilyl)piperazine): C, 35.41; H, 7.43; Cl, 26.13; N, 10.33; Si, 20.70. Found (1st experiment): C, 36.69; H, 8.08; Cl, 22.99; N, 9.92; Si, 21.98. Found (2nd experiment): C, 40.75; H, 8.69; Cl, 3.93; N, 11.52; Si, 24.00.

The ratio of elements in the first experiment is C, 7.8; H, 20.5; N, 1.8; Si, 2.0 and in the second experiment is C, 7.9; H, 20.2; N, 1.9; Si, 2.0 or equivalent to about one piperazine unit, $C_4H_8N_2$, to two silane units, $2C_2H_6Si$, in both cases.

KANSAS CITY 10, MO.

(12) L. W. Breed, F. Baiocchi, and C. Bolze, WADC TR 57-143, Part II, p. 20 (1957).

Notes

A department for short papers of immediate interest.

Effect of Sodium in the Preparation of Organolithium Compounds

CONRAD W. KAMIENSKI AND DONALD L. ESMAY

Received March 10, 1960

The sodium content of the lithium metal has been reported recently to affect the ease of preparation of *p*-dimethylaminophenyllithium,[1] of *tert*-butyllithium,[2] and of *n*-butyllithium[3] by the metal-

$$RX + 2Li \longrightarrow RLi + LiX \qquad (1)$$

organic halide reaction (1). These observations prompt us to report some results we have obtained in this connection. While the most striking effects have been observed by us in preparations of *p*-dimethylaminophenyllithium and *tert*-butyllithium, we have also determined that the ease of preparation of *n*-butyllithium and phenyllithium is affected to some extent by the sodium content of the lithium metal

In our hands, lithium metal containing less than 0.005% sodium[4] could not be made to react at all with *p*-bromodimethylaniline in ethyl ether. Excellent yields (over 95%) of *p*-dimethylaminophenyllithium were obtained when either lithium wire or lithium ribbon containing about 0.02% sodium[5] was treated with *p*-bromodimethylaniline in ethyl ether.

In comparative reactions of the two grades of lithium metal with bromobenzene and with *n*-butyl bromide in diethyl ether, the differences in yields were considered significant for *n*-butyllithium (15% or greater) but not for phenyllithium (less than 10%). In both cases the physical appearances and, to a lesser extent, the rate of the reactions were affected by the amount of sodium present in the lithium metal. The best over-all preparations of phenyllithium and *n*-butyllithium were obtained using the lithium metal containing about 0.02% sodium.[5]

The ease of preparation of organolithium compounds in hydrocarbon solvents has also been found by us to be related to the sodium content of the lithium metal used. For example, we have been able to prepare *tert*-butyllithium in pentane consistently in yields over 80% provided that we use a dispersion prepared from lithium metal containing 2% sodium.

We do not know at this time the critical or optimum concentration of sodium in the lithium metal that is necessary to ensure that a satisfactory organolithium preparation can be made. Preliminary results indicate that this concentration varies with the organic halide substrate used. Additional studies are being carried out.

EXPERIMENTAL

p-Dimethylaminophenyllithium. A. In a 250-ml., three necked, round bottomed flask, equipped with mechanical stirrer, reflux condenser, and dropping funnel (the latter two fitted with gas inlets for argon), was placed 1.2 g. of finely cut lithium metal ribbon ("regular"[5] grade) and 50 ml. of anhydrous ethyl ether. The lithium metal was cut directly into the flask in an exit flow of argon to keep the cut surface shiny. To the stirred suspension in the flask was added, *all at once*, 3–4 ml. of a solution of 15.6 g. (0.078 mole) of *p*-bromodimethylaniline[6] in 60 ml. of ether. On heating the mixture to reflux the reaction was initiated after about 5 to 10 min. time as evidenced by a reddish brown coloration of the suspension and pitting of the metal surface. The remainder of the solution was added over a 1-hr. period with refluxing evidenced throughout. Stirring and refluxing were then continued over a 3-hr. period with a gradual brightening and disappearance of the metal. After allowing the mixture to cool, the contents of the flask were filtered through a glass wool plug (under argon) into a 100-ml. graduated dropping funnel (total volume, 101 ml.). A 2-ml. aliquot of the clear supernatant liquid was taken, hydrolyzed, and titrated with standard acid, using thymol blue as indicator (yield, 97%). The remaining solution in the dropping funnel was carbonated by gradual addition to a Dry Ice–ether slurry. The crude yield of *p*-dimethylaminobenzoic acid (m.p. 200°, lit., m.p. 240–241°) obtained after work-up was 65%.

B. This was a duplicate of Run A except that "low sodium"[4] lithium metal was used. No reaction was observed even on prolonged refluxing and stirring after addition of the total amount of *p*-bromodimethylaniline. When small chips of "regular"[5] grade lithium metal were added to this mixture immediate, vigorous reaction with these chips was observed. However, reaction ceased as soon as the chips were used up.

C. This was a duplicate of Run A except that lithium wire was used. Results were essentially identical with those of Run A.

tert-Butyllithium. In a 1-l., three necked, round bottomed flask, equipped with mechanical stirrer, reflux condenser, and dropping funnel (the latter two fitted with gas inlets for argon) was placed 120 g. of lithium dispersion [15% in a petrolatum (20%)–mineral oil (65%) mixture] and 200 ml. of dry, "unsaturate-free"[7] *n*-pentane. The lithium metal

(1) J. B. Wright and E. S. Gutsell, *J. Am. Chem. Soc.*, 81, 5193 (1959), ref. 10.

(2) M. Stiles and R. P. Mayer, *J. Am. Chem. Soc.*, **81**, 1497 (1959) ref. 38b.

(3) J. A. Beel, W. G. Koch, G. E. Tomasi, D. E. Hermansen, and P. Fleetwood, *J. Org. Chem.*, 24, 2036 (1959).

(4) Lithium Corp. of America "low-sodium" grade lithium.

(5) Lithium Corp. of America "regular" grade lithium as currently produced.

(6) The *p*-bromodimethylaniline used in these runs was Eastman Kodak's practical grade which was recrystallized once from Synasol before use (m.p. 53–55°, lit. m.p., 55°).

contained 2% of sodium. The mixture was stirred and heated to reflux. The dropwise addition of a solution of 92.6 g. (1.0 mole) of *tert*-butyl chloride[8] in 250 ml. of dry "unsaturate-free" *n*-pentane was then begun. After addition of about 5 ml. of the halide solution, the rate of reflux increased appreciably and the source of heat was removed. The remainder of the halide solution was then added over a 2.5-hr. period, at a rate such that sustained reflux was maintained throughout the addition. The reaction mixture was stirred for 0.5 hr. longer. The product solution was then filtered away from the residue of lithium chloride and excess metal through a sintered glass filter tube,[9] into a graduated dropping funnel (total volume, 589 ml.). Three-milliliter aliquots of the clear solution were then taken, hydrolyzed in flasks containing 10 ml. of standard 0.5*N* acid, and back-titrated with standard 0.1*N* base to a phenolphthalein end point. The yield of *tert*-butyllithium (based on *tert*-butyl chloride) was 89%.

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LITHIUM CORP. OF AMERICA, INC.
MINNEAPOLIS 16, MINN.

(7) The *n*-pentane was a 99 mole % (Phillips "Pure") grade which had been stirred with concd. sulfuric acid for 3 days, separated, washed with 5% sodium bicarbonate solution, washed with water, dried over calcium chloride (anhyd.) and, finally, dried over sodium ribbon.

(8) The *tert*-butyl chloride was obtained from Matheson, Coleman and Bell (purified grade); b.p. 51–52°, n_D^{20}, 1.3851.

(9) Ace Glass Co., Cat. No. 8575—porosity "E."

The Preparation of Grignard Reagents under Helium and Argon

F. H. OWENS, R. P. FELLMANN, AND F. E. ZIMMERMAN

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Grignard reagents prepared by conventional methods generally contain excess magnesium halide arising from a Wurtz-type reaction (Equation 1), and various preparative methods have been used to avoid this undesirable reaction.[1] Several investigators[2] have shown that the course of a Grignard

$$2RX + Mg \longrightarrow R{-}R + MgX_2 \qquad (1)$$

reaction can be altered by varying the amount of magnesium halide.

Recently we have found that the preparation of Grignard reagents under helium or argon, rather than the customary nitrogen or ether, consistently leads to higher yields and to smaller amounts of coupling products. The Grignard reagents listed in Table I were prepared by the dropwise addition of the organic halide to a 10% excess of magnesium metal in ether. The Grignard reagents prepared under helium or argon were clear, almost colorless solutions while those prepared under nitrogen or ether were cloudy, dark-colored solutions. One-milliliter samples were titrated with hydrochloric acid and with silver nitrate to determine the amount of excess halide. The values shown represent the average of several experiments in which the reproducibility was excellent.

TABLE I

GRIGNARD REAGENTS PREPARED UNDER HELIUM, ARGON, NITROGEN, AND ETHER

Halide	Prepared under	Yield,[a] %	Excess Halide,[b] %
n-Butyl chloride	Helium	99.0	0.0
n-Butyl chloride	Nitrogen	91.0	2.2
n-Butyl bromide	Helium	97.5	1.1
n-Butyl bromide	Argon	97.8	1.0
n-Butyl bromide	Nitrogen	80.1	15.2
n-Butyl bromide	Ether	89.0	7.7
Cyclohexyl bromide	Helium	68.3	38.5
Cyclohexyl bromide	Nitrogen	30.5	75.4
Bromobenzene	Helium	99.0	0.0
Bromobenzene	Argon	95.2	2.1
Bromobenzene	Nitrogen	85.0	8.0
Bromobenzene	Ether	88.3	5.7
Iodobenzene	Helium	81.0	10.2
Iodobenzene	Nitrogen	70.4	16.5
Benzyl bromide	Helium	91.3	7.6
Benzyl bromide	Nitrogen	62.2	20.3
Benzyl bromide	Ether	53.0	25.8

[a] Based on the acid titration. [b] The per cent excess halide is the quotient of the difference between the total base and halide titrations and the total base titration.

The principal advantages which accrue from this method are that (1) purification of the purging gas is unnecessary; (2) higher yields of the Grignard reagent are obtained; and (3) there is little or no contamination by coupling products. Furthermore, dilution of the halide with ether is not required so that concentrated solutions of the Grignard reagent are obtainable, and only 10% excess magnesium is used as compared with the one- to three-mole excess used in some preparations.[1]

EXPERIMENTAL

Magnesium. Domal High Purity, sublimed magnesium granules (Dominion Magnesium Co., Ltd., Haley, Ont.) was used.

Diethyl ether. Mallinckrodt analytical reagent ether containing 5×10^{-6} % sodium diethyldithiocarbamate was used without further treatment.

Organic halides were obtained from Distillation Products Industries and were dried over calcium chloride prior to use.

Nitrogen. Prepurified grade (Air Reduction Sales Co.) containing less than 0.002% oxygen and 0.0012% water was used without further treatment.

Helium was obtained from the Matheson Co., Inc. Minimum purity, 99.99%, used without further treatment.

Argon, obtained from the Matheson Co., Inc. Minimum purity, 99.998%, was used without further treatment.

Preparation of the Grignard reagents. The apparatus consisted of a three necked, round bottom flask equipped with a Dry Ice reflux condenser attached to a mercury bubbler,

(1) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., New York, 1954, Chap. II.

(2) C. G. Swain and H. B. Boyles, *J. Am. Chem. Soc.*, **73**, 871 (1951); E. T. McBee, O. R. Pierce, and J. F. Higgins, *J. Am. Chem. Soc.*, **74**, 1736 (1952); A. C. Cope, *J. Am. Chem. Soc.*, **56**, 1578 (1934); R. C. Huston and A. H. Agett, *J. Org. Chem.*, **6**, 123 (1941).

a Teflon stirrer, and a pressure-equalizing dropping funnel. One neck of the flask was equipped with a rubber serum cap through which gas was admitted *via* a hypodermic needle which allowed the gas to pass over the mixture. When no purging gas was used, the Dry Ice condenser was replaced by an air-cooled condenser, and the ether was allowed to reflux so that a small amount constantly escaped from the top of the condenser which was protected from the atmosphere by a drying tube containing Drierite.

The Grignard reagents listed in Table I were prepared by the dropwise addition of the organic halide to a 10% excess of the magnesium metal in ether so that the final Grignard solution was approximately 2*N* in RMgX. When all of the halide had been added, the solution was heated under reflux from 2–3 hr., allowed to cool to room temperature, and was transferred to rubber serum-capped bottles by means of a hypodermic syringe. One-milliliter samples were titrated with 0.1*N* hydrochloric acid and with 0.1*N* silver nitrate using the Volhard method.[3]

ROHM & HAAS CO.
BRISTOL, PA.

(3) W. Reiman, III, J. D. Neuss, and B. Naiman, *Quantitative Analysis*, McGraw-Hill Book Co., Inc., New York, 1951, p. 270.

A Test for Peroxides in Vinyl Ethers

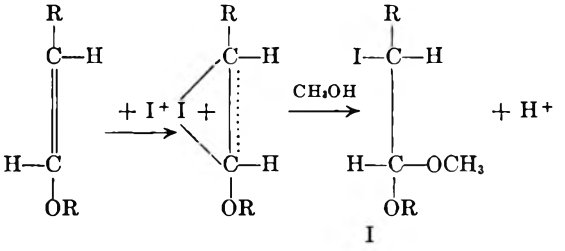
R. K. SUMMERBELL AND D. KAREN ANDERSON HYDE

Received April 8, 1960

The hazards involved in evaporating or distilling ethers that contain peroxides are well recognized. In safety conscious laboratories a routine test is employed periodically to make certain that samples of ethers that have developed a dangerous peroxide content are discarded. The usual test[1] is to add acidified or neutral aqueous or alcoholic iodide to the suspected sample, or *vice versa* and a brown coloration is positive. The test is readily performed quantitatively.[2a,b] The purpose of this note is to point out that this test as usually performed is not valid in the presence of vinyl ethers and to suggest a modified procedure with which vinyl ethers do not interfere.

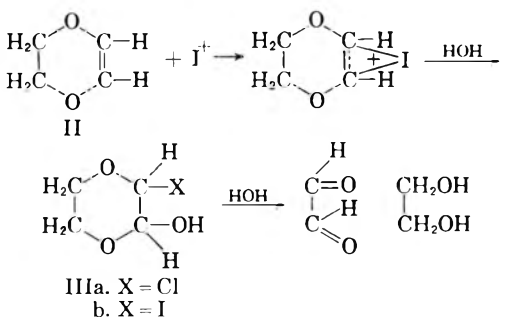
The reason for the failure of the usual form of the test is the immediate reaction of the liberated iodine with the vinyl ether. We became interested in the reaction when, during preliminary studies of the relative rates of iodine liberation by isomeric tetrachlorinated dioxanes,[3] we noticed that addition of water caused a rapid fading of the iodine color. Apparently the double bonded product from which vicinal halogens had just been removed by iodide ions was in turn adding back the iodine. The related parent compound, dioxene, was found to react with aqueous iodine as fast as mixing took place. It was then realized that a dioxene was a type of vinyl ether and that the observed reaction was closely related to the valuable quantitative method of Siggia and Edsberg[4] for determination of vinyl ethers by titration with aqueous methanolic iodine. These authors do not mention interference by peroxides, perhaps because it is so obvious, nor did they have occasion to point out the corollary: *that vinyl ethers would negate the usual peroxide test.* In view of the increasing commercial availability of vinyl ethers and the extreme hazards of handling ethers that contain peroxides, we think the corollary should be emphasized.

There is some evidence available concerning the course of these related reactions. Siggia and Edsberg[4] isolated an iodine-containing organic product from the reaction of methanolic iodine with butyl vinyl ethers, the analysis of which was consistent with the formula of an iodoacetal, I. The following mechanism explains this result:



I

In the case of our modified vinyl ether, II, the reaction would proceed further:



We have identified the glyoxal and the ethylene glycol by isolation of appropriate derivatives. The intermediate, IIIb, is the iodine analogue of one postulated by Salomaa.[5] To account for the first order kinetics of the hydrolysis of *trans*-2,3-dichloro-*p*-dioxane,[6] he proposed that the hydrolysis of IIIa was much more rapid than that of the parent dichloro compound. The iodine compound, IIIb, should hydrolyze even faster. There is no evidence for the formation of an intermediate diiodo

(1) *Reagent Chemicals*, Am. Chem. Soc. Specifications (1955), American Chemical Society, Washington, D. C.

(2) (a) K. V. Kopatnur and M. Jelling, *J. Am. Chem. Soc.*, **63**, 1432 (1941).

(b) Union Carbide Chemical Co. *Ethers and Oxides* Booklet number 4764B (1957).

(3) A qualitative difference in rates was first observed by Milton Cooper, Ph.D. dissertation, Northwestern University, 1955.

(4) S. Siggia and R. L. Edsberg, *Anal. Chem.* **20**, 762 (1948).

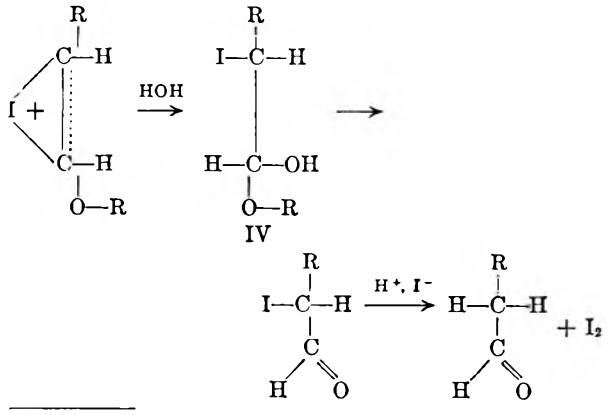
(5) P. Salomaa, *Acta. Chem. Scand.*, **8**, 744 (1954).

(6) R. K. Summerbell and Hans E. Lunk, *J. Am. Chem. Soc.*, **79**, 4802 (1957).

compound as proposed some years ago in a related situation.[7]

The proposed mechanism led us to the prediction that the use of a solvent less polar than aqueous methanol would materially reduce the velocity of iodine uptake by vinyl ethers. This was found to be the case. As the ratio of methanol to water was increased, the reaction tended to become more quantitative[8] with ordinary vinyl ethers, but also to take considerably more time to reach completion. By using a solvent of sufficiently low dielectric content, it should be possible to so reduce the rate of iodine uptake that interference with the usual peroxide test would be inconsequential. Peroxide-free dioxane was found to be the solvent of choice for this purpose, as considerable water must be admixed before the rate of uptake of iodine becomes appreciable. The use of pure dioxane as the major solvent component thus serves as a single and practical modification of the iodide test for peroxides in ethers, a modification that makes the test valid in the presence of vinyl ethers.

We have made several incidental observations concerning the Siggia and Edsberg method. It does not work at all for 2,3-diphenyl-*p*-dioxene.[9] This compound was not only inert to aqueous methanolic iodine, in which it was insoluble, but also to aqueous methanolic iodine solutions, in which it was completely soluble. Failure of this type of vinyl ether to react is probably due to the stabilization of the double bond by resonance with the phenyl groups. The general inferiority of water to methanol as a solvent may be due to the tendency toward halogen-catalyzed polymerization,[10] particularly when two phases are permitted, or even when the limit of solubility is approached. In some cases, Siggia and Edsberg observed a somewhat unsatisfactory end point due to reappearance of iodine on standing. This could be due to air oxidation, but also could be caused by the following sequence:



As both water and methanol are present and competing for the carbonium ion, some of the unstable hemiacetal, IV, as well as the acetal that was actually isolated, I, would form. The iodine regeneration from this source can be prevented by buffers which reduce the hydrogen ion concentration. The reported failures[4] of the method in the case of lauryl vinyl ether and octadecyl vinyl ether result because if water is present, two phases and polymerization result, while if water is excluded, the initial attack of positive iodine is so slow that no reaction is observed. Probably at least one component of the solvent must be capable of participation in the reaction,[11] explaining the failure of the determination using carbon tetrachloride.[4]

EXPERIMENTAL

Aqueous iodine and dioxene. Standard iodine solutions, approximately 0.1*M*, containing also 80 g. of iodate-free potassium iodide per l. were prepared by exact weighing of pure iodine. Arsenious oxide and sodium thiosulfate solutions for back titration were standardized against the iodine solutions.

Dioxene, 0.0123 mole, dissolved in 150 ml. of water containing sodium acetate–acetic acid buffer required 0.0117 moles of iodine for an iodine/ether ratio of 0.951 to give a pale coloration. In a similar experiment when no buffer was used, the iodine/ether ratio was 0.931. Substitution of methanol for part of the water did not change the iodine/ether ratio. Rapid addition of excess iodine and back titration with sodium thiosulfate gave an iodine/ether ratio of 0.949.

The products of reaction were proved by the preparation of derivatives. To a reaction mixture of dioxene titrated with aqueous iodine was added an excess of *p*-nitrophenylhydrazine hydrochloride in water. After slight warming on a steam bath, a dark orange precipitate was formed. It gave the characteristic blue color with alcoholic sodium hydroxide, and a mixed melting point with a pure example of glyoxal *p*-nitrophenyl osazone was not depressed. A solution of 7.3 g. of dioxene in water was titrated with iodine to a pale yellow end point. The total volume of the reaction solution was 150 ml. To half of this solution was added enough 20% sodium hydroxide to make the solution basic. A 1.5-ml. portion of benzoyl chloride was added, and the mixture shaken vigorously with intermittent additions of base. The dibenzoate of ethylene glycol which formed had a melting point of 71.5–72.5°. The yield was 9%. In earlier experiments, a less concentrated solution was used and no benzoate was isolated. Model experiments using the calculated amount of ethylene glycol in the present dilution gave about the same yield, but when the concentration was halved, the yield was cut to the vanishing point.

Failure of 2,3-diphenyl-p-dioxene to react. 2,3-Diphenyl-*p*-dioxene[9] (0.2072 g., 0.00087 mole) was placed in a glass-stoppered Erlenmeyer flask with 150 ml. of methanol and 10.00 ml. of 0.0923*M* iodine solution. Solution was complete. After shaking the solution for 10 min., it was titrated with sodium thiosulfate solution, 10.05 ml. being required. A blank containing 10.00 ml. of the iodine solution required exactly the same volume of thiosulfate solution. In a similar experiment in which the methanol was omitted, a suspension of the diphenyldioxene also failed to react with any aqueous iodine. The starting material was unaltered.

(7) V. I. Easton, *J. Applied Chem. U.S.S.R.*, **12**, 1387 (1939); *Chem. Abstr.*, **34**, 3233 (1940).

(8) Dioxene, unlike other vinyl ethers, reacted practically quantitatively with aqueous iodine.

(9) R. K. Summerbell and D. R. Berger, *J. Am. Chem. Soc.*, **81**, 633 (1959).

(10) D. D. Ely and J. Saunders, *J. Chem. Soc.*, 4167 (1952); 1668 (1954).

(11) K. Kozaki and R. A. Ogg, Jr., *J. Am. Chem. Soc.* **64**, 709 (1942).

Other vinyl ethers and aqueous iodine. Dihydropyran (0.0063 mole) was added to sodium acetate–acetic acid buffered water solution, excess standard iodine added and the excess back titrated; iodine consumed, 0.0039 mole for an ether/iodine ratio of 0.62. The ratio was raised to 0.73 in a similar experiment by the addition of 3 drops of pyridine as a polymerization inhibitor. It was raised still further to 0.91 by employing 80 ml. of methanol as the solvent. Divinyl ether (0.0109 mole), when titrated without buffer, required 0.0091 mole of iodine for a ratio of 0.83. On standing, the iodine color was regenerated. In a similar experiment buffered to *p*H 7 with phosphate, iodine was not regenerated. Vinyl ethyl ether, vinyl butyl ether, and dioxadiene gave iodine/ether ratios of 0.478, 0.381, and 1.58, respectively. In the latter case, even though enough methanol to ensure solution was used, an ether-insoluble solid was formed, direct evidence of extensive polymerization.

Peroxide test. A laboratory sample of ordinary dioxane from a bottle that had been in use several weeks gave a distinct yellow color when a few drops were added to an acidified aqueous solution of potassium iodide. Few samples of dioxane that have been exposed to the air and have not been specifically purified fail to give this test. When 3 drops of vinyl butyl ether was added to 1 ml. of the same dioxane, no test for peroxides could be obtained with water solutions if the volume of the water were equal to that of the dioxane. However, if only a few drops of aqueous potassium iodide and a drop of hydrochloric acid were added to a similar mixture of vinyl ether and the same dioxane, a strong test was obtained. Using mixtures of vinyl ethers and an ether known to contain peroxides, a positive test was always obtained in a 3:1 dioxane-water solution. The dioxane used as solvent was, of course, peroxide-free.[12] A negative test was always obtained when the same ether–peroxide–vinyl ether mixtures were subjected to the usual aqueous iodide test where water was present in large proportion.

An alternative test for the presence of peroxides in ether,[2b] the appearance of a pink or red coloration in the ether on shaking with ferrous thiocyanate solution, did not work in the presence of vinyl ethers, even though the samples under examination were known to contain large amounts of peroxides. In another experiment, a bright pink color was obtained by using a sample of typical sideshelf ethyl ether. When *n*-butyl vinyl ether was added to this test solution, the color gradually faded. The formation of black mercurous oxide on[13] shaking with a globule of metallic mercury was prevented by the presence of small percentages of vinyl ether in samples of ether that would otherwise give the test.

Acknowledgment. We wish to thank the E. I. du Pont Co. and the Research Corp. for research assistantships held by D.K.A.H.

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(12) K. Hess and H. Frahm, *Ber.*, **71**, 2627 (1938); R. N. Feinstein, *J. Org. Chem.*, **24**, 1172 (1959).

(13) C. R. Noller, *Chemistry of Organic Compounds*, W. B. Saunders Co., Philadelphia, 1951, page 139.

Attempted Thermal Rearrangement of Cyclopropylcarbinyl Phenyl Ether

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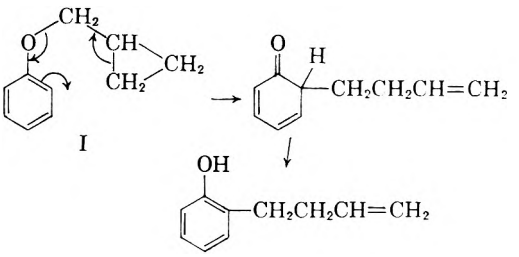
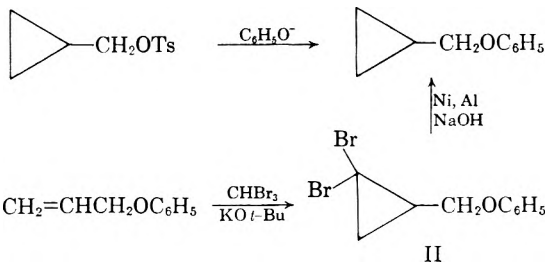
Received March 30, 1960

The cyclic nature of the transition state and the intermediacy of dienones in the Claisen rearrangement has been thoroughly established.[1] The cyclopropyl group sometimes displays chemistry similar to that of a carbon-carbon double bond.[2] It seemed possible, therefore, that the cyclopropylcarbinyl group might replace the allyl group in the Claisen rearrangement. A plausible mechanism can be envisioned and is depicted (1) for the thermal rearrangement of cyclopropylcarbinyl phenyl ether (I)



(1)

Compound I was synthesized by two independent methods: displacement by phenoxide ion on cyclopropylcarbinyl tosylate, and reduction of



2,2-dibromocyclopropylcarbinyl phenyl ether (II), the latter being prepared by the carbene reaction[3] on allyl phenyl ether.

When Compound I was refluxed (214°) for eighteen hours, or heated in a sealed tube at 300° for ten hours, it was recovered unchanged (identical infrared spectrum, negative ferric chloride test).[4] It is apparent, then, that the cyclopropylcarbinyl group does not behave like an allyl group in the Claisen rearrangement, at the ordinary tempera-

(1) For a review, see D. J. Cram in M. S. Newman, *Steric Effects in Organic Chemistry*, John Wiley & Sons, Inc., New York, N. Y., 1956, pp. 295–303. For subsequent work, see especially D. Y. Curtin and R. J. Crawford, *J. Am. Chem. Soc.*, **79**, 3156 (1957); F. Kalberer and H. Schmid, *Helv. Chim. Acta*, **40**, 13, 779 (1957); W. Haegele and H. Schmid, *Helv. Chim. Acta*, **41**, 657 (1958); P. Fahrni and H. Schmid, *Helv. Chim. Acta*, **42**, 1102 (1959); H. L. Goering and R. R. Jacobson, *J. Am. Chem. Soc.*, **80**, 3277 (1958); W. N. White, D. Gwynn, R. Schlitt, C. Girard, and W. Fife, *J. Am. Chem. Soc.*, **80**, 3271 (1958).

(2) For reviews, see R. A. Raphael in E. H. Rodd *The Chemistry of Carbon Compounds*, Elsevier Publishing Co., Amsterdam, 1953, Vol. IIA, pp. 25–28; E. Vogel, *Fortschr. Chem. Forsch.*, **3**, 430 (1955); E. Vogel, *Angew. Chem.*, **72**, 4 (1960).

(3) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **76**, 6162 (1954).

(4) Compound I was readily attacked both by acid and by potassium metal; the products have not yet been identified.

tures at which the rearrangement is generally executed.[5]

EXPERIMENTAL[6]

2,2-Dibromocyclopropylcarbinyl phenyl ether (II). To a stirred suspension of anhydrous potassium *t*-butoxide (0.5 mole) in a solution of 165 g. (1.2 moles) of allyl phenyl ether and 100 ml. of pentane there was added, during 1 hr., 126.5 g. (0.5 mole) of bromoform. After 5 hr. at room temperature (200 ml. of pentane was added to facilitate stirring), hydrolysis, extraction with pentane, drying over magnesium sulfate and distillation gave 133 g. of recovered allyl phenyl ether and 41.2 g. of material, b.p. 119–126° at 1 mm. which solidified at room temperature. After several recrystallizations from ethanol, the product (31.5 g., 21%) melted at 53–54°.

Anal. Calcd. for $C_{10}H_{10}Br_2O$: C, 39.23; H, 3.27; Br, 52.32. Found: C, 39.21; H, 3.31; Br, 52.43.

Cyclopropylcarbinyl phenyl ether (I). *A. Reduction of* II. To a mixture of 100 ml. of 95% ethanol, 60 g. of Raney nickel-aluminum alloy, and 10 g. (0.033 mole) of II was added in 1 hr. 600 ml. of 10% sodium hydroxide.[7] After two additional hours of reflux the mixture was filtered and the nickel was washed successively with 100 ml. of 10% sodium hydroxide and with 400 ml. of pentane. The aqueous layers were poured into 400 ml. of cooled hydrochloric acid, then extracted with pentane. The combined pentane extracts gave 3.0 g. (62%) of cyclopropylcarbinyl phenyl ether (I), b.p. 51–53° at 2 mm., n_D^{25} 1.5199.

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.17. Found: C, 81.11; H, 8.29.

B. Displacement on cyclopropylcarbinyl tosylate by phenoxide ion. Cyclopropylcarbinyl tosylate was prepared by a procedure analogous to that used by Bergstrom and Siegel[8] for the benzenesulfonate. *p*-Toluenesulfonyl chloride (19.0 g., 0.1 mole) and 50 ml. of methylene chloride was added, at −3 to +3° during 45 min. to a mixture of 26.4 ml. of 2,4,6-collidine and 7.2 g. (0.1 mole) of cyclopropylcarbinol. Additional methylene chloride (25 ml.) was added, the mixture was stirred at 0° for 2 hr., and the collidine then neutralized with 25 ml. of 10*N* sulfuric acid, the temperature being kept below 15°. Layers were separated, the aqueous layer was extracted with methylene chloride, and the combined organic layers extracted with three 20-ml. portions of ice cold 2.5*N* sulfuric acid, then dried over potassium carbonate. The solvent was removed under reduced pressure with no external heat.

The red oil which remained was dissolved in 50 ml. of anhydrous ether and added at 0° over 30 min. to a suspension of sodium phenoxide (from 250 g. of phenol and 34.5 g. of sodium) in 200 ml. of ether. The solution was stirred at room temperature for 1.5 days, refluxed for 4 days, filtered, and washed successively with 10% alkali and with water. After drying and removal of the solvent there was obtained 3.5 g. (23%) of crude product which on fractionation gave 1.0 g. of pure cyclopropylcarbinyl phenyl ether, n_D^{25} 1.5199, whose infrared spectrum was identical with that prepared above.

Attempted thermal rearrangement of I. One milliliter of I was refluxed (214°) at atmospheric pressure for 6 hr. The infrared spectrum was unchanged, and 12 hr. of additional reflux also resulted in no change. One milliliter of I, sealed in an 11-ml. tube, was heated at 300 ± 4° for 10 hr., and recovered unchanged (infrared spectrum, negative ferric chloride test).

Acknowledgment. We are deeply indebted to the Upjohn Company, Kalamazoo, Michigan, for partial support of this work in the form of a fellowship grant.

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(5) Pyrolysis of certain cyclopropylcarbinyl derivatives at 500–520°, however, does lead to rearrangements; see C. G. Overberger and A. E. Borchert, *J. Am. Chem. Soc.*, **82**, 1007 (1960).

(6) Analyses by Spang Microanalytical Laboratory, P. O. Box 1111, Ann Arbor, Mich.

(7) D. Papa, E. Schwenk, and B. Whitman, *J. Org. Chem.*, **7**, 587 (1942).

(8) C. G. Bergstrom and S. Siegel, *J. Am. Chem. Soc.*, **74**, 145 (1952).

Synthesis of β-Lactones from β-Hydroxyacids

E. TESTA, L. FONTANELLA, AND L. MARIANI

Received April 1, 1960

As a part of a study on compounds active on the central nervous system[1] we recently described a new general method of synthesis of β-lactones, (diazotization of α,α-disubstituted β-aminoacids in acetic acid at low temperature).[2] The β-lactones are useful intermediates for pharmacologically active compounds (α-alkyltropic acids and derivatives,[3a,b] dihydro 1,3-oxazine-2,4-diones,[4] α-methylatropine[5]).

Many β-lactones are recorded in literature, which were obtained by different methods.[6] However, recently two processes for the preparation of β-lactones by dehydration of the corresponding β-hydroxyacids have been published: Diassi and Dylion[7] cyclized yohimbic acid to the corresponding β-lactone by means of pyridine and ethyl chloroformate; Sheehan, *et al.*[8] cyclized *N*-trityl-L-serine by means of *N*,*N*′-diisopropylcarbodiimide. Their work prompted us to communicate our experiences in this field.

EXPERIMENTAL

When a benzene solution of α,α-diethyl-β-hydroxypropionic acid[2,5,9] was treated at 10° to 15° with 1 mole of thionyl chloride and 1 mole of pyridine, and water added after 30 min. and the mixture extracted with benzene a crystalline compound separated from the aqueous layer.

(1) Paper XV of this series see E. Testa, L. Fontanella, G. F. Cristiani, and L. Mariani, *Helv. Chim. Acta*, **42**, 2370 (1959).

(2) E. Testa, L. Fontanella, G. F. Criastiani, and L. Mariani, *Ann.*, in press.

(3) (a) R. Fusco and E. Testa, *Farmaco* [*Ed. sci.*], **12**, 828 (1957); (b) E. Testa, *Farmaco* [*Ed. sci.*], **12**, 837 (1957).

(4) E. Testa, L. Fontanella, G. F. Cristiani, and G. G. Gallo, *J. Org. Chem.*, **24**, 1928 (1959).

(5) G. Melone, A. Vecchi, G. Pagani, and E. Testa, *J. Org. Chem.*, in press.

(6) H. E. Zaugg, *Org. Reactions*, 307 (1954).

(7) P. A. Diassi and C. M. Dylion, *J. Am. Chem. Soc.*, **80**, 3746 (1958).

(8) J. C. Sheehan, K. Hasspacher, and Y. Lieh Yeh, *J. Am. Chem. Soc.*, **81**, 6086 (1959).

(9) B. J. Ludwig, *J. Am. Chem. Soc.*, **72**, 5329 (1950).

The compound was identified as bis(β-carboxy-β-ethylbutyl) sulfite, m.p. 142–144° (from ethyl ether–petroleum ether (b.p. 45–60°)).

Anal. Calcd. for $C_{14}H_{26}O_7S$: C, 49.69; H, 7.71; S, 9.48. Found: C, 49.65; H, 7.65; S, 9.51.

The organic layer was dried over sodium sulfate and distilled; 8.5% of *α,α-diethyl-β-propiolactone* (I) was isolated, b.p. 65°–70° (7 mm., air bath).

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.59; H, 9.43. Found: C, 65.59; H, 9.44.

Compound I was identical with an authentic sample of α,α-diethyl-β-propiolactone.[2] Its structure was confirmed by conversion of I into the known α,α-diethyl-β-hydroxypropionic acid[2,4,9] (m.p. 60–62°); the infrared spectrum of I shows a typical band at 1815 cm.$^{-1}$

The cyclization reaction with thionyl chloride and pyridine occurred also with α-phenyl-α-*n*-propyl-β-hydroxypropionic acid[2,4]: the corresponding β-lactone[2] (b.p. 110–115°/0.5 mm., air bath) was isolated in 5.3% yield. In this case, no formation of a sulfite derivative was noted. The lactone shows a typical band at 1815 cm.$^{-1}$ α-Phenyl-α-*n*-propyl-β-propiolactone was hydrolized to the known α-phenyl-α-*n*-propyl-β-hydroxypropionic acid[10] (m.p. 104–107°).

The method described allows the preparation of β-lactones directly from β-hydroxycarboxylic acids, though in low yields.

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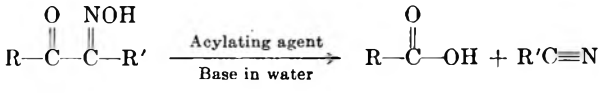
(10) E. Testa, L. Fontanella, G. F. Cristiani, and F. Fava, *Ann.*, **619**, 47 (1958).

α-Oximino Ketones. VIII. The Second Order Beckmann Rearrangement in Alcohols

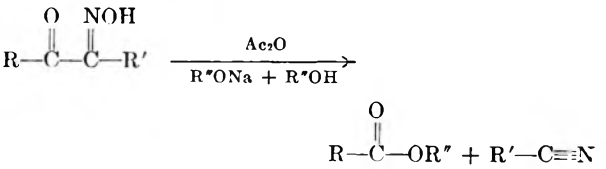
ARTHUR F. FERRIS, GRANNIS S. JOHNSON, AND FRANCIS E. GOULD

Received March 3, 1960

When α-oximino ketones possessing the *anti* configuration are treated with strong acids or acid chlorides, or when they are dissolved in aqueous base and treated with acylating agents, they are cleaved to nitriles and carboxylic acids, a reaction which has been termed a "second order" Beckmann rearrangement.[1] Recent work in this laboratory has shown that when a salt of 2,6-dioximinocyclohexanone in alcoholic base is treated with an acid anhydride, it is cleaved to ethyl 5-cyano-2-oximinovalerate.[2]

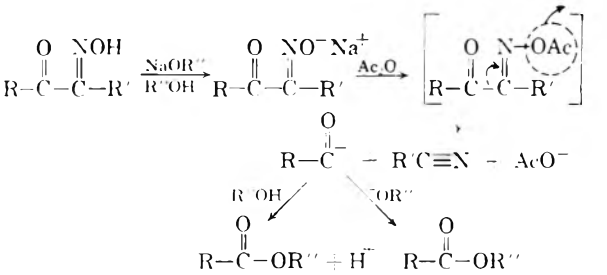


It has been found now that formation of esters is characteristic of simple α-oximino ketones as well as of 2,6-dioximinocyclohexanone when the second order Beckmann rearrangement is carried out in alcohols. The yields of esters obtained by the action of acetic anhydride on solutions of four



α-oximino ketones in alcoholic sodium alkoxides are reported in Table I. No attempt was made to isolate the low molecular weight nitrile products obtained when R′ was hydrogen or a methyl group, but when R′ was the phenyl group benzonitrile was obtained as expected. The tendency of the anhydride to react with the oxime instead of the alcohol can be explained on the basis discussed previously,[2] namely that the oxime anion is much more effective in attacking anhydride than the neutral alcohol molecule.

The fact that esters are obtained when the second order Beckmann rearrangement is carried out in alcohols provides additional confirmation for the mechanistic interpretation of the reaction presented previously.[1b] Thus if the rearrangement involves first formation of the acylated α-oximino ketone and second concurrent departure of the acetate anion and shift of the electron pair between the oxime carbon and the carbonyl carbon to form a nitrile and an oxocarbonium ion, it would be expected when the solvent is an alcohol that the oxocarbonium ion would attack the alcohol or combine with the alkoxide anion to form an ester, and that is exactly the result observed. The



alternative hypotheses that the reaction is initiated by attack of the alkoxide ion on the carbonyl carbon or involves concurrent attack at the carbonyl carbon and departure of the acetate ion have been considered in earlier work[3] and rejected on the basis of the fact that treatment of an α-acyloximino ketone in alcohol with an amine or other weak base leads to formation of the same ester product obtained when alkoxide is used.

EXPERIMENTAL[4]

α-Oximino ketones. 2-Oximino-1-phenyl-1-propanone and α-benzil monoxime were purchased from Distillation Prod-

(1) (a) A. H. Blatt and R. P. Barnes, *J. Am. Chem. Soc.*, **56**, 1148 (1934); (b) A. F. Ferris, *J. Org. Chem.*, **25**, 12 (1960). References to earlier work are given in these papers.

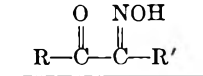
(2) A. F. Ferris, G. S. Johnson, F. E. Gould, and H. Stange, *J. Org. Chem.*, **25**, 1302 (1960).

(3) A. F. Ferris, G. S. Johnson, and F. E. Gould, *J. Org. Chem.*, **25**, 496 (1960).

(4) All melting points and boiling points are uncorrected.

TABLE I

SECOND ORDER BECKMANN REARRANGEMENTS OF α-OXIMINO KETONES IN ALCOHOLS[a]



α-Oximino Ketone			Products and Yields[b]	
R	R′	Alcohol	Ester	Nitrile
C_6H_5	CH_3	CH_3OH	$C_6H_5CO_2CH_3$ (54%)	[c]
		C_2H_5OH	$C_6H_5CO_2C_2H_5$ (73%)	[c]
C_6H_5	C_6H_5	C_2H_5OH	$C_6H_5CO_2C_2H_5$ (75%)	C_6H_5CN (81%)
$C_6H_5CH_2$	C_6H_5	C_2H_5OH	$C_6H_5CH_2CC_2C_2H_5$ (43%)	C_6H_5CN (52%)
$C_6H_5CH{=}CH$	H	C_2H_5OH	$C_6H_5CH{=}CHCO_2C_2H_5$ (57%)	[c]

[a] In all cases the base was the sodium alkoxide corresponding to the alcohol and the acylating agent was acetic anhydride. [b] All yields are based on starting α-oximino ketone not recovered. [c] Not isolated.

ucts Industries, Rochester, N. Y. 1,3-Diphenyl-1-oximino-2-propanone has been described previously.[1b] 1-Oximino-4-phenyl-3-buten-2-one was prepared by the method of Foulds and Robinson[5] using butyl instead of isoamyl nitrite. It melted at 137–139° (lit.,[6] m.p. 143–144°).

Rearrangements. Two typical experiments are described below. The other rearrangements were carried out and products worked up in essentially the same manner.

Rearrangement of α-benzil monoxime in ethanol. A solution of sodium ethoxide in ethanol was prepared by dissolving 12.0 g. (0.52 g.-atom) of sodium in 1500 ml. of ethanol, and 112.5 g. (0.50 mole) of α-benzil monoxime was dissolved in it. During 30 min. 55.0 g. (0.54 mole) of acetic anhydride was added dropwise with stirring. The temperature rose steadily to a maximum of 55°, then dropped to 30° during the next 30 min. The ethanol was evaporated under reduced pressure, and the residue was taken up in 500 ml. of ether. The solid which failed to dissolve (sodium acetate) was removed by filtration and washed with ether. The filtrate was washed with two 200-ml. portions of 5% sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the ether under reduced pressure left a mixture of solid and liquid. The mixture was taken up in 200 ml. of hexane, and the solid, which failed to dissolve, was recovered by filtration, washed with hexane, and dried. The filtrate separated into two layers. The upper (hexane) layer was removed, and the lower layer was washed with several small portions of hexane until it crystallized. The solid recovered by filtration amounted to 40.0 g. and that from the filtrate to 2.5 g. The 42.5 g. of solid was shown to be unchanged α-benzil monoxime by melting point and mixed melting point.

The hexane solution was evaporated under reduced pressure, and the liquid residue was distilled *in vacuo*. Three fractions were obtained: I, 12.0 g., b.p. 81.5–82.5° (19 mm.), n_D^{25} 1.5257; II, 25.0 g., b.p. 82.5–101° (19 mm.), n_D^{25} 1.5162; and III, 24.0 g., b.p. 101–102° (19 mm.), n_D^{25} 1.5041. Fraction I gave an infrared spectrum identical with that of benzonitrile and Fraction III a spectrum identical with that of ethyl benzoate. Fraction II was estimated from its index of refraction to contain 56% benzonitrile and 44% ethyl benzoate. Total recoveries thus were 26.0 g. (81%) of benzonitrile and 35.0 g. (75%) of ethyl benzoate.

Rearrangement of 1-oximino-4-phenyl-3-buten-2-one. A solution of sodium ethoxide in ethanol was prepared by dissolving 10.0 g. (0.435 g.-atom) of sodium in 1000 ml. of ethanol, and 52.5 g. (0.30 mole) of 1-oximino-4-phenyl-3-buten-2-one was added. Some solid, probably sodium salt of the oxime, remained in suspension. Then 43.0 g. (0.42 mole) of acetic anhydride was added with stirring during 30 min., the temperature being kept at 20–30° by cooling. After stirring 15 min. more the mixture was filtered and the solvent was evaporated under reduced pressure. The residue was taken up in 250 ml. of ether, and the ether solution was filtered, washed with 100 ml. of 5% sodium bicarbonate solution, dried over magnesium sulfate, and evaporated. The liquid residue was distilled under reduced pressure to give 35.0 g. of ethyl cinnamate, b.p. 142–146° (19 mm.), containing a little solid. On redistillation there was obtained 30.0 g. (57%) of pure ethyl cinnamate, b.p. 114° (2.6 mm.), n_D^{28} 1.5555. The infrared spectrum of this material was identical with that of authentic ethyl cinnamate.

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(5) R. P. Foulds and R. Robinson, *J. Chem. Soc.*, **103**, 1768 (1913).

(6) L. Claisen and O. Manasse, *Ber.*, **22**, 529 (1889).

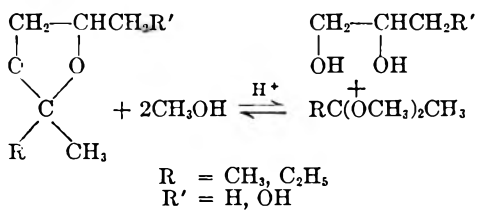
The Preparation of Three Ketone Acetals by Alcohol Interchange with Dioxolanes

N. B. LORETTE AND W. L. HOWARD

Received February 15, 1960

The usual methods for the preparation of ketals are the reaction of an ortho ester with a ketone[1] and the addition of two moles of an alcohol to a substituted acetylene.[2] Recently a method for the preparation of ketals directly from simple ketones and alcohols was reported.[3] The success of this method is dependent upon the use of a low reaction temperature (<−20°) because the amount of the ketal formed is inversely related to the temperature of the reaction mixture. Each of the above methods requires either an uncommon reagent or inconvenient temperatures.

Two ketals have now been prepared by using readily available dioxolanes and methanol.



(1) L. Claisen, *Ber.*, **29**, 1005 (1896).

(2) D. B. Killian, G. F. Hennion, and H. A. Nieuwland, *J. Am. Chem. Soc.*, **56**, 1384 (1934).

(3) N. B. Lorette, W. L. Howard, and J. H. Brown, Jr., *J. Org. Chem.*, **24**, 1731 (1959).

The reaction is shifted in the direction of the ketal by continuous removal of the ketal as an azeotrope with an excess of the alcohol used. The equilibrium also can be shifted in the direction of the ketal by decreasing the temperature and even at temperatures of 30 to 60° the reaction is rapid and this method of ketal preparation is effective.

This reaction has been used for the preparation of acetone dimethyl and diethyl acetals from 2,2-dimethyl-4-methylol-1,3-dioxolane and butanone dimethyl acetal from 2-ethyl-2-methyl-4-methylol-1,3-dioxolane. The reaction also provides a convenient method for the methanolysis of isopropylidene derivatives of diols, as the by-product ketal can be easily removed as its azeotrope with methanol at 61°.

EXPERIMENTAL

Effect of temperature on the equilibrium. Samples A and B of 15 ml. each were taken from a common stock solution composed of 0.25 mole of 2,2-dimethyl-4-methylol-1,3-dioxolane, 1.0 mole of methanol, and 1 drop of sulfuric acid. For a period of 10 min. sample A was kept at 62° and B at 0°. At the end of this time, the solutions were made basic by the addition of 5 ml. of a stock solution of sodium methylate in methanol. By infrared spectroscopy the per cent of dioxolane converted to acetone dimethyl acetal was determined for each sample: A, 17%; B, 21%. The conversion was estimated by computing the initial and final concentrations of acetone dimethyl acetal calculated from its absorption coefficient determined in solutions of similar composition with an authentic sample. The precision is about 5%.

Preparation of acetone dimethyl acetal. A solution composed of 1 mole of 2,2-dimethyl-4-methylol-1,3-dioxolane, 15 moles of methanol, and 1 drop of sulfuric acid was distilled through a 3-foot column packed with 1/8-in. helices and equipped with an automatic distillation head. The pressure was 220 mm. and the overhead temperature was 32–35°. (At atmospheric pressure methanol and acetone dimethyl acetal form an azeotrope, b.p. 61–62°, the composition of which is 45% and 55% by weight respectively.) With a reflux ratio of 20 to 30, 156 g. of a mixture of methanol and acetone dimethyl acetal was collected. The distillate contained 0.72 mole of acetone dimethyl acetal. Following the procedure described by Bond and Klar,[4] the azeotrope solution was washed with 13–15% aqueous sodium hydroxide solution, dried with potassium carbonate, and distilled to give pure acetone dimethyl acetal, b.p. 80° (760 mm.), n_D^{25} 1.3748 (lit.[2] b.p. 78–80°, n_D^{20} 1.3746).

Using 1 mole of 2,2,4-trimethyl-1,3-dioxolane, 6 moles of methanol, and 0.5 g. *p*-toluenesulfonic acid a 52% yield of acetone dimethyl acetal was obtained.

Preparation of butanone dimethyl acetal. A solution composed of 1 mole of 2-ethyl-2-methyl-4-methylol-1,3-dioxolane, 14 moles of methanol, and 1 drop of sulfuric acid was distilled. (At atmospheric pressure methanol and butanone dimethyl acetal distill as an azeotrope, b.p. 64.5°, 18.5% acetal by weight.) The pressure was 220 mm. and the overhead temperature was 33–36°. After 325 ml. of distillate was collected with a reflux ratio of 20, the distillation was stopped. After adding 150 ml. of xylene to the distillate, it was washed three times with 10% sodium hydroxide solution, dried with potassium carbonate, and distilled at atmospheric pressure. A 25-ml. (0.18 mole) fraction of butanone dimethyl acetal was collected, b.p. 106–107° (760 mm.), n_D^{24} 1.3918 (lit.[3] n_D^{24} 1.3915).

The undistilled residue of the reaction solution was made basic with sodium methylate and distilled. The distillate was 0.65 mole of 2-ethyl-2-methyl-4-methylol-1,3-dioxolane and the residue was 0.33 mole of glycerine which had the same infrared spectrum as a pure sample.

Preparation of acetone diethyl acetal. In the manner already described, a solution composed of 1 mole of 2,2-dimethyl-4-methylol-1,3-dioxolane, 15 moles of ethanol, and 0.5 g. of *p*-toluenesulfonic acid was slowly distilled at 100 mm. pressure. A 385-ml. fraction of distillate (b.p. 33–36°) was collected which was shown by infrared spectroscopy to be 6.8% (vol.) of acetone diethyl acetal. No attempt was made to separate the acetone diethyl acetal from the ethanol.

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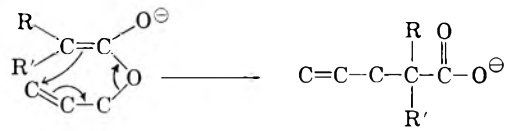
(4) G. C. Bond and L. A. Klar, U. S. Patent 2,827,495 (1958).

Preparation of 2,2-Dialkyl-4-pentenoic Acids

KENT C. BRANNOCK, HERMAN S. PRIDGEN, AND BENJAMIN THOMPSON

Received March 16, 1960

The rearrangement of the enolate anions of allyl esters, where either R or R' is aryl, is well known.[1]



It has also been reported that allyl acetate gives 4-pentenoic acid on treatment with sodium.[2] In the present investigation, however, treatment of allyl acetate with sodium hydride gave allyl acetoacetate as the only identifiable product.

A more favorable case for rearrangement to occur was that of an allyl ester of an acid having only one hydrogen atom in the α-position, as such compounds do not ordinarily undergo the acetoacetic ester condensation. Treatment of allyl isobutyrate and methallyl isobutyrate with sodium hydride gave 2,2-dimethyl-4-pentenoic acid and 2,2,4-trimethyl-4-pentenoic acid, respectively. When sodium methoxide or potassium *tert*-butoxide was used instead of sodium hydride, no rearrangement products were obtained.

EXPERIMENTAL

2,2-Dimethyl-4-pentenoic acid. A mixture of sodium hydride, 36 g. (1.5 moles), dispersed in mineral oil and 200 ml. of toluene was heated to 110°, and allyl isobutyrate, 192 g. (1.5 moles), was added dropwise over a 3.5-hr. period. Heating was continued for 1 hr. at 110°. The reaction mixture

(1) (a) R. T. Arnold and S. Searles, Jr., *J. Am. Chem. Soc.*, **71**, 1150 (1949); (b) R. T. Arnold, W. E. Parham, and R. M. Dodson, *J. Am. Chem. Soc.*, **71**, 2439 (1949); (c) R. T. Arnold, U.S. Patent **2,526,108** (1950); (d) P. N. Craig, U.S. Patent **2,618,637** (1952); (e) R. T. Arnold and G. E. Ullyot, U.S. Patent **2,650,231** (1953).

(2) Heou-Feo Tseou and Yih-Teh Yang, *J. Chinese Chem. Soc.*, **5**, 224 (1937); *Chem. Zentr.*, **108**, II, 3309 (1937).

became quite thick and difficult to stir as the reaction proceeded. The mixture was cooled and 25 ml. of methanol was added to decompose any unused sodium hydride. Then 600 ml. of 7% hydrochloric acid solution was added. The organic phase was separated and distilled to give, after removal of toluene and other low-boiling materials, 126 g. (66%) of 2,2-dimethyl-4-pentenoic acid, b.p. 82–83° (4 mm.), n_D^{20} 1.4337; reported[3] b.p. 104–108° (20 mm.)

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.6; H, 9.4; neut. equiv. 128. Found: C, 65.7; H, 9.5; neut. equiv. 129.

2,2,4-Trimethyl-4-pentenoic acid. Under the conditions described above, methallyl isobutyrate and sodium hydride gave 2,2,4-trimethyl 4 pentenoic acid in 68% yield, b.p. 78–81° (1.5–2 mm.), n_D^{20} 1.4421.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.6; H, 9.9; neut. equiv. 142. Found: C, 67.2; H, 9.9; neut. equiv. 143.

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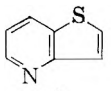
(3) R. F. Brown and N. M. Van Gulick, *J. Am. Chem. Soc.*, **77**, 1092 (1955).

Catalytic Interaction of 2-Vinylpyridine and Hydrogen Sulfide[1]

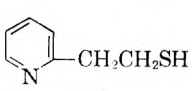
L. H. KLEMM AND DAVID REED

Received March 4, 1960

Moore and Greensfelder[2] have described the synthesis of benzothiophene in 60% yield from styrene and hydrogen sulfide using a flow apparatus, a ferrous sulfide–alumina catalyst, and a temperature of 600–625°. Besides benzothiophene and unchanged starting materials other substances identified in the effluent were hydrogen, a tar-like polymer, and small amounts of benzene, ethene, and probably ethane. By use of similar conditions we have been able to isolate, albeit in only 1.6% yield, a compound which appears to be the previously unknown thieno[3,2-*b*]pyridine (I) from 2-vinylpyridine and hydrogen sulfide. Other products identified in the gases condensable above −70° from



I



II

the reaction effluent were ethyl mercaptan, diethyl sulfide, pyridine, thiophene, sulfur, and hydrogen sulfide, but not unchanged 2-vinylpyridine. A material balance showed that at least half of the nitrogen atoms in the influent were retained on the column, perhaps as polymeric or strongly adsorbed[3] species. The formation of the products can be rationalized by the assumption that hydrogen sulfide adds to 2-vinylpyridine to form the intermediate 2-(2-pyridyl)ethyl mercaptan (II) which undergoes hydrogenolysis (by hydrogen sulfide) to ethyl mercaptan, pyridine, and sulfur and dehydrocyclization to I. In addition, condensation of ethyl mercaptan with 2-vinylpyridine followed by hydrogenolysis and subsequent dehydrocyclization could account for the formations of diethyl sulfide and thiophene, respectively.

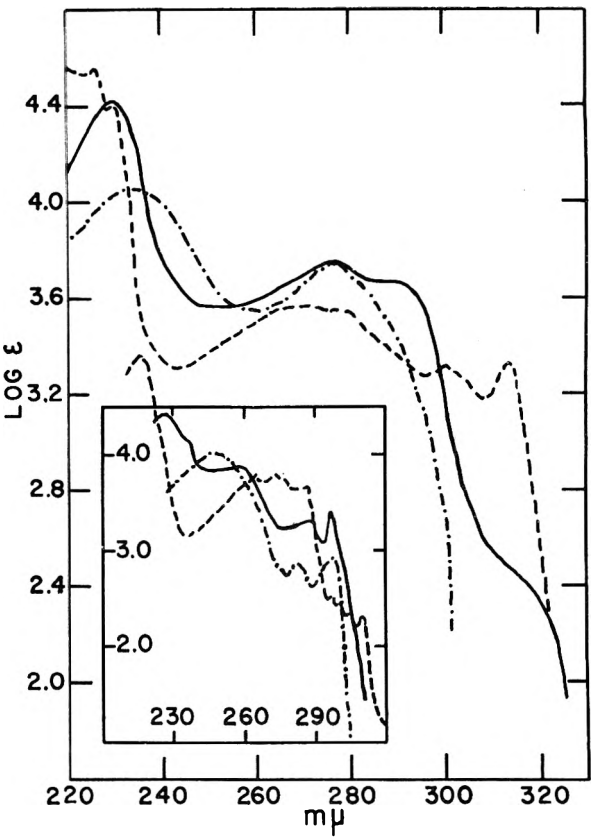


Fig. 1. Comparison of ultraviolet spectra. Large graph: ——— thieno[3,2-*b*]pyridine; – – – – quinoline; –·–·–·– 2-vinylpyridine. Inset graph: ——— benzothiophene; – – – – naphthalene; –·–·– styrene.

Structure I was assigned to the faintly yellow liquid obtained from fractional distillation of the crude reaction product on the basis of its b.p. (82–84°/2 mm., estimated b.p. 240°/760 mm.; *cf.* quinoline,[4] b.p. 239°), its ultraviolet absorption spectrum (nearly a composite of the spectra of quinoline[5] and 2-vinylpyridine,[6] *cf.* the spectrum

(1) Abstracted from the M.S. thesis of David D. Reed, University of Oregon, June 1957. Further details concerning the apparatus used may be obtained by consultation of this thesis.

(2) R. J. Moore and B. S. Greensfelder, *J. Am. Chem. Soc.*, 69, 2008 (1947).

(3) In preliminary chromatographic studies conducted in this laboratory the unusually strong adsorbability of aromatic nitrogen heterocycles (as compared to the corresponding arenes) on alumina has been noted.

(4) R. L. Shriner, R. C. Fuson, D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., J. Wiley & Sons, New York, 1956, p. 297.

(5) R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, J. Wiley & Sons, New York, 1951.

(6) R. P. Mariella, L. F. A. Peterson, and R. C. Ferris, *J. Am. Chem. Soc.*, **70**, 1494 (1948).

of benzothiophene[5] with the spectra of naphthalene[5] and styrene,[7] Fig. 1),[8] its reaction with methyl iodide to form a high melting solid containing both nitrogen and sulfur, and its conversion to a crystalline picrate of elementary analyses appropriate for I monopicrate.

Hansch and Carpenter[9] were unable to isolate any thienopyridine upon treating 4-vinylpyridine with hydrogen sulfide in the manner of Moore and Greensfelder.[2] Instead, they obtained a yellow liquid which formed a crystalline dipicrate and was presumed to be β,β-di(4-pyridyl)ethyl sulfide.

EXPERIMENTAL

The apparatus used was modified from that previously reported.[1,2] The ferrous sulfide–alumina catalyst was prepared by impregnating activated alumina (Fisher Scientific Co., 8–14 mesh) with 1.25*M* aqueous ferric nitrate solution, sulfiding, and calcining.[2] Commercial hydrogen sulfide was used directly from the cylinder. 2-Vinylpyridine (Reilly Tar and Chemical Corp., Indianapolis) was distilled from its inhibitor just prior to use. In a typical run which furnished maximum yields of total products condensable above 0°, the reaction temperature was 603 ± 3°; the flow rates of hydrogen sulfide and 2-vinylpyridine were 475 ml./min. and 29.5 g./hr., respectively (molar ratio 4.1:1); the calculated contact time (assuming the catalyst bed was a total void, *i.e.*, 700 ml.) was 24 sec.; and the total reaction time was 80 min.

The dark liquid (15 g.) which collected in air- and ice water-cooled receivers was distilled under reduced pressure in a nitrogen atmosphere. From earlier fractions of distillate were obtained ethyl mercaptan (positive colorimetric test with sodium nitroprusside, converted to ethyl 2,4-dinitrophenyl sulfide), diethyl sulfide (converted to sulfone), pyridine (converted to picrate), thiophene (converted to 2-mercurichloride derivative), and sulfur. Sulfur and each of the preceding crystalline derivatives were identified by melting point and mixture melting point with authentic samples of the same substances.

Thieno[3,2-b]pyridine (I) was collected from the higher boiling fraction as a yellow liquid, b.p. 82–84° (2 mm.), yield 0.8 g. (1.6%); $\lambda_{max}^{C_2H_5OH}$ 230 mμ (log ε 4.42), 278 (3.71), 285–290 (3.65)-shoulder, *ca.* 315 (2.4)-shoulder; soluble in ethanol, ether, benzene, and dilute hydrochloric acid; insoluble in water and aqueous sodium hydroxide. I darkened upon exposure to air at room temperature for a few hours, but it remained yellow for several weeks when stored under nitrogen at 0°.

Treatment of I with an equimolar quantity of picric acid in methanol gave green-yellow needles of *picrate*, recrystallized from ethyl acetate to constant m.p., 195.5–197.5°.

Anal. Calcd. for $C_{13}H_8N_4O_7S$: C, 42.86; H, 2.21; N, 15.38; S, 8.80. Found: C, 43.17; H, 2.18; N, 15.38; S, 8.26.

Treatment of I with excess methyl iodide gave pale yellow needles, presumably the methiodide, m.p. 217–219.5° with previous darkening, not obtained sufficiently pure for elementary analysis but giving positive qualitative sodium-fusion tests for the presence of nitrogen and sulfur.

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EUGENE, ORE.

(7) G. Allard, *Helv. Chim. Acta*, **19**, 1270 (1936).

(8) W. Herz and L. Tsai, *J. Am. Chem. Soc.*, **75**, 5122 (1953) have noted a "marked resemblance" between the spectra of isoquinoline and thieno[2,3-*c*]pyridine.

(9) C. Hansch and W. Carpenter, *J. Org. Chem.*, **22**, 936 (1957).

3-Hydroxycoumarins

K. N. TRIVEDI AND SURESH SETHNA

Received March 30, 1960

3-Hydroxycoumarin has an inhibiting effect on the growth of *avena* roots[1] and 3-aminocoumarins, which are intermediates in the synthesis of 3-hydroxycoumarins, are found to have antibacterial properties.[2] The present work deals with the synthesis of some substituted 3-hydroxycoumarins and a study of the pattern of substitution in 3-hydroxycoumarin.

5-Bromo-, 3,5-dibromo-, 3-nitro-, 5-nitro-, and 3,5-dinitrosalicylaldehyde, methyl 2,4-dihydroxy-3-formylbenzoate and 2,4-dihydroxy-3-formylacetophenone were condensed according to Shaw, McMillen, and Armstrong[3] with acetylglycine in the presence of sodium acetate and acetic anhydride and the 3-acetamidocoumarins formed hydrolyzed with alcoholic 3*N*-hydrochloric acid to the 3-hydroxycoumarins. The intermediate 3-aminocoumarins could not be isolated even under controlled hydrolysis with acid or alkali.

The ketonic character of the 3-hydroxycoumarin has been shown by the formation of a phenylhydrazone and a quinoxaline derivative with *o*-phenylenediamine.[4] It is now found that 3-hydroxycoumarin gives the isonitroso derivative with nitrous acid. With bromine in acetic acid it gave the 4-bromoderivative and with iodine and iodic acid the 4-iodo derivative, both of which gave the original coumarin on reduction with zinc and acetic acid. Further bromination did not succeed, but the 6-bromo- and 6,8-dibromo-3-hydroxycoumarin were brominated in the 4-position. 3-Acetoxycoumarin underwent Fries migration to give the 4-acetyl derivative which was also obtained in the Friedel-Crafts acetylation of 3-hydroxycoumarin. On oxidation it gave salicylic acid. 3-Hydroxycoumarin when treated with formaldehyde gave 4-4′-methylenebis(3-hydroxycoumarin).

EXPERIMENTAL

Synthesis of 3-hydroxycoumarins. An equimolecular mixture of the salicylaldehyde derivative, acetylglycine, and anhydrous sodium acetate and acetic anhydride (2 moles) was heated on a steam bath for 1 hr. The 3-acetamidocoumarin derivative obtained on dilution with water was crystallized from acetic acid (Table I).

The acetamidocoumarin was dissolved in a minimum quantity of alcohol and refluxed with 3*N* hydrochloric acid for 3 to 4 hr. The 3-hydroxycoumarin obtained on cooling

(1) R. H. Goodwin and G. Taves, *Am. J. Botany*, **37**, 224 (1950).

(2) G. Rodighiero and C. Antonello, *Bull. Chim. Farm.*, **97**, 592 (1958).

(3) K. N. F. Shaw, A. McMillen, and M. D. Armstrong, *J. Org. Chem.*, **21**, 601 (1956).

(4) E. Erlenmeyer, Jr., and W. Stadlin, *Ann.*, **337**, 283 (1904).

TABLE I

3-ACETAMIDOCOUMARIN DERIVATIVES

No.	Aldehyde	3-Acetamido-coumarin	M.P.	Formula	Analyses	
					Found	Calcd.
1	5-Bromosalicylaldehyde	6-Bromo-,[a]	261–262°	$C_{11}H_8O_3NBr$	Br, 28.57	Br, 28.36
2	3,5-Dibromosalicylaldehyde	6,8-Dibromo-,	279°	$C_{11}H_7O_3NBr_2$	Br, 44.66	Br, 44.32
3	5-Nitrosalicylaldehyde	6-Nitro-,	278°	$C_{11}H_8O_5N_2$	N, 11.09	N, 11.3
4	3-Nitrosalicylaldehyde	8-Nitro-,	268°	$C_{11}H_8O_5N_2$	N, 11.14	N, 11.3
5	3,5-Dinitrosalicylaldehyde	6,8-Dinitro-,	225°	$C_{11}H_7O_7N_3$	N, 14.54	N, 14.33
6	Methyl-2,4-dihydroxy-3-formylbenzoate	5-Acetoxy-6-carbomethoxy-,	255°	$C_{15}H_{13}O_7N$	N, 4.57	N, 4.52
7	2,4-Dihydroxy-3-formyl-acetophenone	5-Acetoxy-6-acetyl-,	290°	$C_{15}H_{13}O_6N$	N, 4.95	N, 4.62

[a] F. W. Linch (*J. Chem. Soc.*, 1758 (1912)) prepared it by a different route and gave the m.p. 266°. The hydrolysis of this product with dilute sulfuric acid did not give the 3-aminocoumarin derivative as reported by Linch but gave the 3-hydroxycoumarin derivative.

TABLE II

3-HYDROXYCOUMARIN DERIVATIVES

No.	3-Hydroxycoumarin	M.P.	Formula	Analyses	
				Found	Calcd.
1	6-Bromo-,	252°	$C_9H_5O_3Br$	Br, 33.23	Br, 33.02
2	6,8-Dibromo-,	261°	$C_9H_4O_3Br_2$	Br, 49.82	Br, 50.0
3	6-Nitro-,	256°	$C_9H_5O_5N$	N, 6.9	N, 6.76
4	8-Nitro-,	220°	$C_9H_5O_5N$	N, 6.7	N, 6.76
5	6,8-Dinitro-,	185°	$C_9H_4O_7N_2$	N, 10.8	N, 11.11
6	5-Hydroxy-6-carbomethoxy-,	225°	$C_{11}H_8O_6$	C, 60.24 H, 3.62	C, 60.0 H, 3.64
7	5-Hydroxy-6-acetyl-,	230°	$C_{11}H_8O_5$	C, 55.52 H, 3.02	C, 55.9 H, 3.39
8	4-Bromo-,[a]	210°	$C_9H_5O_3Br$	Br, 33.15	Br, 33.02
9	4,6-Dibromo-,[b]	273°	$C_9H_4O_4Br_2$	Br, 50.15	Br, 50.0
10	4,6,8-Tribromo-,[c]	230°	$C_9H_9O_3Br_3$	Br, 59.6	Br, 60.1

[a] Obtained by the bromination of 3-hydroxycoumarin. [b] Obtained by the bromination of 6-bromo-3-hydroxycoumarin. [c] Obtained by the bromination of 6,8-dibromo-3-hydroxycoumarin.

was crystallized from alcohol (Table II). All the 3-hydroxycoumarins gave a characteristic green coloration with alcoholic ferric chloride, and were soluble in sodium hydroxide solution in the cold on standing.

4-Isonitroso-2,3-diketochroman. A mixture of 3-hydroxy coumarin (1 g.) in a minimum quantity of acetic acid and 5 ml. concd. hydrochloric acid was kept in an ice bath and sodium nitrite solution (0.5 g. in 5 ml. of water) was added dropwise. Sodium bicarbonate solution was added to neutralize the solution, which was then extracted with ether. The product obtained from ether crystallized from a benzene-ligroin mixture in stout yellow needles, m.p. 185° dec.

Anal. Calcd. for $C_9H_5O_4N$: N, 7.3. Found: N, 7.1.

Brominations. To 3-hydroxycoumarin or its derivative in acetic acid a molecular quantity of bromine in acetic acid was added and the reaction mixture stirred for 0.5 hr. The product which separated was crystallized from acetic acid (Table II).

4-Iodo-3-hydroxycoumarin. To 3-hydroxycoumarin (1.72 g.) and iodine (1.16 g.) dissolved in a minimum quantity of alcohol, iodic acid (0.4 g.) was added with stirring. The product which separated was filtered and crystallized from alcohol as pale yellow needles, m.p. 223° dec.

Anal. Calcd. for $C_9H_5O_3I$: I, 44.06. Found: I, 43.74.

Reductions. 4-Bromo- or 4-iodo-3-hydroxycoumarin (0.5 g.) was dissolved in acetic acid (25 ml.) and zinc dust (1 g.) was added. The reaction mixture was refluxed for 2 hr. It was filtered hot and diluted with water. The product which separated was crystallized from alcohol; melting point and mixed melting point with 3-hydroxycoumarin was 151°.

3-Acetoxycoumarin was obtained by heating 3-hydroxycoumarin with pyridine and acetic anhydride. It crystallized from benzene in colorless needles; m.p. 105–106°. It did not give any coloration with alcoholic ferric chloride.

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.71; H, 3.93. Found: C, 64.81; H, 4.3.

4-Acetyl-3-hydroxycoumarin. A mixture of 3-acetoxycoumarin (1 mole) and anhydrous aluminum chloride (2 moles) was heated in an oil bath at 140° for 2 hr. The reaction mixture was worked up as usual. The product obtained was dried and extracted with hot petroleum ether (b.p. 60–80°). The product obtained on repeated crystallization from the same solvent gave colorless needles, m.p. 85°. The same product was obtained in the Friedel-Crafts acetylation of 3-hydroxycoumarin (1.6 g.) by heating it with anhydrous aluminum chloride (2.5 g.) and acetic anhydride (4 ml.) on a steam bath for 3 hr. It gave a green coloration with alcoholic ferric chloride.

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.71; H, 3.93. Found: C, 64.84; H, 3.88.

The 2:4-dinitrophenylhydrazone, prepared as usual, melted at 236–238° dec.

Anal. Calcd. for $C_{17}H_{11}O_7N_4$: N, 11.59. Found: N, 11.7.

Oxidation. 4-Acetyl-3-hydroxycoumarin (1 g.) was dissolved in sodium hydroxide (10%; 10 cc.) and heated with potassium permanganate (0.5 g.) on a steam bath for 3 hr.

The product obtained on working up as usual melted at 156°. Mixed melting point with salicylic acid was not lowered.

4,4'-Methylenebis(3-hydroxycoumarin). A mixture of 3-hydroxycoumarin (1 g.), alcohol (20 ml.), and formalin (40% soln. 3 ml.) was refluxed for 3 hr. The separated product was filtered hot and crystallized from alcohol as colorless needles, m.p. 266°.

Anal. Calcd. for $C_{19}H_{12}O_6$: C, 67.85; H, 3.57. Found: C, 67.46; H, 3.35.

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The Mechanism of the Rearrangement of 2-Phenyl-4-hydroxymethylene-5-oxazolone[1,2]

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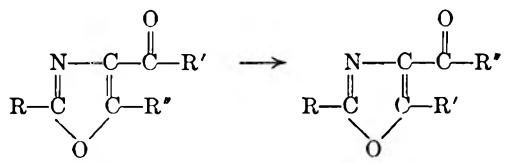
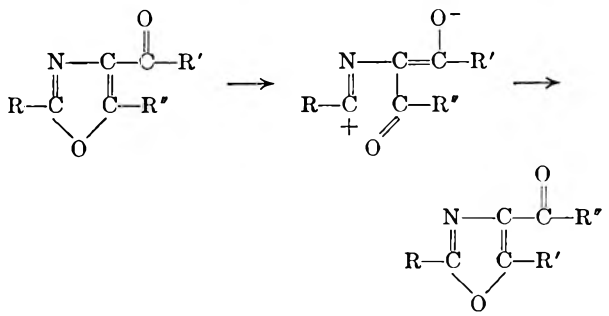
Received February 29, 1960

Synthetic work directed toward the synthesis of the erroneously postulated thiazolidine-oxazolone structure for penicillin led to a considerable advance in the chemistry of oxazolones. During the course of these studies a substance isomeric with 2-benzyl-4-hydroxymethylene-5-oxazolone was isolated from a reaction involving the latter compound. This isomeric compound was subsequently proved to be 2-benzyloxazole-4-carboxylic acid.[4a] Later several examples of the same general type of rearrangement came to light. The reaction can be formulated in general as an intramolecular rearrangement of 5-substituted oxazoles having a carbonyl carbon at C_4.[4b]



A direct interchange of R' and R" is rather unlikely. A more plausible mechanism, suggested by Cornforth,[4b] involves oxazole ring opening at C_2 followed by recyclization at the carbonyl oxygen.



We have substantiated this mechanism with C^{14} as a tracer.

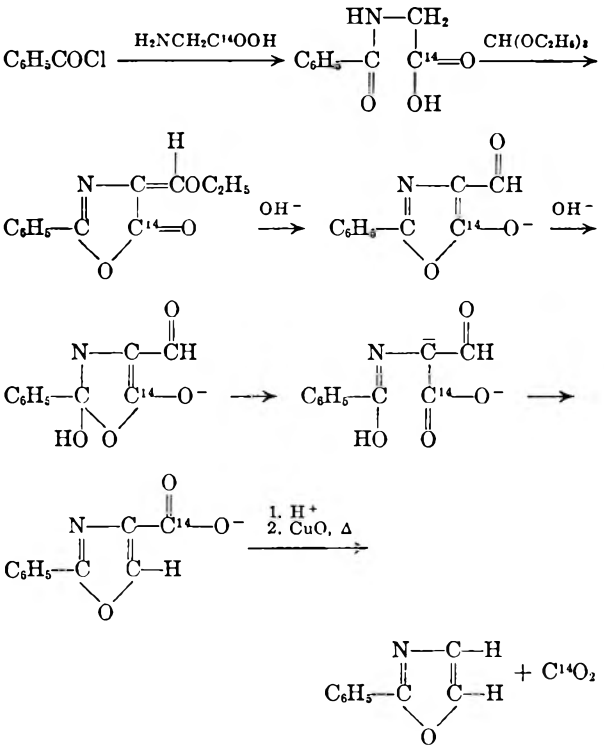


Table I shows that all of the radioactive carbon was in the carbon dioxide obtained by decarboxylation of the rearrangement product, 2-phenyloxazole-4-carboxylic acid.

TABLE I

COUNTING DATA FOR PERTINENT COMPOUNDS

Compound	Sample, Wt., Mg.	Count[a] per Min.	Background Count per Min.	Av. Count[b] per Min.
2-Phenyloxazole-4-carboxylic acid	106.2	2946	28	
	76.2	3024	28	2957
Barium carbonate	129.3	3166	30	
	122.1	3156	30	3131
2-Phenyloxazole	238.5	31	30	0

[a] After coincidence correction was applied. [b] All samples were of infinite thickness so that the total count is proportional to the specific activity.

Several attempts were made to prepare 2-phenyl-5-ethoxyoxazole-4-carboxylic acid from 2-phenyl-4-bromo-5-ethoxyoxazole *via* reaction with cuprous cyanide and with *n*-butyllithium. Neither reaction was successful under a wide variety of conditions.

(1) Abstracted from a Masters thesis by Dan Powers.

(2) Presented before the 134th meeting of the American Chemical Society, Chicago, Ill., Sept. 12, 1958.

(3) Present address: Department of Chemistry, Washington University, Seattle, Wash.

(4) H. T. Clarke, J. R. Johnson, and Sir Robert Robinson, *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949: (a) p. 694, (b) pp. 699–700, (c) p. 803.

EXPERIMENTAL

Hippuric-carboxyl-C^{14} acid. Glycine-1-C^{14} (3.48 mC./mM.; 0.5 mC. total activity; 10.8 mg.) was dissolved in water, and diluted to 10 ml. in a 10-ml. volumetric flask. Five cubic centimeters of this solution was pipeted into a solution prepared by dissolving 5.4 g. of inactive glycine and 12.5 g. of sodium hydroxide in 75 ml. of water. Benzoyl chloride (10 g.; 8.5 ml.) was then added and the mixture shaken vigorously until solution of the benzoyl chloride was complete. The solution was then acidified, filtered with suction, washed with water, and pressed as free of water as possible. The crude mixture was thoroughly mixed in the filter with two separate portions of ethyl ether and filtered. The yield of crude hippuric acid was 10 g. (78%).

2-Phenyl-4-ethoxymethylene-5-oxazolone-5-C^{14}. The 10 g. of hippuric acid obtained in the preceding preparation was mixed with 10 g. of inactive hippuric acid, added to a flask containing 12 ml. of acetic anhydride and 20 ml. of ethyl orthoformate and treated as previously described.[4o] The yield of oxazolone was 5 g. (22%).

2-Phenyloxazole-4-carboxylic-carboxyl-C^{14} acid. The hydrolysis and rearrangement of the oxazolone were carried out according to the procedure of Cornforth and Cookson.[5] The yield of a 2-phenyloxazole-4-carboxylic acid was 1.2 g. (67%).

Decarboxylation of 2-phenyloxazole-4-carboxylic-carboxyl-C^{14} acid. The acid was decarboxylated by distilling over copper(II) oxide (bath temperature 270–280°). The carbon dioxide was absorbed in 0.2*N* barium hydroxide solution. The precipitated barium carbonate was isolated by filtration, washed successively with distilled water, acetone and ether, dried, and then counted.

The oxazole distillate was dissolved in ether and washed with aqueous sodium bicarbonate. The ether solution was dried, the ether evaporated, and the residual 2-phenyloxazole counted. The melting point of the picrate was 115–116° and was undepressed when mixed with an authentic specimen.

Acknowledgment. The authors are grateful to the University of Wichita for a special grant for financial support of this investigation.

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(5) J. W. Cornforth and E. Cookson, *J. Chem. Soc.*, 1086 (1952).

The Free Radical Induced Rearrangement of 2-Methoxytetrahydropyran to Methyl Valerate

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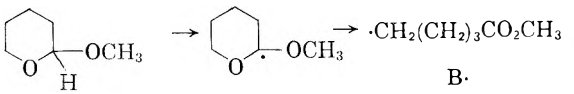
Acetals have been reported to react in a free radical chain reaction induced by alkoxy radicals yielding hydrocarbons and carbonyl-containing compounds as the main products.[2] The mechanism proposed to account for these products involves the abstraction of a hydrogen atom from the carbon atom adjacent to the oxygen producing a free radical, which undergoes decomposition into an alkyl radical and the carbonyl-containing compound.

$$R_2\dot{C}OR' \longrightarrow R_2C{=}O + R'\cdot$$

The investigation of 2-methoxytetrahydropyran (I) was undertaken to determine if this cyclic acetal could be rearranged to methyl valerate (II) *via* the following free radical chain sequence:



I A· B·

$$B\cdot + I \rightarrow CH_3(CH_2)_3CO_2CH_3 + A\cdot$$

II

The reaction of radical A· to form radical B· is the same type of elimination encountered in the reaction of Kuhn and Wellman. However, in the case of the cyclic radical A·, the elimination reaction amounts to a rearrangement of the radical.

Reactions in which di-*t*-butyl peroxide was thermally decomposed in the presence of 2-methoxytetrahydropyran have shown that rearrangement does in fact take place. Listed in Table I are the products obtained by heating 2-methoxytetrahydropyran with di-*t*-butyl peroxide at 120–130°.

TABLE I

PRODUCTS OBTAINED FROM THE DECOMPOSITION OF DI-*t*-BUTYL PEROXIDE IN 2-METHOXYTETRAHYDROPYRAN

	Moles	
	Run 1[a]	Run 2[b]
t-Butyl alcohol	0.21	0.18
Acetone	trace	trace
Methane	trace	trace
Methyl valerate	0.12	0.13
Residue	0.048 (m.w. 412)	(12.5 g.)
Recovered		
2-Methoxytetrahydropyran	0.08	0.25
Di-*t*-butyl peroxide	0.03	0.017

[a] 0.39 mole I, 0.15 mole di-*t*-butyl peroxide. [b] 0.48 mole I, 0.12 mole di-*t*-butyl peroxide.

The valerate ester was detected by the appearance of a strong ester carbonyl absorption at 5.76 μ in the infrared spectrum of the fraction collected at the boiling point of 2-methoxytetrahydropyran and methyl valerate (127°). The gas-liquid partition chromatographic analysis of this fraction showed the presence of two components with retention times corresponding to methyl valerate and 2-methoxytetrahydropyran. Chemical evidence of a valerate ester was obtained by preparation of the *p*-toluidide of valeric acid from the mixture. Conversion of the methyl ester to the *n*-butyl ester through an ester exchange reaction yielded *n*-butyl valerate which could be separated by distillation.

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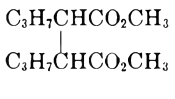
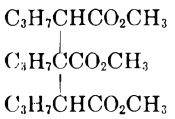
(2) L. P. Kuhn and C. Wellman, *J. Org. Chem.*, 22, 774 (1956).

The molecular weight of the residue obtained in Run 1 was 412. This implies that there are 3.56 methyl valerate or 2-methoxytetrahydropyran units per mole of residue. The formation of derivatives of succinic and tricarballylic acid esters by decomposition of peroxides in the presence of esters has been reported by Karasch, Jensen, and Urry.[3] This suggests that the residue in this reaction may well be formed by similar free radical reactions of methyl valerate leading to structures such as IIIa and IIIb. The infrared spectrum of the residue of

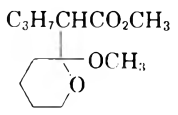


IIIa

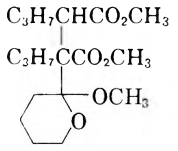


IIIb

Run 1 was very similar to that of the radical coupling product obtained from the reaction of methyl valerate and di-*t*-butyl peroxide. This spectrum does, however, contain several absorption bands (9.25, 9.45, and 9.68 μ) which are similar in wave length, intensity ratio, and band shape to 2-alkyl substituted 2-methoxytetrahydropyran. This suggests that part of the radical coupling reactions involve radical A· yielding structures such as IIIc and IIId in the residue. The molecular



IIIc

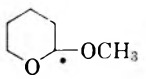


IIId

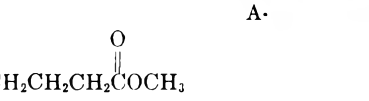
weight of the residue indicates that tetramers and probably higher molecular weight coupling products are also present.

These products and their observed distribution can be satisfactorily accounted for by the following sequence of reactions:

1) $(CH_3)_3COOC(CH_3)_3 \longrightarrow 2(CH_3)_3CO\cdot$

2) $(CH_3)_3CO\cdot + I \longrightarrow (CH_3)_3COH +$ 

A·

3) A· $\longrightarrow$ 

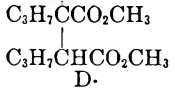
B·

4) B· + I $\longrightarrow$ II + A·

5) $(CH_3)_3CO\cdot$, A· or B· + II $\longrightarrow$ $(CH_3)_3COH + CH_3CH_2CH_2\dot{C}HCO_2CH_3$

or I or II C·

6) 2C· $\longrightarrow$ IIIa

7) $(CH_3)_3CO\cdot$, A· or B· + IIIa $\longrightarrow$ $(CH_3)_3COH$ or I or II + 

D·

8) C· + D· $\longrightarrow$ IIIb

8b) A· + C· $\longrightarrow$ IIIc

8c) A· + D· $\longrightarrow$ IIId

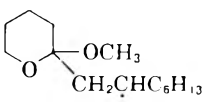
In reactions leading to radical coupling products, a relationship exists between the amount of initiator and the amount of coupling products. The stoichiometry requires one mole of initiator per mole of dimeric product and an additional mole of initiator for each additional unit in the product. The residue in Run 1, 0.047 mole of material with an average of 3.56 units per molecule, requires 0.12 mole of initiator which is in agreement with the peroxide consumed in the reaction.

The presence of radical B· in the reaction mixture was demonstrated by employing a terminal olefin, 1-octene, as the radical scavenger. Addition of radical B· to 1-octene would give the adduct radical which on chain transfer with I would yield methyl tridecanoate as the 1:1 addition product.

9) B· + $C_6H_{13}CH{=}CH_2 \longrightarrow C_6H_{13}CH(CH_2)_5CO_2CH_3$

10) $C_6H_{13}CH(CH_2)_5CO_2CH_3 + I \longrightarrow C_{12}H_{25}CO_2CH_3 + A\cdot$

The presence of methyl tridecanoate in the 1:1 addition product was confirmed by conversion of the ester to the *p*-toluidide. The infrared spectrum of the 1:1 addition product, however, indicated the presence of an undetermined amount of material containing a tetrahydropyran ring. Although it has not been specifically identified, the appearance of absorption bands at 9.25, 9.45, and 9.68 μ which are similar in wave length, intensity ratio, and band shape to those of a 2-alkyl-2-methoxytetrahydropyran, indicates that the material may be 2-octyl-2-methoxytetrahydropyran resulting from the addition of the unrearranged radical A· to the terminal olefin.

A· + $C_6H_{13}CH{=}CH_2 \longrightarrow$  11

EXPERIMENTAL[4]

The 2-methoxytetrahydropyran was prepared by a method described previously[5] and distilled at 63–64° at 85 mm.; n_D^{25} 1.4227. The di-*t*-butyl peroxide (Shell Chemical Co.) was redistilled before using; b.p. 47° at 75 mm.; n_D^{25} 1.3887. A 10-foot column packed with Dow Corning 550 Silicone Fluid on Celite with helium as the carrier gas was used for the gas-liquid partition chromatographic analysis.

(3) M. S. Karasch, E. V. Jensen, and W. H. Urry, *J. Org. Chem.*, **10**, 386 (1945).

(4) All melting points and boiling points are uncorrected. The author is indebted to Dr. W. J. Potts of the Spectroscopy Laboratory of the Dow Chemical Co. for aid in interpreting the infrared spectra.

(5) G. F. Wood and D. M. Kramer, *J. Am. Chem. Soc.*, 69, 2246 (1947).

Reaction of 2-methoxytetrahydropyran with di-t-butyl peroxide. A reaction mixture consisting of 46 g. (0.39 mole) of 2-methoxytetrahydropyran and 21.5 g. (0.15 mole) of di-*t*-butyl peroxide was heated at 120–125° for 44 hr. During the course of the heating, material boiling at 83–90° was distilled through an 8-inch Vigreux column as fast as it was formed. At the end of the heating period the reaction mixture was distilled through the same column and material boiling up to 120° was combined with the earlier cut. The combined fractions (21.0 g.) were analyzed by infrared as 0.21 mole of *t*-butyl alcohol and 0.03 mole of unchanged di-*t*-butyl peroxide. The reaction mixture was further distilled until the pot temperature reached 200° yielding 23 g. of material boiling at 120–129°. Analysis of this fraction by gas-liquid partition chromatography showed two peaks, with retention times identical to 2-methoxytetrahydropyran and methyl valerate. Infrared analysis of the mixture showed a very strong ester carbonyl absorption at 5.76 μ. Both infrared analysis and gas-liquid partition chromatography showed the ester content of the mixture to be 40%. The distillation residue amounting to 19.5 g. had a molecular weight of 412. The infrared spectrum of the residue showed it to consist mainly of a product similar to that obtained from the reaction of di-*t*-butyl peroxide and methyl valerate with additional absorption bands at 9.25, 9.45 and 9.68 μ.

p-Toluidide of valeric acid. A portion of the ester-containing mixture was added to the reaction mixture of ethylmagnesium bromide and *p*-toluidine in ether. Hydrolysis yielded the *p*-toluidide of *n*-valeric acid which after recrystallization from dilute alcohol melted at 70°; reported[6] m.p. 70°. A mixed melting point with an authentic sample showed no depression.

n-Butyl valerate. In another reaction 56 g. (0.48 mole) of 2-methoxytetrahydropyran and 17.5 g. (0.12 mole) of di-*t*-butyl peroxide were heated at 125–130° for 23 hr. During the course of the heating, 16.5 g. of material was distilled through an 8-inch Vigreux column at 82–85° which on infrared analysis proved to consist of 13.5 g. (0.18 moles) of *t*-butyl alcohol, a trace amount of acetone, and 2.5 g. of unchanged peroxide (0.017 mole). Further distillation at the end of the heating period yielded 42 g. of material boiling at 126–128° leaving a high boiling residue (pot temperature 210°) amounting to 12.5 g. Infrared analysis of the distillate showed it to consist of 32% methyl valerate (0.13 mole) and the remainder, unchanged 2-methoxytetrahydropyran. This mixture was refluxed for 6 hr. in 100 g. of *n*-butyl alcohol containing 0.025 g. of metallic sodium. During the course of the refluxing, 4.2 g. of methyl alcohol (0.13 mole) were removed by distillation through an 8 inch Vigreux column. The unchanged *n*-butyl alcohol and 2-methoxytetrahydropyran were removed by further distillation. The infrared spectrum of this mixture showed no ester carbonyl present. The remaining material was *n*-butyl valerate which distilled at 119–121° at 104 mm. (n_D^{25} 1.4143) and amounted to 17 g. (0.11 mole). The infrared spectrum of this material was identical with that of an authentic sample of *n*-butyl valerate.

The reaction of 2-methoxytetrahydropyran and 1-octene. Over a period of 24 hr. a solution consisting of 1-octene (33.6 g., 0.30 mole) and di-*t*-butyl peroxide (8.8 g., 0.06 mole) was slowly added to 2-methoxytetrahydropyran (150 g., 1.29 moles) heated to reflux temperature (127°). On distillation through an 8 inch Vigreux column, the reaction mixture yielded about 6 g. of *t*-butyl alcohol and 124 g. of unchanged 2-methoxytetrahydropyran. The residue was distilled through a 12-inch Holzmann column and yielded a fraction amounting to 6.0 g. (b.p. 90–110° at 0.7 mm., n_D^{25} 1.4430) which on infrared examination was found to consist mainly of methyl tridecanoate. Absorptions at 9.25, 9.45, and 9.68 μ in the infrared spectrum of the sample indicate the presence of a pyran ring but are different from those of 2-methoxytetrahydropyran. Reaction of a portion of the 1:1 addition product with the reaction mixture obtained from ethylmagnesium bromide and *p*-toluidine yielded the *p*-toluicide of *n*-tridecanoic acid; m.p. 87–88°, reported[7] m.p. 87°. A high boiling residue amounting to 30 g. remained after distillation of the 1:1 addition product (pot temperature 150°), presumably telomeric products.

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(6) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 222.

(7) W. H. Urry and E. S. Huyser, *J. Am. Chem. Soc.*, 75, 4876 (1953).

Adducts with *N*-Substituted Acrylamides[1]

Irwin L. Honigberg[2] and Walter H. Hartung[3]

Received February 23, 1960

Acrylamides, especially the *N*-substituted products, appear as attractive reagents for the synthesis of isomers and analogs of amino acids and peptide-like compounds. The reactions which come under consideration may be summarized as in Fig. 1. Reactions of type (c) are adaptations of the Michael reaction[4] and of type (b) have been employed by Mattocks and Hartung.[5]

EXPERIMENTAL

Acrylamides. By allowing acrylyl chloride[6] to react with an appropriate amine, the following *N*-substituted acrylamides were obtained: Acrylanilide[7] (I), m.p. 105–106°; *p*-acrylotoluidide[8] (II), m.p. 140–141°; diethyl acrylamidomalonate[9] (III), $C_{10}H_{15}NO_5$, yield 56%, m.p. 106–107°; ethyl acrylamidoacetate[10] (IV); diethyl acrylamidobenzylmalonate[11,12] (V), $C_{17}H_{21}NO_5$, yield 62%, m.p. 84–86°.

From cinnamyl chloride[13] and diethyl aminomalonate was

(1) No. 21 in Amino Acid Series. For No. 20 see L. Neelakantan and W. H. Hartung, *J. Org. Chem.*, 24, 1943 (1959). Work done at the University of North Carolina.

(2) Supported in part by funds from the Sterling-Winthrop Research Foundation and in part by the American Foundation for Pharmaceutical Education. This assistance is gratefully acknowledged. Present address: Midwest Research Institute, Kansas City, Missouri.

(3) Present address: Medical College of Virginia, Richmond, Virginia.

(4) *Cf.* C. S. Marvel and M. P. Stoddard, *J. Org. Chem.*, 3, 198 (1938); J. R. Shekelton and C. D. Lewis, *J. Am. Chem. Soc.*, 67, 310 (1945).

(5) A. M. Mattocks and W. H. Hartung, *J. Am. Chem. Soc.*, 68, 2018 (1946).

(6) Prepared by the procedure of H. C. Brown, *J. Am. Chem. Soc.*, 60, 1325 (1938), and C. H. Stempel, *et al.*, *J. Am. Chem. Soc.*, 72, 2299 (1950), in yields of 70–80%.

(7) M. Moureu, *Bull. soc. chim. France* [3] 421 (1893).

(8) M. Moureu, *Bull. soc. chim. France* [3] 422 (1893).

(9) Calcd.: N, 6.11. Found: N, 5.95, 6.13.

(10) See under compound IX below.

(11) Calcd.: N, 4.37. Found: N, 4.24, 4.14.

(12) The intermediate is described by J. H. R. Beaujon and W. H. Hartung, *J. Am. Pharm. Assoc.*, 41, 578 (1952).

(13) H. Meyer, Sitzber., *Akad. Wiss. Wien, Math. naturiv. Kl. Abt IIB;* 110, 329 (1901).

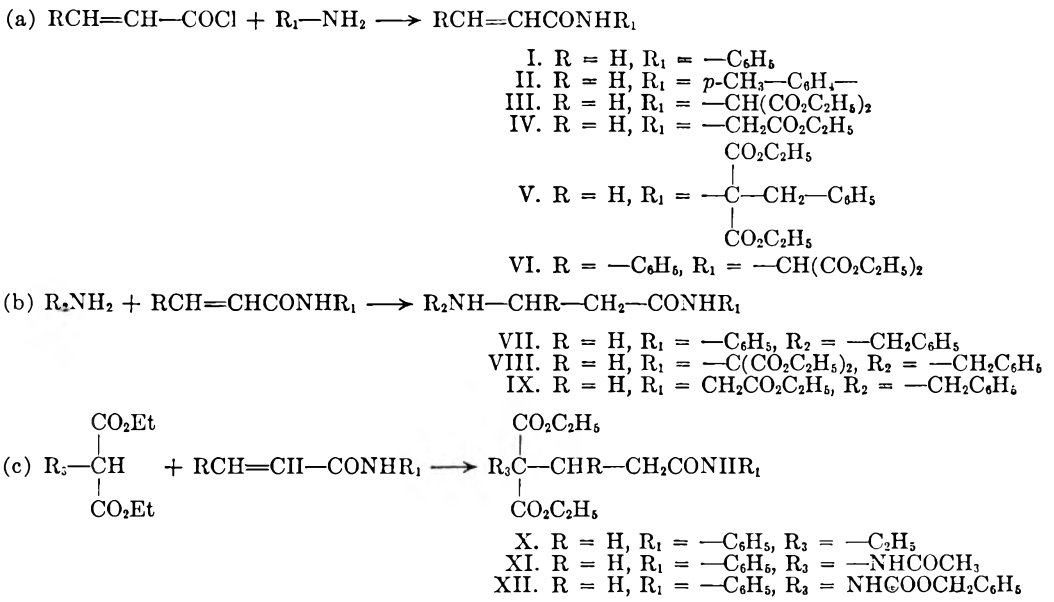


Fig. 1. Synthesis of amino acid isomers and analogs, using *N*-substituted acrylamides

obtained diethyl cinnamamidomalonate[14] (VI), $C_{16}H_{19}NO_5$, yield 91%, m.p. 92–94°.

Amine adducts. β-Benzylaminopropionanilide hydrochloride (VII). A solution of 7.4 g. of I (0.05 mole) and 10.9 g. of benzylamine (0.10 mole) in 25 ml. of anhydrous ethanol was placed in a stoppered flask at room temperature for 2 days with occasional shaking. The solution was then transferred to an evaporating dish and the alcohol evaporated on a hot water bath, the residual red viscous oil was taken up in ether, washed with ten 10-ml. portions of water to remove excess benzylamine, and dried over sodium sulfate. To the dried ethereal solution was added 0.05 mole hydrogen chloride dissolved in 16 ml. of ethanol; the flocculent precipitate which formed was augmented by allowing the solution to stand overnight in the refrigerator. The crude yield of crystals was 13.5 g., 93%. Recrystallized from water, the product melted 260–261°.

Anal. Calcd. for $C_{16}H_{19}N_2OCl \cdot 2H_2O$: N, 8.57. Found: N, 8.55, 8.63.

Diethyl β-benzylaminopropionamidomalonate (VIII). A solution of 2.29 g. of III (0.01 mole), 1.17 g. of benzylamine (0.011 mole) in 10 ml. of absolute ethanol, in a stoppered flask was shaken intermittently; after 5 hr. III had all dissolved; after 48 hr. the ethanol and excess benzylamine were removed under reduced pressure. As the residual product was low melting, it was converted to the hydrochloride; yield, practically quantitative; m.p. 238–239°.

Anal. Calcd. for $C_{17}H_{25}N_2O_5Cl$: N, 7.51. Found: N, 7.46, 7.66.

Ethyl β-benzylaminopropionamidoacetate hydrochloride (IX). A solution of 1.6 g. of IV (0.01 mole) and 1.17 g. of benzylamine (0.001 mole) in 4 ml. of absolute ethanol was allowed to stand at room temperature for 24 hr. To this was added 0.365 g. hydrogen (chloride (0.01 mole) in dry ethanol; on cooling a crystalline precipitate formed; a second crop was obtained by adding ether to the mother liquors; the combined products were recrystallized from ethanol, obtained 2.0 g., yield 66.5%, m.p. 197–198.5°. This product was a hemihydrate.

Anal. Calcd. for $C_{14}H_{21}N_2O_3Cl \cdot {}^1/_2\ H_2O$: N, 9.04. Found: N, 9.04, 9.02.

The melted salt, on cooling solidified without apparent decomposition and remelted at 173–175°, and is very hygroscopic; this is presumably the anhydrous salt.

(14) *Anal.* Calcd.: C, 62.94; H, 6.26; N, 4.58. Found: C, 63.39; H, 6.31; N, 4.76.

Michael additions. 4,4-Dicarbethoxycaproanilide (X). To a stirred solution of sodium ethoxide, prepared from 0.077 g. of sodium (0.0033 g.-atom) in 30 ml. of anhydrous ethanol was added 3.76 g. of diethyl ethylmalonate (0.02 mole); then was added 2.94 g. of I (0.02 mole). The solution was warmed for 5 hr. to 70–80° and then allowed to stand at room temperature for 4 days; the solution was transferred to an evaporating dish, by addition of acetic acid the *p*H was adjusted to 6, and the ethanol evaporated in a current of air. The crude product crystallized partially, the crystals were removed, weighing 5.2 g., 77.5%; recrystallized from ethanol-water, m.p. 89°.

Anal. Calcd. for $C_{18}H_{25}NO_5$: N, 4.17. Found: N, 3.98, 3.99.

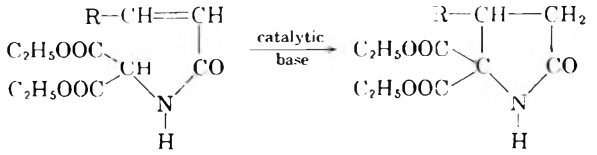
4-Acetamido-4,4-dicarbethoxybutyroanilide (XI). To a stirred solution of 0.080 g. sodium (0.0035 g.-atom) in 40 ml. of ethanol was added 4.5 g. of diethyl acetamidomalonate (0.0275 mole); when solution was complete there was added 3.65 g. of I (0.0275 mole). After 30 min. of intermittent stirring solution was complete. The container was stoppered and sealed with paraffin and allowed to stand for 2 days, at which time there was a solid mass of crystals. The product was transferred to an evaporating dish, neutralized with acetic acid (3 drops), and the ethanol evaporated in stream of air. The resulting solid, crystallized from dilute ethanol, weighed 4.1 g., yield, 40%, and melted 143°.

Anal. Calcd. for $C_{18}H_{24}N_2O_6$: N, 7.69. Found: N, 7.77, 7.42.

4-Carbobenzyloxyamido-4,4-dicarbethoxybutyroanilide (XII). To a solution of 0.80 g. of sodium (0.0035 g.-atom) in 30 ml. anhydrous ethanol was added 6.18 g. diethyl carbobenzyloxyaminomalonate[12] (0.02 mole), followed by 2.94 g. of I (0.02 mole); the container was stoppered, sealed with paraffin, and allowed to stand at room temperature for a week. The reaction mixture developed a red color. The solution was then transferred to an evaporating dish, neutralized with acetic acid (3 drops), and the alcohol removed in a stream of air. The red-brown residue was crystallized several times from dilute ethanol, affording 7.7 g. of colorless crystals, yield 85%, m.p. 99–100°.

Anal. Calcd. for $C_{24}H_{28}N_2O_7$: N, 6.14. Found: N, 5.93, 6.14.

Ethyl cinnamamidoglycine (XIII) *by decarbethoxylation of VI.* Acrylamidomalonic esters, containing within a single molecule all the requisite functional groups to undergo the Michael reaction, were examined for possible pyrrolidone formation,[15] perhaps, according to a scheme that may be indicated as follows:



Accordingly a solution was prepared from 0.023 g. of sodium (0.001 g.-atom) in 250 ml. of anhydrous ethanol, and to this was added 2.73 g. of VI (0.009 mole); the container was fitted with a reflux condenser with calcium chloride tube at the upper opening. The solution was refluxed for 12 hr.; it was then neutralized with acetic acid, the first portion of ethanol was removed by distillation, and the final portion was allowed to evaporate at room temperature. The product, weighing 2.0 g., crystallized first from dilute ethanol and then from benzene–petroleum ether (b.p. 30–60°), melted at 107–108°. The expected pyrrolidinone melts 96–98°.[15] The product still gave a positive test for ethylenic bond; molecular weight determination gave values of 220–230.

Anal. Calcd. for $C_{12}H_{15}NO_3$, m.w., 233: C, 66.95; H, 6.44; N, 6.01. Found: C, 66.98, 66.89; H, 6.35, 6.40; N, 5.86, 5.94.

An authentic sample of ethyl cinnamamidoacetate was prepared from cinnamyl chloride and ethyl glycinate, m.p. 109°; the melting point when mixed with product obtained was not depressed.

Such decarbethoxylation probably proceeds by the same mechanism by which diethyl diphenylmalonate and diethyl phenylethylmalonate form ethyl diphenylacetate and ethyl α-phenylbutyrate, respectively, when heated in an alcoholic solution containing an equivalent of sodium ethoxide.[16]

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(15) G. H. Cocolas and W. H. Hartung, *J. Am. Chem. Soc.*, **79**, 5203 (1957).

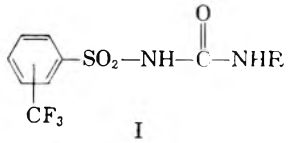
(16) A. C. Cope and S. M. McElvain, *J. Am. Chem. Soc.*, **54**, 4319 (1932).

1-Alkyl-3-(α,α,α-trifluorotolylsulfonyl)ureas

HARRY L. YALE AND FRANCIS SOWINSKI

Received April 6, 1960

We are reporting the preparation of a group of 1-alkyl-3-(α,α,α-trifluorotolylsulfonyl)ureas(I). These compounds are now being evaluated for hypoglycemic activity.[1]



I

The literature on the procedures which may be employed for the synthesis of compounds like I has been reviewed recently.[2a,b] In our approach, the α,α,α-trifluoro-o- and -m-tolyl derivatives were prepared as shown in Chart I. The synthesis of the *p*-derivative differed only in the procedures used for the preparation of the intermediate (α,α,α - trifluoro - *p* - tolyl)sulfonamide (Chart II A,B)

Chart I

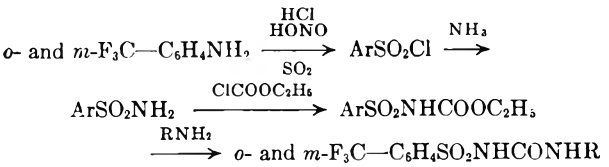
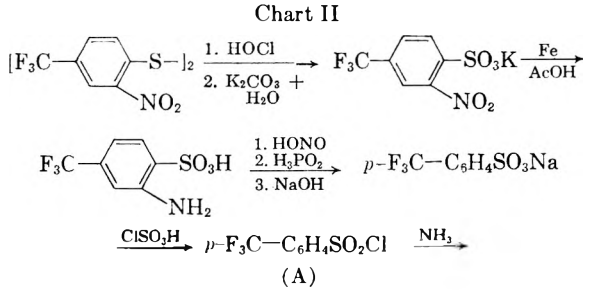
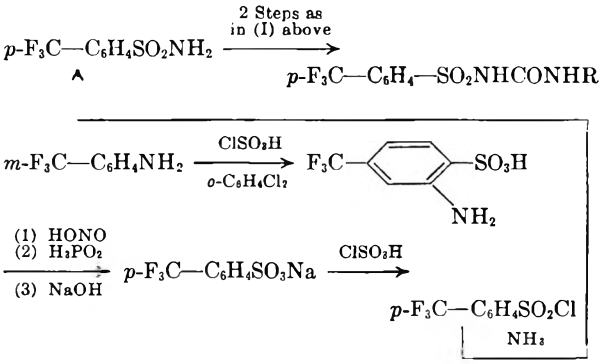


Chart II



(A)



(B)

Kracker and Herrlein[3a] have reported that one mole each of α,α,α-trifluoro-*m*-toluidine and chlorosulfonic acid in *o*-dichlorobenzene at 180° gave 4 - amino - α,α,α - trifluoro - *o* - toluenesulfonic acid. Similarly, Zitscher and Kehlen[3b] stated that α,α,α-trifluoro-*m*-acetotoluidide and an excess of fuming sulfuric acid in tetrachloroethane at 145° gave 4-acetamido-α,α,α-trifluoro-*o*-toluenesulfonic acid. Neither group of workers provided proof for their structural assignments. We have repeated[4] the procedure described by Kracker and Herrlein and obtained an amino-α,α,α-trifluorotoluenesulfonic acid whose infrared spectrum was identical with that obtained from the 2-amino-α,α,α-

(1) The role of the trifluoromethyl group in medicinal chemistry has been reviewed by H. L. Yale, *J. Med. Pharm. Chem.*, **1**, 121 (1959).

(2a) D. R. Cassady, C. Ainsworth, N. R. Easton, M. Livesey, M. V. Sigal, Jr., and E. Van Heyningen, *J. Org. Chem.*, **23**, 923 (1958); (b) F. J. Marshall and M. V. Sigal, Jr., *J. Org. Chem.*, **23**, 927 (1958).

(3a) H. Kracker and F. Herrlein, U.S. Patent 2,119,882, June 7, 1938; (b) A. Zitscher and H. Kehlen, U. S. Patent 2,141,893, Dec. 27, 1938.

(4) This experiment was carried out by Dr. W. B. McDowell of the Chemical Development Section, Squibb Institute for Medical Research.

TABLE I

COMPOUNDS OF THE GENERAL FORMULA $F_3C—C_6H_4—SO_2NHY$

Position of $—CF_3$	Y	Formula	Yield, %	M.P.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2	—H	$C_7H_6F_3NO_2S$[a]	80	186–188	37.36	2.69		37.34	3.06	
3	—H	$C_7H_6F_3NO_2S$[b]	65	111–112	37.36	2.69		37.29	2.58	
4	—H	$C_7H_6F_3NO_2S$[c]	68	176–177	37.36	2.69		37.30	2.63	
2	$—CO_2C_2H_5$	$C_{10}H_{10}F_3NO_4S$[b]	87	131–132	40.41	3.39		40.93	3.63	
3	$—CO_2C_2H_5$	$C_{10}H_{10}F_3NO_4S$[d]	69	68–69	40.41	3.39		40.36	3.58	
4	$—CO_2C_2H_5$	$C_{10}H_{10}F_3NO_4S$[d]	81	93–95	40.41	3.39		40.47	3.69	
2	$—CONHC_4H_9$-*n*	$C_{12}H_{15}F_3N_2O_3S$[c]	49	134–135	44.44	4.66	8.64	44.50	4.88	8.95
2	$—CONHC_6H_{11}$	$C_{14}H_{17}F_3N_2O_3S$[c]	52	172–173	47.98	4.89	7.99[e]	47.71	4.84	8.27
3	$—CONHC_4H_9$-*n*	$C_{12}H_{15}F_3N_2O_3S$[c]	63	113–114	44.44	4.66	8.64	44.41	4.79	8.80
3	$—CONHC_6H_{11}$	$C_{14}H_{17}F_3N_2O_3S$[c]	42	132–133	47.98	4.89	7.99[f]	48.76	5.16	7.89
4	$—CONHC_4H_9$-*n*	$C_{12}H_{15}F_3N_2O_3S$[c]	62	127–128	44.44	4.66	8.64	44.42	4.51	8.65
4	$—CONHC_6H_{11}$	$C_{14}H_{17}F_3N_2O_3S$[c]	43	177–178	47.98	4.89	7.99	48.13	5.01	8.08

[a] Recrystallized from 95% ethanol. [b] Recrystallized from benzene. [c] Recrystallized from aqueous ethanol. [d] Recrystallized from benzene-hexane (1:1). [e] Calcd.: S, 9.15; Found: S, 9.01. [f] Calcd.: S, 9.15; Found: S, 9.43.

trifluoro-*p*-toluenesulfonic acid prepared according to Chart II, A. Furthermore, each sulfonic acid, when subjected to the sequence of reactions indicated in Chart II, A and B, gave identical sulfonamide and carbamate derivatives. The structure of the product from the Kracker and Herrlein procedure is, consequently, 2-amino-α,α,α-trifluoro-*p*-toluenesulfonic acid and it may be inferred that the Zitscher and Kehlen product must have been 2-acetamido-α,α,α-trifluoro-*p*-toluenesulfonic acid.

Two observations made during the synthesis of the 1-alkyl-3-(α,α,α-trifluorotolylsulfonyl)ureas are worthy of mention. In this series of sulfonylureas, there was a great tendency to form fairly stable salts with the excess of amine present during the reaction with the carbamate. These could, in some instances, be isolated and were stable to recrystallization. Decomposition was effected by solution in warm aqueous sodium hydroxide followed by acidification with dilute hydrochloric acid. In addition, with cyclohexylamine, a small amount of dicyclohexylurea was isolated as a by-product of the reaction.

EXPERIMENTAL

All melting points and boiling points are uncorrected.

The preparation below is typical of the syntheses in the *o*- and *m*-tolylsulfonylurea series.

Analytical data not given in the text will be found in Table I.

1-Butyl-3-(α,α,α-trifluoro-o-tolylsulfonyl)urea. α,α,α-Trifluoro-o-toluenesulfonyl chloride.[5] α,α,α-Trifluoro-*o*-toluidine,[6] 48.6 g. (0.3 mole), 105 ml. of concd. hydrochloric acid, and 30 ml. of glacial acetic acid at −5 to 0° were treated dropwise, with a solution of 22.8 g. (0.3 mole) of sodium nitrite in 45 ml. of water. The diazotized solution was allowed to warm to 4° and then added to 6 g. of cuprous chloride in 400 ml. of a saturated solution of sulfur dioxide in glacial acetic acid, also at 4°. The vigorous reaction accompanied by considerable frothing caused a rise in temperature to 27°. One-half hour later, the reaction mixture was poured into 1 l. of ice-water and the product extracted with ether. The ether extract was washed until neutral with saturated aqueous sodium bicarbonate solution, then dried, concentrated, and distilled to give 53.5 g. (72% yield) of the *sulfonyl chloride*, b.p. 123–126° (5 mm.).

Anal. Calcd. for $C_7H_4ClF_3O_2S$: C, 34.37; H, 1.65. Found: C, 34.29; H, 1.75.

α,α,α-Trifluoro-o-toluenesulfonamide. To 550 ml. (8.1 moles) of concd. aqueous ammonia was added a solution of 66.1 g. (0.27 mole) of the sulfonyl chloride in 50 ml. of anhydrous ether, dropwise. The mixture was warmed gradually to 70°, kept at 70° for 1 hr., cooled, the solid filtered and recrystallized from aqueous ethanol to give 48.7 g. (80% yield) of the *sulfonamide*, m.p. 184–185°.

Ethyl (α,α,α-trifluoro-o-tolylsulfonyl)carbamate. To 47.7 g. (0.21 mole) of the sulfonamide, 76.3 g. of anhydrous potassium carbonate and 250 ml. of dry acetone was added 30.4 g. (0.28 mole) of ethyl chloroformate. The mixture was stirred and refluxed overnight, cooled, and the solid filtered with suction, dissolved in 500 ml. of water, the aqueous solution filtered, and the filtrate acidified with dilute hydrochloric acid. The solid which separated was filtered and dried to give 54.5 g. (87% yield) of carbamate, m.p. 130–132°. An analytical sample was recrystallized twice from benzene and melted at 131–133°.

1-Butyl-3-(α,α,α-trifluoro-o-tolylsulfonyl)urea. A solution of 23.4 g. (0.08 mole) of the carbamate in 36.5 g. (0.5 mole) of *n*-butylamine was concentrated at 5 mm. and room temperature to remove excess amine and the residue heated by means of an oil bath at an internal temperature of 115–120° at 5 mm. for 3 hr. and then cooled. The residual solid was dissolved in warm 1% aqueous sodium hydroxide solution, the solution acidified with dilute hydrochloric acid, the precipitated solid filtered and recrystallized from aqueous alcohol to give 12.7 g. (49% yield) of product, m.p. 134–135°.

1-Butyl-3-(α,α,α-trifluoro-p-tolylsulfonyl)urea. (Chart II, A) *2-Nitro-α,α,α-trifluoro-p-toluenesulfonyl chloride.*[7] Chlorine gas was passed into a stirred suspension of 408 g. (0.9 mole) of 4,4′-bis(trifluoromethyl)-2,2′-dinitrodiphenyldisulfide[8] in 1800 ml. of 90% acetic acid at such a rate that the temperature was maintained at 50–55°. The oxidation

(5) This procedure described is essentially that of H. Meerwein, G. Dittmar, R. Göllner, K. Hafner, F. Mensch, and O. Steinfort, *Chem. Ber.*, 90, 841 (1957).

(6) Obtained from Maumee Chemical Co., Toledo 5, Ohio.

(7) This procedure is alluded to by A. H. Knight, Brit. Patent 732,121, but no experimental details are presented.

(8) A. I. Kiprianov and L. M. Yagupolskii, *Zhur. Obshcheĭ Khim.*, 22, 2209 (1952); *Chem. Abstr.*, 47, 4769 (1953).

required about 5 hr. Excess chlorine was swept out with nitrogen, the mixture was filtered, and the filtrate concentrated *in vacuo* on the steam bath. The residual oil was extracted with 500 ml. of toluene, the extract was treated with Darco, filtered, dried, and concentrated to give 434 g. (81% yield) of crude sulfonyl chloride as a dark oil. This was used without further purification.

Potassium 2-nitro-α,α,α-trifluoro-p-toluenesulfonate. A suspension of 5.8 g. (0.02 mole) of 2-nitro-α,α,α-trifluoro-*p*-toluenesulfonyl chloride, 3 g. (0.02 mole) of anhydrous potassium carbonate, and 24 ml. of water was stirred and refluxed for 1 hr., filtered, and cooled to give 6.1 g. (98% yield) of the potassium salt, as broad yellow plates. An analytical sample was recrystallized from 90% ethanol; when heated in an open flame, the compound decomposed without melting.

Anal. Calcd. for $C_7H_3F_3KNO_5S$: K, 12.64. Found K, 12.39.

2-Amino-α,α,α-trifluoro-p-toluenesulfonic acid. The solution of the potassium salt obtained as in the previous example by the treatment of 428 g. (1.48 moles) of 2-nitro-α,α,α-trifluoro-*p*-toluenesulfonyl chloride with 225 g. (1.64 moles) of anhydrous potassium carbonate and 1750 ml. of water, was reduced by the procedure of Wertheim.[9] The yield of air-dried amino derivative was 286.4 g. (80%). An analytical sample was obtained from dimethylformamide-ether; this material decomposed in an open flame without melting.

Anal. Calcd. for $C_7H_6F_3NO_3S$: C, 34.85; H, 2.51. Found: C, 34.78; H, 2.62.

Sodium α,α,α-trifluoro-p-toluenesulfonate.[10] To the diazonium compound obtained from 270 g. (1.12 moles) of the amino compound[7] was added dropwise 582 ml. (5.6 moles) of 50% hypophosphorous acid, maintaining the temperature at 0 to 5°; the reaction mixture was kept for 48 hr. at 5°, filtered, and the filtrate concentrated to about one fourth its original volume and cooled. The precipitated solid was filtered and extracted with 3 l. of boiling methanol. The methanol extract was made strongly alkaline with 50% aqueous sodium hydroxide, concentrated, and cooled to give 182.4 g. (65% yield) of the sodium sulfonate.

α,α,α-Trifluoro-p-toluenesulfonyl chloride. To 116.5 g. (1.0 mole) of chlorosulfonic acid was added in small portions a total of 49.6 g. (0.2 mole) of the sodium sulfonate. Subsequently, the mixture was heated for 1 hr. on the steam bath, cooled somewhat, and poured on about 1 kg. of ice. The crystalline sulfonyl chloride which separated was filtered, washed well with water, and used directly in the next step.

α,α,α-Trifluoro-p-toluenesulfonamide. The sulfonyl chloride obtained in the previous step was added rapidly, with stirring, to 600 ml. of cold concd. aqueous ammonia, the mixture was slowly warmed by means of a steam bath to 75–80° and kept at this temperature for 1 hr. The mixture was cooled, the solid filtered and recrystallized from aqueous alcohol to give 30.6 g. (68% yield over-all for the last two steps) of sulfonamide, m.p. 176–177°.

Ethyl α,α,α-trifluoro-p-tolylsulfonylcarbamate. Employing the procedure described above, 30.6 g. (0.14 mole) of the sulfonamide, 49 g. (0.35 mole) of anhydrous potassium carbonate, and 19.6 g. (0.18 mole) of ethyl chloroformate afforded 28.6 g. (71% yield) of the crude ethyl carbamate, m.p. 85–87°. An analytical sample recrystallized from benzene-hexane (1:1), melted at 93–95°.

1-Butyl-3-(α,α,α-trifluoro-p-tolylsulfonyl)urea. From 8.9 g. (0.03 mole) of the ethyl carbamate and 11.5 g. (0.1 mole) of *n*-butylamine, by the procedure above, there was obtained 6.0 g. (62% yield) of product, m.p. 127–128° after recrystallization from aqueous ethanol.

Alternate procedure to ethyl α,α,α-trifluoro-p-tolylsulfonylcarbamate. Chart II, B. α,α,α-Trifluoro-*m*-toluidine and chlorosulfonic acid according to the procedure of Kracker and Herrlein[3a] gave a 95% yield of an amino-α,α,α-trifluorosulfonic acid whose infrared spectrum was identical with that obtained above. This acid, 241 g. (1.0 mole), when diazotized and the diazonium group reductively eliminated, gave 146 g. (59% yield) of sodium *α,α,α-trifluoro-p-toluenesulfonate.*

Anal. Calcd. for $C_7H_4F_3NaO_3S$: S, 12.92. Found: S, 12.97.

The sodium salt, 17.4 g. (0.07 mole) and 46.5 g. (0.39 mole) of chlorosulfonic acid gave the *sulfonyl chloride*, and this without purification was treated with 200 ml. of concd. aqueous ammonia to give 9.8 g. (62% yield in two steps) of *α,α,α-trifluoro-p-toluenesulfonamide*, m.p. 176–177°; a mixture melting point with the product obtained above was 176–177°, and the infrared spectra of both products were identical. The sulfonamide, 9.8 g., gave an 81% yield of ethyl *α,α,α-trifluoro-p-tolylsulfonylcarbamate*, m.p. 93–94°; a mixture melting point with the product obtained above was 93–94°, and the infrared spectra of both products were identical.

Isolation of the cyclohexylamine salt of 1-cyclohexyl-3-(α,α,α-trifluoro-p-tolylsulfonyl)urea and 1,3-dicyclohexylurea from the reaction of cyclohexylamine with α,α,α-trifluoro-p-tolylsulfonylcarbamate. A solution of 20.8 g. (0.07 mole) of ethyl α,α,α-trifluoro-*p*-tolylsulfonylcarbamate and 50 g. (0.5 mole) of cyclohexylamine was treated as above. The pyrolysis product crystallized spontaneously and was recrystallized from aqueous ethanol to give the pure salt, m.p. 177–179°.

Anal. Calcd. for $C_{14}H_{17}F_3N_2O_3S \cdot C_6H_{13}N$: C, 53.44; H, 6.73; N, 9.35. Found: C, 53.25; H, 6.29; N, 9.43.

The salt was dissolved in 300 ml. of warm 0.5*N* aqueous sodium hydroxide and filtered from 0.9 g. of 1,3-dicyclohexylurea, m.p. 226–227°.[11] The warm filtrate was acidified with aqueous hydrochloric acid. The precipitated solid was filtered and recrystallized from 95% ethanol to give 10.5 g. (43% yield) of 1-cyclohexyl-3-(α,α,α-trifluoro-*p*-tolylsulfonyl)urea, m.p. 177–178°.

Acknowledgment. The authors are indebted to Mr. J. F. Alicino and his associates for the microanalyses reported and to Dr. Nettie Coy and Miss Barbara Keeler for the infrared spectra.

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(9) E. Wertheim, *Org. Syntheses*, Coll. Vol. II, 471 (1943).

(10) This compound was screened for ascaricidal activity but no description of its synthesis is reported; *cf. J. Am. Pharm. Assoc.*, 38, 570 (1949).

(11) A. Skita and H. Rolfes, *Ber.*, 53, 1242 (1920) have reported the melting point for 1,3-dicyclohexylurea as 229–230°.

Indole-3-alkanamides

DONALD G. CROSBY, JAMES B. BOYD, AND HERBERT E. JOHNSON

Received April 12, 1960

Since the first implication of indole-3-acetic acid in the growth of plants,[1] the series of indole-3-alkanoic acids has received a great deal of attention from both chemists and biologists. Although the acetic acid was first prepared by Ellinger in 1904,[2] it was not until twenty-one years later that its amide was reported[3] and still another twenty-

(1) F. Kögl, A. J. Haagen-Smit, and H. Erxleben, *Z. physicl. Chem.*, 228, 90(1934).

(2) A. Ellinger, *Ber.*, 37, 1801 (1904).

(3) R. Majima and T. Hoshino, *Ber.*, 58, 2046 (1925).

TABLE I

INDOLE-3-ALKANAMIDES

Compound	M.p.	Yield, %	% N		Growth Stimulation[a]		
			Calcd.	Found	$10^{-4}M$	$10^{-5}M$	$10^{-6}M$
Indole-3-acetamide	149–151°	70	16.1	—	400	90	0
Indole-3-propionamide	131.5–133°	80	14.9[b]	14.8	70	0	0
Indole-3-butyramide	117–118°	40	13.9	13.8	100	120	0
Indole-3-valeramide	127–128°	87	13.0	12.9	50	0	0
Indole-3-caproamide	134.5–136°	99	12.2	11.9	350	400	300

[a] Per cent of control elongation. Indole-3-acetic acid at 10^{-6} M = 400. Values greater than 40 are statistically-significant at the 1% level. [b] *Anal.* calcd. for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.43. Found: C, 70.4; H, 6.70.

seven years before the biological activity of this amide was described.[4] Despite the wide variety of derivatives of other indole acids which have been examined, and the importance ascribed to their effect on plant growth, no data have been available on the preparation and biological properties of other simple amides of this series.

Early attempts to prepare indole amides through the intermediate acid chlorides were unsuccessful,[5] although Shaw and co-workers later were able to obtain indole-3-acetamide by this method.[6] In the present work, amides were prepared by reaction of an ethereal solution of the acid chloride, prepared from the acid and phosphorus pentachloride, with excess concentrated ammonium hydroxide followed by isolation and recrystallization. Their properties are shown in Table I.

Ammonolysis of methyl indole-3-propionate has been mentioned in the literature.[7] However, the melting point of the product was 205°, 72° higher than that of our preparation. Upon repetition of the ammonolysis of the ester, we obtained a compound which exhibited a melting point, mixed melting point, and infrared spectrum identical with those of indole-3-propionamide obtained through the acid chloride. In addition, hydrolysis of both amide samples to indole-3-propionic acid was demonstrated through the use of paper chromatography.

The purified amides were bioassayed by the method of Nitsch and Nitsch,[8] in which elongation of sections of oat first-internodes was measured. The results presented in Table I are distinctly different from those obtained with the corresponding acids.[9] In general, the amides exhibit a lower order of activity than the acids; the possibility that the high value for indole-3-acetamide at 10^{-4} M could be due to the presence of a small amount of indole-3-acetic acid present as an impurity is unlikely because of the chromatographic homogeneity of the sample. The high degree of stimulation observed with the caproamide is unusual and does not coincide with the lowered activity of the corresponding indole-3-caproic acid relative to the acetic acid or with the decreasing activity of the other amides as chain length increases.

EXPERIMENTAL[10]

General preparation of amides. The indole-3-alkanoic acid was dissolved or suspended in anhydrous ether in a flask equipped for the exclusion of moisture. The mixture was stirred magnetically and chilled while a 10% molar excess of phosphorus pentachloride was added, and stirring was continued for 1 hr. The resulting solution was then added dropwise to a large excess of concd. ammonium hydroxide which was stirred and chilled in ice during the addition. After 30 min., the ether was removed in a stream of air or nitrogen, the aqueous layer filtered, and the solid remaining on the filter washed with cold water and air dried. Chloroform, ethyl acetate, and benzene were found to be suitable solvents for recrystallization of the crude amides.

Bioassay. Sections of first internodes of dark-grown oat seedlings (*Avena sativa* L., Var. Brighton), 4.0 mm. in length, were rotated at 1 r.p.m. in citrate-phosphate buffer (*p*H 5.0) which contained 2% sucrose. The indole amides were incorporated in the buffer at concentrations of 10^{-4} to $10^{-7}M$, and at the end of about 20 hr. the final length of each section was measured with the aid of a photographic enlarger. Results were expressed as the average increase in length of eight sections compared with that of the controls.

Acknowledgment. We wish to express our appreciation to Mr. Quentin Quick and his group for microanalyses, to Mr. Roy Spencer, Jr., for the bioassay measurements, and to Dr. H. E. Fritz for gifts of indole-3-valeric and indole-3-caproic acids.

NOTE ADDED IN PROOF. In May, 1960, C. H. Fawcett, R. L. Wain, and F. Wightman [*Proc. Royal Soc. Series B*, 152, 231 (1960)] reported synthesis of several of these indole-3-alkanamides by ester ammonolysis.

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(4) J. A. Bentley and S. Housley, *J. Exptl. Botany*, **3**, 393 (1952).

(5) J. W. Baker and F. C. Happold, *Biochem. J.*, **34**, 657 (1940).

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(7) H. T. Huang and C. Niemann, *J. Am. Chem. Soc.*, 74, 5963 (1952).

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(9) C. H. Fawcett, R. L. Wain, and F. Wightman, *Nature*, **181**, 1387 (1958).

(10) All melting points were measured in a Vanderkamp block and are corrected.

L-Tyrosyl-L-phenylalanine

F. H. C. STEWART

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The dipeptides derived from L-tyrosine and L-phenylalanine have been mentioned in the literature from time to time, mainly in connection with enzymatic hydrolysis studies.[1,2] In particular, L-tyrosyl-L-phenylalanine and various derivatives are referred to, but in only a few cases have any of these compounds been obtained pure and characterized. The synthesis of the pure dipeptide and several of its derivatives by conventional methods is described here.

EXPERIMENTAL

N,O-Biscarbobenzoxy-L-tyrosine. There are considerable differences in the reported properties of this derivative.

Treatment of L-tyrosine in the normal way with excess carbobenzoxy chloride and alkali gave a noncrystalline white powder, m.p. 85–86°; $[\alpha]_D^{22}$ + 3.7° (*c* 10, acetic acid). Pannemann, Marx, and Arens[3] give m.p. 115–121° (indefinite); $[\alpha]_D^{24°}$ +4.5° (*c* 10, acetic acid), while Katchalski and Sela[4] report colorless needles, m.p. 117°; $[\alpha]_D^{20°}$ −5° (c 10, acetic acid).

N,O-Biscarbobenzoxy-L-tyrosyl-L-phenylalanine. An ice cold solution of 3.0 g. of *N,O*-biscarbobenzoxy-L-tyrosine and 0.7 g. of triethylamine in 14 ml. of tetrahydrofuran was treated dropwise with 0.9 g. of isobutyl chlorocarbonate. After stirring for 5 min. a solution of 1.1 g. of L-phenylalanine in 6.4 ml of *N* NaOH was added in one lot. The mixture was stirred for 30 min., and acidified. The oil which separated soon solidified and was recrystallized from ethyl acetate–hexane, yield 3.1 g. (78%) m.p. 179–181°. Recrystallization from ethanol raised the m.p. to 182–184°. $[\alpha]_D^{21°}$ +6.1° (*c* 1, acetic acid).

Anal. Calcd. for $C_{34}H_{32}O_8N_2$: C, 68.4; H, 5.4; N, 4.7. Found: C, 68.6; H, 5.6; N, 4.7.

N-Carbobenzoxy-L-tyrosyl-L-phenylalanine. A dried ethereal solution of the azide obtained in the usual way[5] from 6.2 g. of *N*-carbobenzoxy-L-tyrosyl hydrazide was mixed with an ether solution of ethyl L-phenylalanate obtained from 4.3 g. of the hydrochloride. The mixed solution was kept overnight at 0° and the precipitated crude ethyl *N*-carbobenzoxy-L-tyrosyl-L-phenylalanate filtered and washed with ether. The yield of amorphous solid was 5.0 g. (55%).

Treatment of 2.0 g. of this ester with 9.2 ml. of *N* sodium hydroxide and 5 ml. of dioxane, followed by acidification, gave *N*-carbobenzoxy-L-tyrosyl-L-phenylalanine, which was recrystallized from aqueous ethanol. Yield, 1.7 g. (90%), m.p. 175–176°; $[\alpha]_D^{22°}$ +2.1° (*c* 1, *N* sodium hydroxide).

Anal. Calcd. for $C_{26}H_{26}O_6N_2$: C, 67.5; H, 5.6; N, 6.0. Found: C, 67.6; H, 5.8; N, 6.0.

The compound was also obtained in low yield (11%; m.p. 174.5–175.5°) by a mixed anhydride coupling of *N*-carbobenzoxy-L-tyrosine with L-phenylalanine using isobutyl chlorocarbonate.

L-Tyrosyl-L-phenylalanine. A solution of 3.4 g. of *N,O*-biscarbobenzoxy-L-tyrosyl-L-phenylalanine in 30 ml. of 4*M* hydrogen bromide in glacial acetic acid was warmed to 70° for 10 min., cooled and diluted with ether. The oily precipitate was dissolved in water and the solution neutralized to litmus with aqueous potassium carbonate. On addition of ethanol the dipeptide separated slowly as colorless needles of the monohydrate, yield 0.8 g. (42%), m.p. 308–310° dec.; $[\alpha]_D^{21°}$ +17.7° (*c* 0.5, 2*N* hydrochloric acid). The water of hydration was very firmly bound.

Anal. Calcd. for $C_{18}H_{22}O_5N_2$: C, 62.3; H, 6.4; N, 8.1. Found: C, 62.4; H, 6.5; N, 8.3.

The dipeptide was also obtained by treating *N*-carbobenzoxy-L-tyrosyl-L-phenylalanine with hydrogen bromide in acetic acid at room temperature. Recrystallized from water, m.p. 310–312° dec.; $[\alpha]_D^{22.5°}$ +17.2° (*c* 0.267, 2*N* hydrochloric acid).

N-Formyl-L-tyrosyl-L-phenylalanine. The ethyl ester[6] was obtained in very poor yield by the *N,N'*-dicyclohexylcarbodiimide[7] coupling of *N*-formyl-L-tyrosine and ethyl L-phenylalanate. It was repeatedly recrystallized from aqueous ethanol, m.p. 174–175°; $[\alpha]_D^{21°}$ +2.4° (*c* 1, ethanol). Treatment of 50 mg. of the ester with 0.4 ml. of *N* sodium hydroxide, followed by acidification gave 40.6 mg. (88%) of the product, which formed colorless needles from aqueous ethanol, m.p. 247–248° dec.

Anal. Calcd. for $C_{19}H_{20}O_5N_2$: N, 7.9. Found: N, 7.8.

This derivative was also obtained by warming 100 mg. of L-tyrosyl-L-phenylalanine with 0.6 ml. of a 2:1 mixture of 90% formic acid and acetic anhydride. It was recrystallized from aqueous ethanol, m.p. 246–247° (alone and mixed with above product), yield 35 mg. (30%).

Acknowledgment. The author is indebted to Dr. V. du Vigneaud in whose laboratory at Cornell University Medical College, New York, this work was partly carried out, and to Mr. J. Albert for the microanalyses.

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(1) K. Blau, and S. G. Waley, *Biochem. J.*, **57**, 538 (1954).
(2) L. E. Baker, *J. Biol. Chem.*, **193**, 809 (1951).
(3) H. J. Pannemann, A. F. Marx, and J. F. Arens, *Rec. trav. chim.*, **78**, 487 (1959).
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An Unusual Transfer Reaction in the Steroid Series

N. L. WENDLER AND D. TAUB

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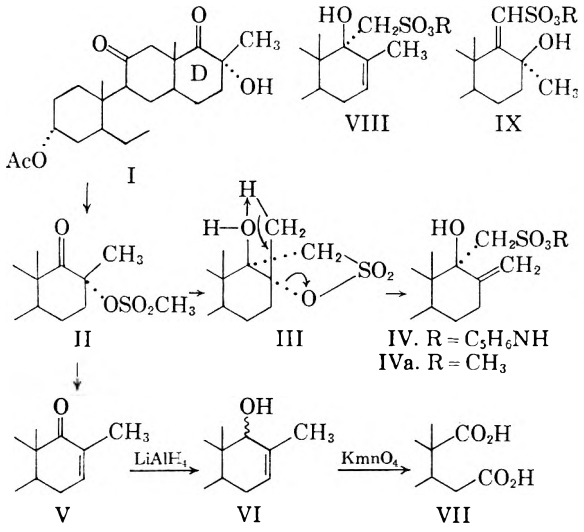
The unusual reactivity of the ketolic system, 3α-acetoxy-17α-hydroxy-17β-methyl-D-homo-5β-androstane-11,17a-dione (I), has been referred to recently.[1] The reaction of this substance with methanesulfonyl chloride in pyridine at 0° affords, in addition to the normal mesylate (II),[1a] an isomeric substance, m.p. 142–144° (25–30%), exhibiting strong hydroxyl absorption in the infrared.

(1) (a) N. L. Wendler, D. Taub, S. Dobriner, and D. K. Fukushima, *J. Am. Chem. Soc.*, **78**, 5027 (1956) Footnote 14. See also (b) N. L. Wendler and D. Taub, *J. Org. Chem.*, **23**, 953 (1958).

This compound consequently has been formulated as the inner aldol (III).[2] On refluxing in pyridine (conditions which convert II→V[1a]), III was transformed to the pyridinium salt of a sulfonic acid, assigned structure IV on the basis of the following evidence:

The pyridinium salt was water soluble and could be titrated with perchloric acid to give an equivalent weight in excellent agreement with that calculated for IV or an isomer. Treatment of the pyridinium salt in methanol with ethereal diazomethane converted it to the corresponding methyl ester IVa. This ester exhibited no maximum in the ultraviolet, but possessed OH absorption at 2.83 μ as well as intense double bond absorption at 6.04 μ in the infrared. Although this ester was essentially inert to neutral permanganate, it did react slowly with osmium tetroxide thereby chemically confirming the presence of a double bond.



The lack of ultraviolet absorption is inconsistent with the isomeric possibility IX; the data are incompatible as well with the alternate structure VIII as this double bonded type, *e.g.* VI, exhibits no double bond absorption in the infrared under comparable conditions of measurement (see Experimental) and is readily oxidized by neutral permanganate to the etiobilianic acid VII.[1] Finally, the NMR spectrum was consistent with IVa and, by establishing the absence of any D-ring methyl group, clearly eliminated structures VIII and IX.[3]

The formation of the exomethylenic system IV would appear to constitute an example of the Arnold-Schinz mechanism of cyclicly assisted dehydration.[4]

EXPERIMENTAL[5]

Reaction of 3α-aceloxy-17α-hydroxy-17β-methyl-D-homo-5β-androstane-11,17a-dione (I) *with methanesulfonyl chloride.* A solution of 4.1 g. of I in 15 cc. of anhydrous pyridine was treated at 0° with 4 cc. of methanesulfonyl chloride and allowed to stand at 0° for 16 hr. The reaction product was treated with ice and ether. The ether extract was washed successively with dilute aqueous hydrochloric acid, potassium bicarbonate, and sodium chloride solution. The washed ether solution was dried over magnesium sulfate, filtered, and evaporated to the point of incipient turbidity. This solution deposited 1.5 g. of III over a period of several days. Recrystallization from acetone-hexane afforded III as slender prisms, m.p. 142–144° dec., λ_{max}^{Nujol} 3 μ (OH); 5.85 μ (C=O); 5.8 μ, 8 μ (OAc), 7.4 μ, 8.6 μ (OSO_2).

Anal. Calcd. for $C_{24}H_{36}O_7S$: C, 61.54; H, 7.70; S, 6.84. Found: C, 61.65; H, 7.70; S, 6.49.

Pyridinium salt (IV). A solution of 3 g. of III in 50 cc. of pyridine was refluxed for 2 hr. and evaporated to dryness *in vacuo*. The residue was crystallized from acetone-ether, 2.8 g., m.p. 145–150° λ_{max}^{Nujol} 2.97 μ (OH/NH); 5.89 μ (C=O), 5.79, 8 μ (OAc), 6.1, 6.42 μ (Pyridine).

Anal. Calcd. for $C_{29}H_{41}O_7NS$: C, 63.62; H, 7.49; N, 2.74; S, 5.86; Eq. wt., 547. Found: C, 63.88; H, 7.17; N, 2.57; S, 6.01; Eq. wt., 533.

Methyl ester (IVa). Treatment of the pyridinium salt (IV) in methanol solution with an excess of ethereal diazomethane afforded the methyl ester (VIa) crystallized from ether, m.p. 180.5–182°, $\lambda_{max}^{CHCl_3}$ 2.83 μ (OH); 5.8–5.85 μ, 8 μ (C=O, OAc); 7.3 μ, 8.5–8.6 μ (OSO_2), 6.04 μ (C=C).

Anal. Calcd. for $C_{25}H_{38}O_7S$: C, 62.24; H, 7.88; S, 6.64. Found: C, 62.46; H, 7.85; S, 6.71.

The above ester (100 mg.) was recovered essentially unchanged after oxidation with potassium permanganate (200 mg.) in acetone (15 cc.) at 25° for 2 hr. or after refluxing for 1 hr.

Δ[16]-17-Methyl-D-homo-5β-androstene-3α,11β,17a-triol (VI). A solution of 100 mg. of the $\Delta^{\alpha,\beta}$ ketone (V)[1] in 20 cc. of ether was reduced with 200 mg. of lithium aluminum hydride at room temperature for 5 hr. The isolated triol (VI) crystallized from ether, m.p. *ca.* 280° λ_{max}^{Nujol} 2.81, 3.03 μ (OH).

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.45; H, 10.18. Found: C, 75.49; H, 9.87.

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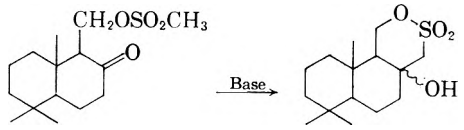
(2) E. Romann, A. J. Frey, P. A. Stadler, and A. Eschenmoser, [*Helv. Chim. Acta.*, **40**, 1900 (1957) Footnote 13] have reported a similar reaction:



We are grateful to Professor R. B. Woodward for calling this reference to our attention.

(3) The authors are grateful to N. R. Trenner and B. Arison for the NMR determination.

(4) R. T. Arnold, *Helv. Chim. Acta.*, **32**, 134 (1949); H. Schinz and G. Schäppi, *Helv. Chim. Acta.* **30**, 1483 (1947).

(5) Melting points were taken on a micro hot stage and are corrected. Infrared spectra were determined on a Baird Associates Infrared Spectrophotometer.

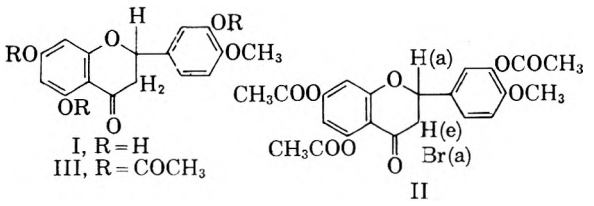
Configuration and Conformation of 3-Bromohesperetin Triacetate. Dimorphs of Hesperetin Triacetate[1,2]

J. H. LOOKER AND MYRON J. HOLM[3]

Received March 21, 1960

Hesperetin (I), the aglycon of the important glycoside hesperidin, has been investigated rather

intensively recently. Of particular interest stereochemically is a study which establishes the absolute configuration of (—)-hesperetin.[4] The present note describes spectral and chemical data which establish the configuration and conformation of 3-bromohesperetin triacetate (II).



II

Hesperetin (I) was obtained from hesperidin by a new, simple method involving heating of the glycoside for 60 to 72 hours in 2% sulfuric acid in 50% ethanol. Acetylation of racemic I gave the triacetate III, which is dimorphous, m.p. 126.5–127° and 143.5–144.5°. Carbon-hydrogen analyses for both high and low-melting forms were in agreement with theory for the triacetate. Neither form lost weight at 100° *in vacuo*, thus indicating that solvation is not responsible for the different melting points. Interconversion of high and low-melting forms was readily effected (Experimental). Thus III is considered dimorphous. Confirmation was obtained from infrared spectral data[5] (Experimental). Solution spectra of the two forms are identical, but solid state spectra of the individual dimorphs differ.

Our melting point data confirm Perkin's observation[6] of a melting point in the vicinity of 127° for III. However, as other workers[7] have assigned a chalcone tetraacetate structure to a hesperetin acetylation product, m.p. 127°, the structure of this substance has been reinvestigated. Acetyl determination under acidic conditions revealed the presence of only three acetoxyl groups. A ferric chloride test was negative, precluding the possibility of a hydroxytriacetoxychalcone structure. The infrared spectrum in carbon tetrachloride showed a band at 1691 cm.$^{-1}$, indicative of a carbonyl group of a flavanone.[8] The ultraviolet spectrum also indicates a flavanone, as the intensity of the broad band at 3140 Å is not as great as that expected for a chalcone.[9] The product gives a positive magnesium-hydrochloric acid test for a flavonoid,[10] although the color develops rather slowly. We conclude that the acetylation product of hesperetin, m.p. 127°, is the flavanone derivative (III).

3-Bromohesperetin triacetate (II), first described by Zemplen and Bognar,[11] was prepared by their general procedure, as recently described.[12] The 3-bromo derivative (II) loses hydrogen bromide in presence of silver acetate–acetic anhydride,[12] and in pyridine, even at −5°, with formation of diosmetin triacetate. The latter reaction in particular involves ready elimination of hydrogen bromide, and thus the hydrogen at carbon-2 is very probably *trans* to the bromine at carbon-3.[13] Infrared spectral data for methylene chloride solutions of II and III show that the keto carbonyl bands are at 1698 and 1693 cm.$^{-1}$, respectively. The small spectral shift of 5 cm.$^{-1}$ indicates that the bromine *alpha* to the carbonyl group probably is in an axial position.[14] Accordingly, the *trans*-hydrogen at carbon-2 also must be axial, as indicated in formula II. The conformation of II is the expected one if the Corey rule[15] pertaining to bromination of ketosteroids under kinetic conditions is extended to the flavanone (III). However, the detailed mechanism may be different in the present case, as the bromination is effected under irradiation with ultraviolet light. These conditions could lead to homolytic steps in the early stages of the bromination. However, the hydrogen bromide subsequently produced may catalyze enolization, and the enol usually postulated then could participate in an ionic bromination process. In view of the apparent conformational stability of II, it is likely that the hydrogen atom at carbon-2 in I and III also is axial.

EXPERIMENTAL[16]

Hydrolysis of hesperidin. A 5.0-g. quantity of hesperidin was suspended in a solution of 2.5 ml. of concd. sulfuric acid in 250 ml. of 50% aqueous ethanol, heated until solu-

(1) From the M.S. (1956) and Ph.D. (1958) theses of Myron James Holm.

(2) This investigation was supported in part by a research grant (E-1703) from the National Institute of Allergic and Infectious Diseases, Public Health Service.

(3) DuPont Postgraduate Teaching Assistant, 1956–1957; Standard Oil of Indiana Foundation Fellow, 1957–1958.

(4) H. Arakawa and M. Nakazaki, *Chem. & Ind. (London)*, 1960, 73.

(5) F. A. Miller, in *Organic Chemistry*, Vol. III, edited by H. Gilman, John Wiley and Sons, New York, N. Y. (1953), p. 139.

(6) A. G. Perkin, *J. Chem. Soc.*, 1031 (1898).

(7) F. Tutin, *J. Chem. Soc.*, 2054 (1910); O. A. Oesterle and R. Kueny, *Arch. Pharm.*, 253, 383 (1915); Y. Asahina, J. Shinoda, and M. Inubuse, *J. Pharm. Soc. Japan*, 48, 207 (1928). The procedure of Tutin was identical with that of Perkin, except for reaction period. Tutin characterized his product by acetyl determination in basic medium. The other workers cited herein utilized acetic anhydride and sodium acetate for acetylation. In our hands, the latter procedure gave hesperetin triacetate.

(8) H. L. Hergert and E. F. Kurth, *J. Am. Chem. Soc.*, 75, 1622 (1953).

(9) Recent data supporting this statement are presented by M. Shimokoriyama, *J. Am. Chem. Soc.*, 79, 214 (1957).

(10) For leading references, see S. Rangaswami and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 16A, 129 (1942).

(11) G. Zemplen and R. Bognar, *Ber.*, 76B, 454 (1943).

(12) J. H. Looker and M. J. Holm, *J. Org. Chem.*, 24, 1019 (1959).

(13) A review of the four centers in a plane generalization is given by D. H. R. Barton, *J. Chem. Soc.*, 1030 (1953).

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(15) E. J. Corey, *J. Am. Chem. Soc.*, 76, 176 (1954).

tion was complete (usually *ca.* 75 hr.) and then an additional 5 hr. The *p*H was adjusted to between 4 and 5. Most of the alcohol was removed by distillation, the residual solution filtered while hot, and the filtrate allowed to cool. The light tan, crude, crystalline hesperetin was collected by filtration and air-dried; yield, 1.78 g. (72%), m.p. 225–227° with softening at 218°. The crude product was recrystallized by solution in hot isopropyl alcohol (10–11 ml.), cooling, and permitting the mixture to stand 12 hr. in a refrigerator. The recrystallized hesperetin (1.15 g.) melted at 228–229.5° (lit.,[6,17] m.p. 226°). The purest hesperetin obtained in this study melted at 228.5–229.2°. By sublimation, a product, m.p. 232.8°, has been previously reported.[18]

Dimorphous forms of hesperetin triacetate. A 7.00-g. quantity of hesperetin, m.p. 226–228°, was dissolved in a mixture of 45 ml. of acetic anhydride in 45 ml. of pyridine and permitted to stand at room temperature for 24 hr. The mixture was poured into 800 ml. of crushed ice-water, and the precipitated product collected and dissolved in 100 ml. of boiling 95% ethanol. Cooling the ethanol solution at 0° for 12 hr. gave 8.00 g. (80%) of the crude triacetate. Recrystallization from 75 ml. of 95% ethanol gave 7.50 g., m.p. 141.5–143.5°, and two additional crystallizations gave 6.68 g. of hesperetin triacetate, m.p. 143.5–144.5°. In another example of this purification, the melting point after the fourth crystallization was 143.5–144.2°. After a fifth crystallization hesperetin triacetate, m.p. 126.5–127°, was obtained.

Anal. Calcd. for $C_{22}H_{20}O_9$: C, 61.67; H, 4.71; CH_3CO, 30.14. Found: (For dimorph, m.p. 126.5–127°): C, 61.89; H, 4.78. (For dimorph, m.p. 143.5–144.5°): C, 61.94; H, 4.98; CH_3CO, 29.6. The residue from the acetyl determination was isolated, recrystallized from ethanol and shown to be hesperetin by melting point and mixed melting point determination.

Hesperetin triacetate, m.p. 143.4–144.2°, was dissolved in hot 95% ethanol, and the resulting solution filtered into a flask containing seed crystals of the dimorph, m.p. 126.5–127°. Upon cooling, the total separated hesperetin triacetate was collected, air-dried, and found to melt 126.5–127°. When the dimorph, m.p. 126.5–127°, was melted on a Kofler hot stage[19] and held at 130–135° for several minutes, crystals grew in the melt and remelted between 145 and 147°. Samples of both dimorphs were weighed, dried in a drying pistol *in vacuo* for 1 hr., and reweighed. No change in weight was observed.

In Nujol mull, the infrared spectrum of the dimorph, m.p. 143.5–144.5°, showed strong or medium absorption bands at 1760, 1685, 1618, 1581, 1520, 1444, 1330, 1279, 1269, 1212, 1190, 1136, 1130, 1076, 1060, 1028, 903, and 809 cm^{-1}. The Nujol spectrum of the dimorph, m.p. 126.5–127°, showed strong or medium absorption bands at 1755, 1670, 1616, 1570, 1515, 1438, 1331, 1282, 1262, 1249, 1210 (broad), 1180, 1129, 1074, 1060, 1025, 899, and 817 cm^{-1}. In carbon tetrachloride solution, the dimorphs gave identical infrared spectra, showing absorption bands at 1775, 1691, 1618, 1437, 1369, 1327, 1188 (broad), 1127, 1073, 1023, and 898 cm^{-1}. The ultraviolet absorption spectrum of the high-melting dimorph in absolute ethanol showed maxima at 220 mμ (ϵ 38.7 × 10^3), 259 mμ (ϵ 11.2 × 10^3), and 314 mμ (ϵ 3.89 × 10^3), and minima at 241 mμ (ϵ 6.22 × 10^3) and 288 mμ (ϵ 1.81 × 10^3).

3-Bromohesperetin triacetate. This substance was prepared as previously described.[11,12] In a potassium bromide pellet, the infrared spectrum of 3-bromohesperetin triacetate showed strong or medium absorption bands at 1771, 1692, 1620, 1580, 1517, 1432, 1372, 1273, 1202, 1180, 1127, 1071, 1022, 903, and 810 cm^{-1}.

Diosmetin triacetate from 3-bromohesperetin triacetate and pyridine. A 0.5-g. sample of 3-bromohesperetin triacetate was dissolved in 20 ml. of cold pyridine and stored for 1 week at −5°. The mixture was then placed in a desiccator containing coned. sulfuric acid. The desiccator was evacuated and stored at −5°. When all of the pyridine had been absorbed by the sulfuric acid, the reaction vessel was removed and the residue triturated with cold methanol. After standing at *ca.* 5° overnight, 0.29 g. (70%) of diosmetin triacetate was collected by filtration and recrystallized from methanol; m.p. 195–197° (lit. m.p.[20] 195–196°). The solid state spectrum (potassium bromide pellet) was identical with that of diosmetin triacetate obtained as previously described.[12]

Anal. Calcd. for $C_{22}H_{18}O_9$: C, 61.97; H, 4.26. Found: C, 62.55, 62.28; H, 4.30, 4.27.

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(16) Melting points are uncorrected and were observed in capillary tubes. The infrared measurements were carried out with a Perkin-Elmer Model 21 double-beam recording spectrophotometer. A Cary recording spectrophotometer was employed for ultraviolet spectral measurements.

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(19) L. Kofler, *Angew. Chem.*, 51, 703 (1938).

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Steroidal Esters of 3-Indoleacetic Acid[1-3]

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As alterations of the lyophilic properties of the alcohol portion might enhance the activity for parthenocarpic fruit induction in the tomato,[4,5] steryl esters of 3-indoleacetic acid have been prepared and tested for biological activity.

Attempts to synthesize the esters using 3-indoleacetyl chloride[6,7] and free sterol in pyridine[8] resulted in the formation of a highly insoluble orange-red material. The preparation of the esters was accomplished by using the free sterol, silver carbonate, and approximately twice the theoretical amount of acyl chloride in benzene or petroleum ether. The products were purified by recrystallization to constant melting point followed by removal of the final traces of free sterol with digitonin.[9]

(1) Journal Article No. 2594 of the Michigan Agricultural Experiment Station.

(2) This research was supported by a grant from the National Science Foundation.

(3) From the masters thesis of J. Hofert, Michigan State University.

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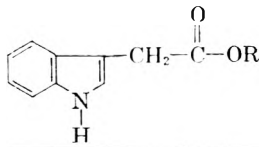
(9) L. F. Fieser, *Natural Products Related to Phenanthrene*, Reinhold Publishing Corp., New York, 1949, p. 102.

TABLE I

PROPERTIES OF STERYL 3-INDOLEACETATES



R	Formula	M.P.[a]	$[\alpha]_D^{23}$ in $CHCl_3$	Yield,[b] %	Carbon		Hydrogen		Nitrogen	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
Cholesteryl	$C_{37}H_{53}NO_2$	194.5–195	−36	80	81.7	82.0	9.8	9.8	2.6	2.7
Ergosteryl	$C_{38}H_{51}NO_2$	179–180	−76	23	82.4	82.3	9.3	9.2	2.5	2.7
7-Dehydrocholesteryl	$C_{37}H_{51}NO_2$	169–170	−55	11	82.0	82.0	9.5	9.3	2.6	2.5
Cholestanyl	$C_{37}H_{55}NO_2$	172–173	+13	64	81.4	81.4	10.2	10.2	2.6	2.5
β-Sitosteryl	$C_{39}H_{57}NO_2$	153–154	−32	7	81.9	81.7	10.0	9.9	2.4	2.5

[a] Corrected. [b] Based on crude material.

Physical properties of the steryl 3-indoleacetates prepared are reported in Table I. Cholesteryl, cholestanyl, and sitosteryl esters displayed indole absorption (280 to 300 mμ), whereas the ergosteryl and 7-dehydrocholesteryl esters also exhibited absorption for their conjugated diene system.

EXPERIMENTAL

Recrystallization of 3-indoleacetic acid. Ten grams of commercial 3-indoleacetic acid was dissolved in 350 ml. of peroxide-free ethyl ether. The small amount of solid remaining was removed by filtration. Two hundred milliliters of dry petroleum ether[10] (b.p. 40–45°) was then slowly added to the filtrate. The solution was stored in the refrigerator overnight at −10° and yielded 8.1 g. of white crystals, m.p. 169–170°. This material was used for the synthesis of 3-indoleacetyl chloride.

A. Preparation in benzene. Cholesteryl 3-indoleacetate. Equal weights (3.0 g.) of cholesterol (0.008 mole, recrystallized from 95% ethanol and dried *in vacuo* at 100°), silver carbonate (0.01 mole) and freshly prepared 3-indoleacetyl chloride[7] (0.016 mole) were shaken in 10 ml. of anhydrous thiophene–free benzene for 18 hr. at 30°. The silver chloride and carbonate were then removed by suction filtration and washed with 10 ml. of benzene. The filtrate was concentrated to dryness under reduced pressure and the residue treated with hot methanol. The white to gray crystals which failed to dissolve were collected by filtering the hot solution. Upon cooling the filtrate to room temperature an amorphous powder precipitated (total yield of crude product based on cholesterol was 80%). One gram of the combined material was treated with 0.8 g. of digitonin.[9] The final product was recrystallized from chloroform-95% ethanol and weighed 0.67 g.

Ergosteryl 3-indoleacetate. The procedure previously described for the preparation of cholesteryl 3-indoleacetate was followed through removal of the silver residues. Concentration of the filtrate *in vacuo* was aided by bubbling nitrogen through the solution. Two solid fractions were obtained, one from filtration and the other from evaporation of the benzene. Complete removal of the solvent yielded a brown tar which could not be purified. The two fractions were recrystallized separately by dissolving in enough chloroform to effect solution and adding an equal volume of 95% ethanol. The two white crystalline fractions were combined and treated with digitonin.[9] Final recrystallization of the product involved dissolving in ethyl ether, evaporation of the solvent at room temperature until crystals began to form, and then adding to this solution an equal volume of petroleum ether (b.p. 40–45°).

7-Dehydrocholesteryl 3-indoleacetate. Using 7-dehydrocholesterol, 3-indoleacetyl chloride and silver carbonate, the mixture was heated at 30° for 18 hr. and filtered. After most of the benzene had been removed by concentration in an atmosphere of nitrogen under reduced pressure, a brown oil formed. Enough chloroform was added to the oil to produce a homogeneous solution which was then volatilized and cooled by passing a stream of nitrogen over the surface. The cooling and concentration caused a brown oil to form from which the cold chloroform was decanted. Addition of 95% ethanol to the supernatant liquid precipitated white crystals which after two-fold recrystallization from chloroform-95% ethanol resulted in the analytical product.

B. Preparation in petroleum ether. Cholestanyl 3-indoleacetate. Equal weights (3.94 g.) of cholestanol (0.01 mole), freshly prepared 3-indoleacetyl chloride (0.02 mole) and silver carbonate (0.1 mole) were refluxed gently in a round bottom flask heated by a water bath at 40–45° in 110 ml. of dry petroleum ether (b.p. 40–45°). A motor stirrer kept the silver carbonate in suspension during the heating period while hydrogen chloride passed through the condenser. After 2 hr. of heating 10 ml. of dry benzene was added and the temperature was maintained until hydrogen chloride evolution ceased. Thirty milliliters more benzene was added and the water bath temperature increased to 55–60° for an additional 30 min. After filtering the silver salts from the warm solution, fractions of material were obtained by additions of petroleum ether. Recrystallizations from absolute ethanol gave the crude products (64% based on cholestanol). Treatment with digitonin and final recrystallization from chloroform-95% ethanol gave the purified product.

β-Sitosteryl 3-indoleacetate. Proportions of sterol, 3-indoleacetyl chloride, silver carbonate, and solvent were used as in the previous preparation. After 3 hr. of heating, hydrogen chloride production ceased, 40 ml. of dry benzene was added and the bath temperature raised to 45–50° for an additional 2 hr. Concentrating the filtrate, removing the silver precipitates, and adding petroleum ether (b.p. 40–45°) gave material which was treated with Norite A, recrystallized three times from 95% ethanol and then purified further by digitonin treatment. A final recrystallization from 95% ethanol gave fluffy flakes of the ester.

Biological properties. Biological activity of the steroidal esters was determined by employing the tomato ovary test[11] and using 3-indoleacetic acid as a control. For all

(10) Washed with sulfuric acid, water, dried over calcium chloride, and distilled over sodium.

(11) S. H. Wittwer, *Univ. of Missouri Bull.*, 371 (1943).

practical purposes, the steryl esters were inactive in this test.

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The Effect of Solvent on the Ultraviolet Absorption Spectra of Phosphine Oxides and Sulfides

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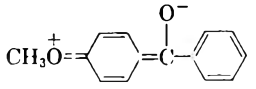
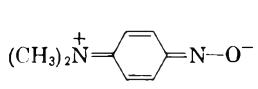
From a study of the effect of solvent on the ultraviolet absorption spectra of sulfones, it was suggested[1] that the sulfur-oxygen bond in sulfones is semipolar and not doubly covalent. It was interesting to study in a similar way the nature of the phosphorus-oxygen and phosphorus-sulfur bonds in phosphine oxides and phosphine sulfides, respectively.

From the data recorded in Table I it is seen that the solvent effect on the absorption spectra of phosphine oxides and phosphine sulfides is analogous to that observed for sulfones.[1] With change of solvent from cyclohexane to ethanol there is practically no change in λ_{max} for phosphine oxides and sulfides, while for ketones, there is a considerable bathochromic shift. This shift is even more pronounced for *p*-nitrosodimethylaniline. In the case of ketones and *p*-nitrosodimethylaniline, polar structures (I and II) make a more significant contribution to the excited state than to the ground state; the excited state is thus more stabilized in a polar solvent and a red shift of the λ_{max} is seen to occur with change of solvent from cyclohexane

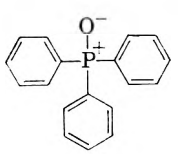


I

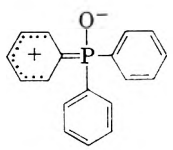


II

to ethanol. If the phosphorus-oxygen and phosphorus-sulfur bonds in phosphine oxides and sulfides are semipolar, both the ground and excited states are zwitterionic (as illustrated by III and IV) and they will be stabilized almost to the same extent in a polar solvent. Hence there will be no significant change in λ_{max} with change of solvent. Such a semipolar concept of the phosphorus-oxygen linkage in phosphine oxides is in conformity with the experimental evidence supplied by the parachors,[2] dipole moments,[3] and bond refractions.[4]



III



IV

TABLE I

SOLVENT EFFECT ON THE ABSORPTION SPECTRA OF TRIARYLPHOSPHINE OXIDES, TRIARYLPHOSPHINE SULFIDES, AND DIARYL KETONES[a]

	C_6H_{12}		C_2H_5OH	
	λ_{max}	ϵ_{max}	λ_{max}	ϵ_{max}
$(C_6H_5)_3PO$	224	23,000	224	26,100
$(p\text{-}CH_3\cdot C_6H_4)_3PO$	231	32,800	232	35,500
$(p\text{-}CH_3O\cdot C_6H_4)_3PO$	244	43,700	246	46,000
$(p\text{-}CH_3\cdot C_6H_4)_3PS$	227	30,800	227	30,300
$(p\text{-}CH_3O\cdot C_6H_4)_3PS$	240	35,300	242	35,300
$(C_6H_5)_2CO$	249	18,900	253	17,500
$(p\text{-}CH_3\cdot C_6H_4)_2CO$	258	22,100	265	20,600
$(p\text{-}CH_3O\cdot C_6H_4)_2CO$	279	22,300	295	21,900
$p\text{-}(CH_3)_2N\cdot C_6H_4\text{'}NO$	393	23,800	428	28,600

[a] The high intensity bands only are given. Wave lengths are in mμ.

EXPERIMENTAL

Tri-p-anisylphosphine oxide. A saturated solution of potassium permanganate was added in excess to tri-*p*-anisylphosphine[5] (3.5 g.) dissolved in glacial acetic acid. After 2 to 3 hr., sodium bisulfite was added to decolorization and the acid was neutralized carefully with ammonium hydroxide. The oil (3 g.) that was obtained solidified on cooling and scratching with a few drops of ether. Recrystallization from petroleum ether (b.p. 60–70°) gave shining needles, melting at 142–143°.

Anal. Calcd. for $C_{21}H_{21}O_4P$: C, 68.45; H, 5.74. Found: C, 68.03; H, 5.64.

Tri-p-anisylphosphine sulfide. A mixture of tri-*p*-anisylphosphine[5] (3.5 g.) and sulfur (0.4 g.) in carbon disulfide (25 ml.) was refluxed for 2 hr. Distillation of the carbon disulfide left an oily product (3.2 g.) which solidified on cooling. It crystallized from ethanol as colorless needles and melted at 109–110°.

Anal. Calcd. for $C_{21}H_{21}O_3PS$: C, 65.63; H, 5.51. Found: C, 65.12; H, 5.36.

Tri-p-tolylphosphine oxide. To *p*-tolylmagnesium bromide prepared from magnesium (5.2 g.) and *p*-bromotoluene (36.7 g.) dissolved in sodium-dried ether (100 ml.) was added phosphoryl chloride (7.6 g.) in dry ether (50 ml.) during the course of 0.5 hr. with vigorous shaking and cooling in a freezing mixture. The resulting complex was decomposed with a saturated solution of ammonium chloride and the ether layer was separated. The aqueous layer was extracted twice with ether and the combined ether extracts were washed with sodium hydroxide solution to remove any di-*p*-tolylphosphinic acid formed. The ethereal extract was dried with anhydrous sodium sulfate and the ether was removed by distillation. The oily product (12 g.) that was left

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(2) S. Sugden, J. B. Reed, and H. Wilkins, *J. Chem. Soc.* 127, 1525 (1925).

(3) K. A. Jensen, *Z. anorg. allgem. Chem.*, 250, 268 (1943).

(4) R. G. Gillis, J. F. Horwood, and G. L. White, *J. Amer. Chem. Soc.*, 80, 2999 (1958).

(5) F. G. Mann and E. J. Chaplin, *J. Chem. Soc.*, 527 (1937).

over solidified on cooling and scratching. Recrystallization from benzene gave crystals melting at 145°. Michaelis,[6] who prepared it by the oxidation of tri-*p*-tolylphosphine, reported the same melting point.

Triphenylphosphine oxide, m.p. 153–154°, was obtained from triphenylphosphine[7] by the method of Michaelis and Soden.[8] Tri-*p*-tolylphosphine sulfide, m.p. 185–186°, was prepared by the action of sulfur on tri-*p*-tolylphosphine[6] as described by Michaelis.[6] *p,p'*-Dimethoxybenzophenone, m.p. 143–144°, was prepared by the method of Bergmann and Harvey.[9] *p,p'*-Dimethylbenzophenone, m.p. 93–94°, was obtained by the Friedel-Crafts reaction of *p*-toluoyl chloride with toluene. The sample of *p*-nitrosodimethylaniline used was recrystallized from petroleum ether (b.p. 30–50°) and melted at 94–95°.

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Preparation of Difunctional Cyanoalkylsilanes by the Grignard Reaction

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Recent reports that the reaction of methylmagnesium bromide with β-cyanoethyltrichlorosilane in diethyl ether results in a low yield of a mixture of products[1] and that a tertiary amine is required as a cosolvent for improved results[2] has prompted us to report on a brief investigation along similar lines. By carrying out the Grignard reaction at −50° in tetrahydrofuran solution, greatly improved selectivity of the Grignard reagent is realized, workup of the products is simplified, and difunctional β-cyanoethylchlorosilanes are readily isolated in good yield. The results of the reaction of methyl- and ethylmagnesium chlorides with β-cyanoethyltrichlorosilane are summarized in Table I.

TABLE I

Reaction Products of β-Cyanoethyltrichlorosilane with Grignard Reagents at −50°[a]

RMgCl	Mole-% Conversion to β-$NC(CH_2)_2$-$SiRCl_2$	Mole-% Conversion to β-$NC(CH_2)_2$-SiR_2Cl
Methyl	73	7
Ethyl	69	9

[a] Grignard reagents and β-cyanoethyltrichlorosilane were allowed to react in equimolar amounts. See Experimental section.

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The effect of reaction temperature on product distribution was examined for the reaction of methylmagnesium chloride with β-cyanoethyltrichlorosilane. The results are summarized in Table II.

TABLE II

Effect of Temperature on Selectivity in the Reaction of β-Cyanoethyltrichlorosilane with Methylmagnesium Chloride[a]

Reaction Temperature	Mole-% Conversion to β-$NC(CH_2)_2$-$Si(CH_3)Cl_2$	Mole-% Conversion to β-$NC(CH_2)_2$-$Si(CH_3)_2Cl$
−50°	73	7
−30°	61.6	10.6
+ 5°	52.4	16.1

[a] Grignard reagent and β-cyanoethyltrichlorosilane were allowed to react in equimolar quantities.

It is noteworthy that as the reaction temperature is raised from −50° to +5° the conversion to β-cyanoethyldichloromethylsilane falls about 20% while an equivalent amount of Grignard reagent is consumed by the formation of by-product β-cyanoethylchlorodimethylsilane. It is likely that at 20–35° reaction of the Grignard reagents will be rather nonselective. In addition, at these temperatures attack of the cyano group by the Grignard reagent probably becomes important. From these results it is concluded that for optimum conversion to difunctional cyanoalkylsilanes the reaction with Grignard reagents should be carried out at −30° or lower.

Experimental

All experiments were carried out following essentially the same procedure. Workup of the reaction products was simplified by removal of the salts by filtration while the reaction mixture was still cold.

β-Cyanoethyldichloromethylsilane (I). To 3.3 moles of β-cyanoethyltrichlorosilane (II) in 1.4 l. of tetrahydrofuran previously cooled to −50° with a Dry Ice–acetone bath there was added over a 2-hr. period the Grignard reagent prepared from 80 g. (3.3 moles) of magnesium turnings treated with excess methyl chloride in 1 l. of tetrahydrofuran. The reaction mixture was stirred for an additional hour as it was allowed to warm to +10° and then rapidly filtered. The filtrate was stripped of solvent under vacuum and refiltered. Flash distillation gave 457 g. of crude product which was fractionally distilled at atmospheric pressure through a 20-inch column packed with Helipak Hastelloy B (0.1 inch × 0.05 inch × 0.1 inch) rated at 20 plates. The forerun b.p. 200–214°/750 mm. (60 g., hydrolyzable chlorine, 34.7%) was a mixture of 34 g. (7% conversion) of β-cyanoethylchlorodimethylsilane (calcd. hydrol. chlorine, 24.0%) and 26 g. of I. The presence of minor amounts of II and β-cyanoethyltrimethylsilane cannot be rigidly

excluded. The main fraction (379 g. + 26 g. from forerun = 405 g. or 73 mole-% conversion) was I, b.p. 215°/750 mm., n_D^{25} 1.4550 (hydrol. chlorine, 42.3%; calcd., 42.2%).

β-Cyanoethylethyldichlorosilane (III). Similar treatment of 254 g. (1.35 moles) of II with ethylmagnesium chloride prepared from 36.4 g (1.5 moles) of magnesium turnings and 97 g. (1.5 moles) of ethyl chloride in a total of 1 l. of tetrahydrofuran at −50° gave after filtration and removal of the solvent, 205 g. of crude product. Fractional distillation gave 168 g. total (conversion, 69 mole-%) of III as the main product (hydrol. chlorine, 37.9%; calcd., 38.9%) b.p. 234–235°/751 mm. and a forerun b.p. 200–234°/751 mm. (hydrol. chlorine, 34.8%) consisting of a mixture of 21.5 g. (conversion, 9 mole-%) of β-cyanoethylchlorodiethylsilane (calcd. hydrol. chlorine, 20.2%) and 5 g. of III.

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Reactions of *t*-Butyl Hypochlorite

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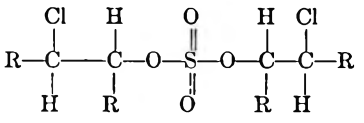
t-Butyl hypochlorite is a highly reactive and versatile intermediate. Walling[1] has recently shown that in the presence of light or free radical initiators it leads to the free radical chlorination of hydrocarbons. Good yields of allylic chlorides are claimed from many olefins with little or no competing addition to the double bond. An older and more familiar reaction of *t*-butyl hypochlorite is its reaction with olefins in the presence of water and a small amount of acid (acetic) to produce chlorohydrins.[2,3] If water is excluded and the *t*-butyl hypochlorite and olefin are treated with a primary or secondary alcohol in the presence of a small amount of *p*-toluenesulfonic acid, a chlorohydrin ether results.[4,5] If acetic acid is substituted for alcohol, then a chlorohydrin ester is the chief product.[4,6]

We have found that if *t*-butyl hypochlorite is added to a solution of an olefin in *t*-butyl alcohol containing more than a catalytic amount of sulfuric acid, then a sulfate of the following general formula results:



where R may be hydrogen or an alkyl group. By-products of the above reaction are believed to be a chloro-*t*-butyl ether and a chloroacid sulfate of the starting olefin.

Phosphoric acid may be used in place of sulfuric acid to give phosphate esters.

EXPERIMENTAL

t-Butyl hypochlorite. A modification of the method described by Teeter and Bell[7] was used. Chlorine (171 g., 2.4 moles) was bubbled into a solution of 96 g. (2.4 moles) of sodium hydroxide and 133 g. (1.8 moles) *t*-butyl alcohol in 1550 g. of water at a temperature of 15–20°. The top oil layer was separated and washed with 200 ml. of 10% sodium carbonate, twice with water, and once with a saturated sodium chloride solution. The product was recovered in 88% yield based on alcohol. It was 99% pure by analysis for active chlorine.

Bis(2-chlorocyclohexyl) sulfate. To a solution of 18.5 g. (0.25 mole) of *t*-butyl alcohol in 150 ml. of benzene there was added 13.3 ml. (0.25 mole) of concd. sulfuric acid while stirring and maintaining the temperature at 25°. Cyclohexene, 41 g. (0.5 mole) was then added, followed by 54.5 g. (0.5 mole) of *t*-butyl hypochlorite which was added dropwise at 25°. Reaction was immediate. The product was washed with water and after removing the solvent under vacuum the solid was crystallized from cyclohexane. The purified product weighed 32 g. (39% yield) and melted at 94°.

Anal. Calcd. for $C_{12}H_{20}O_4SCl_2$: C, 43.5; H, 6.1; S, 29.0; Cl, 21.4. Found: C, 43.4; H, 6.1; S, 29.2; Cl, 21.3.

The chief by-product was probably 1-chloro-2-*t*-butoxy cyclohexane. A cut from a Claisen distillation, b.p. 86–97°/20 mm., weighed 38 g. (40% yield).

Anal. Calcd. for $C_{10}H_{19}OCl$: Cl, 18.6. Found: Cl, 19.6.

Bis(1-chloro-2-propyl)sulfate. To a solution of 74 g. (1.0 mole) of *t*-butyl alcohol in 200 g. of benzene there was added 49 g. (0.5 mole) of concd. sulfuric acid while stirring and cooling. To this solution maintained at 0–5° there was added simultaneously 108.5 g. (1 mole) of *t*-butyl hypochlorite and slightly more than 1 mole of gaseous propylene. The product was neutralized with aqueous sodium hydroxide and washed with water. Claisen distillation gave 56 g. of material (22% yield) boiling 106–114°/1 mm.

Anal. Calcd. for $C_6H_{12}O_4SCl_2$: C, 28.7; H, 4.82; S, 28.3; Cl, 12.7. Found: C, 29.0; H, 4.8; S, 28.1; Cl, 12.5.

Tris(2-chlorocyclohexyl)phosphate. To a solution of 26 g. of 85% phosphoric acid (0.23 mole) in 74 g. (1.0 mole) of *t*-butyl alcohol and 200 g. of benzene there was added 82 g. (1.0 mole) of cyclohexene followed by the dropwise addition of 108.5 g. (1.0 mole) of *t*-butyl hypochlorite at 20–25°. After 2 hr. at this temperature the reactants were heated for 1 hr. at 40° for completion. The product was neutralized with 1*N* sodium hydroxide and thoroughly washed with water. The solvent and medium boiling products were removed from a Claisen still to a kettle temperature of 100° at 1 mm. The residue was taken as product and corresponded to a 34% yield.

Anal. Calcd. for $C_{18}H_{30}PCl_3$: C, 48.2; H, 6.75; P, 6.92; Cl, 23.8. Found: C, 49.6; H, 7.0; P, 6.0; Cl, 23.1.

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α-Indanone from β-Propiolactone

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The preparation of α-tetralone by condensation of benzene with γ-butyrolactone in the presence of excess aluminum chloride was reported several years ago.[1,2] This reaction does not appear to have been extended to the preparation of α-indanone from β-propiolactone, although a mixture of β-phenylpropionic acid (62%) and phenyl vinyl ketone (15%) was obtained in one study,[3a] while no product—β-phenylpropionic acid was expected—was isolated in another.[3b] In the present report use of excess aluminum chloride has given α-indanone in *ca.* 80% yield when the lactone was added to an excess of aluminum chloride and benzene. The reverse order of addition (aluminum chloride added to lactone and benzene)[1,2] gave only a 30% yield.

The present method has the usual advantage of a one-step synthesis from available starting material and presumably can be extended to the preparation of substituted and polycyclic compounds. Previous one-step procedures employed the much more expensive β-chloropropionyl chloride (55% yield)[4] and acrylyl chloride (3% yield).[5] α-Indanone also has been prepared from indene[6] and indane[7,8] by oxidative procedures; from β-phenylpropionic acid by cyclization with polyphosphoric acid,[9,10] with fluosulfonic acid,[11] with trifluoroacetic anhydride,[12] and with aluminum chloride-sodium chloride;[13] and from β-phenylpropionyl chloride by cyclization with aluminum chloride.[14]

EXPERIMENTAL

A solution of 43.5 g. (0.605 mole) of β-propiolactone in 100 ml. of benzene was added dropwise during 45 min. to a stirred mixture of 300 g. (2.25 moles) of anhydrous aluminum chloride and 400 ml. of sodium-dried, thiophene-free benzene. The mixture was heated for 18 hr. under reflux, cooled, and poured over ice and hydrochloric acid. The aqueous layer was extracted with ether and the combined organic phases were washed with water, 0.1*N* potassium hydroxide solution and water, then dried over sodium sulfate. Solvent was removed by flash distillation and the residue was distilled through a 30-cm. spiral-wound column with total reflux head. Indanone (61.5 g., 77%) boiled at 84–85°/1.5 mm., m.p. 40° (lit.[9] m.p. 40–42°); its 2,4-dinitrophenylhydrazone melted at 256.5–257.5° (lit.[15] m.p. 258°).

The distillation residue (46.5 g.) was extracted with petroleum ether (b.p. 60–80°) in a Soxhlet extractor. Concentration of the extract yielded 10.1 g. of yellow oil, whose infrared spectrum showed it to be mainly indanone. The oil was dissolved in a minimum of ethanol and added to a solution of 15 g. of 2,4-dinitrophenylhydrazine in ethanol. The immediate precipitate of indanone-2,4-dinitrophenylhydrazone was filtered and crystallized from ethyl acetate, then from glacial acetic acid; wt., 7.4 g. (4%), m.p. 256–257°. The total yield of indanone was thus 81%.

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Communications TO THE EDITOR

The Reaction of *N*-Chlorobenzamide with Potassium Fluoride

Sir:

We should like to report an unusual example of the Hofmann reaction occurring in a nonaqueous medium. A mixture of 15.5 g. (0.1 mole) of *N*-chlorobenzamide[1] and 2.9 g. (0.05 mole) of anhydrous potassium fluoride in 100 ml. of dry benzene was refluxed for 12 hr., during which time the mixture became orange colored. After cooling, filtration gave 13.5 g. of colorless solid from which the organic material was extracted with and recrystallized from ethanol to yield *N*-benzoyl-*N'*-phenylurea, m.p. 206–208° (reported, 206°).[2] A portion of the alcohol solution gave a positive test for chloride ion with silver nitrate, whereas *N*-chlorobenzamide does not.

This reaction of *N*-chlorobenzamide with potassium fluoride also takes place when dry cyclohexene is used as solvent. Refluxing 15.5 g. (0.1 mole) of *N*-chlorobenzamide with 5.8 g. (0.1 mole) of potassium fluoride gave 14.5 g. of precipitate from which the urea was extracted. This would seem to indicate that formation of phenyl isocyanate is the rate-determining step in the reaction, and is followed by immediate reaction with *N*-chlorobenzamide to form the urea. If this were not the case, the predominant reaction would be simply the formation of a mole of phenyl isocyanate when equimolar proportions of reactants were used. The reaction does not occur in the absence of potassium fluoride, since refluxing a mixture of *N*-chlorobenzamide and dry benzene yields no urea.

A probable mechanism of formation is suggested below, with phenyl isocyanate as the likely intermediate. The same product, *N*-benzoyl-*N'*-phenylurea, was obtained by the authors by refluxing *N*-chlorobenzamide with phenyl isocyanate in dry benzene and purifying the product by recrystallization from ethanol.

The reaction of *N*-chlorobenzamide with phenyl isocyanate is probably best represented as:

$$C_6H_5{-}N{=}C{=}O + C_6H_5CONH \longrightarrow$$

$$C_6H_5{-}N{=}C(OH){-}N(Cl){-}COC_6H_5$$

$$C_6H_5NHCO{-}N(Cl){-}COC_6H_5 + H_2O \longrightarrow$$

$$C_6H_5NHCONHCOC_6H_5 + HOCl$$

Although the chlorine-containing addition product has not been isolated and identified, it would be anticipated that its hydrolysis would be rapid to yield the urea. Preliminary results do not distinguish between formation of *N*-fluorobenzamide followed by dehydrofluorination and rearrangement,

$$C_6H_5CONH(Cl) + K^+F^- \longrightarrow C_6H_5CONH(F) + K^+Cl^-$$

$$C_6H_5CONH(F) \rightarrow HF + [C_6H_5{-}C(=O){-}N] \longrightarrow C_6H_5NCO$$

and a mechanism involving behavior of fluoride ion as a base:

$$C_6H_5CONH(Cl) + F^- \longrightarrow HF + [C_6H_5CO{-}N{-}Cl] \longrightarrow$$

$$Cl^- + [C_6H_5C(=O){-}N] \longrightarrow C_6H_5NCO$$

The latter would agree with a publication[3] indicating the applicability of fluoride ion as a base for decarboxylation, and with the mechanism of the Hofmann rearrangement in aqueous media. This suggests a possible general usefulness of potassium fluoride as a base in anhydrous media for many reactions, which is currently being studied.

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Crystalline Glucomannan from Slash Pine

Sir:

In 1951, Yundt[1] reported the isolation of a crystalline fragment from slash pine hemicellulose which contained mannose units. Other sugar units were not fully identified. Later a similar crystalline material was isolated by Nelson[2] who found that glucose as well as mannose residues were present.

(1) A. P. Yundt, *Tappi*, 34, 94 (1951).

(2) R. Nelson, Buckeye Cellulose Corp., personal communication.

Using the techniques suggested by Yundt, with slight modifications, and starting with a slash pine holocellulose, a crystalline glucomannan was isolated, which, on hydrolysis, gave 77% mannose and 23% glucose. Small amounts of ash, but no other sugar units were present.

The sugars were identified chromatographically and by the preparation of crystalline derivatives. The rod-shaped crystals were about 2.5 μ long and showed strong birefringence under polarized light. X-ray powder diagrams and chromatographic data were obtained at various stages of the purification, in the course of which other sugar units (xylose and galactose) were gradually removed. The final X-ray diffraction of the dry material showed relatively sharp peaks.

In future work, the degree of polymerization of the glucomannan fragment, its physicochemical properties, and the oligosaccharides obtained on graded hydrolysis will be studied.

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Preparation of 1,2,3,4,5-Pentamethylcyclopentadiene, 1,2,3,4,5,5-Hexamethylcyclopentadiene, and 1,2,3,4,5-Pentamethylcyclopentadienylcarbinol

Sir:

The author wishes to report the synthesis of the novel compounds: 1,2,3,4,5-pentamethylcyclopentadiene (I), 1,2,3,4,5,5-hexamethylcyclopentadiene (II), and 1,2,3,4,5-pentamethylcyclopentadienylcarbinol (III). These compounds have been unavailable thus far due to inherent difficulties in the exhaustive methylation of cyclopentadiene. They are of obvious interest as nondimerizing cyclopentadiene derivatives, for instance, in photoisomerization reactions.[1] Of special interest are the derived nonclassical cations, one of which is intensely colored.[2]

Preparation of I: Treatment of tiglaldehyde with 2-butenyl-2-lithium[3] gave di(*sec*)-2-butenylcarbinol (IV), b.p. 56.3° (1.5 mm.) n_D^{20} 1.4719 ν(C=C) 1632 cm.$^{-1}$ (m). Oxidation of IV with active manganese dioxide[4] in pentane gave di(*sec*)-2-butenyl ketone (V) in good yield, b.p. 58.0° (4.2 mm.) n_D^{20} 1.4731. $\lambda_{max}^{C_2H_5OH}$ 239.6, 328 mμ, ϵ_{max} 1.22 $\times$ 10^4, 47. ν(C=C—C=O), 1642 cm.$^{-1}$ (vs). Cyclization of V in formic acid–phosphoric acid in accordance with the Nazarov ring closure[5] gave in good yield 2,3,4,5-tetramethylcyclopent-2-en-1-one (VI) b.p. 59.8° (3.3 mm.) n_D^{20} 1.4772. $\lambda_{max}^{C_2H_5OH}$ 236, 302 mμ; ϵ_{max}, 1.39 $\times$ 10^4, 97.6. ν(C=O), 1700 cm.$^{-1}$ (vs); ν(C=C), 1650 cm.$^{-1}$ (s). Treatment of VI with methyllithium gave the expected tertiary alcohol as the initial product. Water was lost spontaneously upon addition of a trace of iodine; distillation of the product yielded I (75%), b.p. 58.3° (13.5 mm.) n_D^{20} 1.4748. Mass spec. mol. wt. 136. $\lambda_{max}^{isooctane}$ 232 (sh), 248, 265 (sh) mμ ϵ_{max} 2780, 3180, 2730. ν(C=C—C=C), 1653 cm.$^{-1}$ (m), 1620 cm.$^{-1}$ (w).

Preparation of II: Addition of I to one equivalent of sodamide[6] in liquid ammonia gave smoothly pentamethylcyclopentadienyl sodium (VII); addition of one equivalent of methyl iodide to VII gave II (67% yield), b.p. 52.8° (6.4 mm.) n_D^{20} 1.4719; mass spec. mol. wt. 150. $\lambda_{max}^{isooctane}$ 252.4 mμ ϵ_{max} 4140. ν(C=C—C=C) 1654 cm.$^{-1}$ (m), 1620 cm.$^{-1}$ (w). A characteristic strong band occurred at 1080 cm.$^{-1}$ nmr spectrum (40 M.c.) in c.p.s. rel. to internal $Si(CH_3)_4$ capillary: −36.4, rel. area 6 (*gem*-dimethyl); −67.8, rel. area 12 (four vinyl methyl groups).

Preparation of III: VII was prepared as above. The ammonia was removed, finally *in vacuo*. The residue was dispersed in tetrahydrofuran (distilled from lithium aluminum hydride); 1 equivalent of ethyl chloroformate (VIII) was now added. After 1-hr. reflux, sodium chloride was removed by filtration. Tetrahydrofuran and excess VIII were removed by distillation. The ester residue was reduced with lithium aluminum hydride in ether. The product was III in 52% yield, b.p. 65.5° (1.1 mm.) n_D^{20} 1.4955. The distillate crystallized, m.p. 30.5°: λ isooctane 262.4 mμ (ϵ, 3230); ν(O—H), 3580 cm.$^{-1}$ (vs); ν(C=C—C=C) 1656 cm.$^{-1}$ (m); ν(C—O) 1040 cm.$^{-1}$ (vs).

Anal. Calcd. for I ($C_{10}H_{16}$): C, 88.14; H, 11.86. Found: C, 87.89; H, 12.02. Calcd. for II ($C_{11}H_{18}$): C, 87.90; H, 12.10. Found: C, 87.74; H, 11.91. Calcd. for III ($C_{11}H_{18}O$): C, 79.44; H, 10.93. Found: C, 79.71; H, 10.99. I, II, and III were homogeneous in vapor phase chromatography. Absorption above 3000 cm.$^{-1}$ or at 870–900 cm.$^{-1}$ characteristic of exocyclic methylene is absent in the infrared spectra of all three compounds. IV, V, and VI gave satisfactory C—H analyses.

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