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Dehydration of *cis*- and *trans*-2-Phenylcyclohexanols[1]

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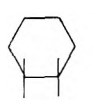
The dehydration of *trans*-2-phenylcyclohexanol by 85% phosphoric acid has been reinvestigated using infrared, ultraviolet, and mass spectrometry to ascertain the composition of the products. Extensive rearrangement occurs to give a product containing *ca.* 14% 1-phenylcyclohexene, 20% unconjugated 3- and 4-phenylcyclohexenes, 17% benzalcyclopentane, 46% unconjugated 1-, 3-, and 4-benzylcyclopentene and 4% 1,3-endoethylene-1,2,3,4-tetrahydronaphthalene. These findings are in substantial agreement with results independently obtained by Schaeffer and Collins,[3] as is the observation that dehydration of *cis*-2-phenylcyclohexanol involves substantially no rearrangement.

Pyrolysis of 2-phenylcyclohexyl methyl sulfite[4] led to 57% 1-phenylcyclohexene and 43% 3-phenylcyclohexene with less than 2% ring contraction product starting with the *cis* isomer. On the other hand, in the case of the *trans* isomer about 21% of the pyrolysis product had suffered ring contraction.

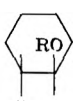
Introduction. It was reported earlier,[5] on the basis of refractive index measurements, that in the dehydration of the 2-phenylcyclohexanols by 85% phosphoric acid, the *cis* isomer (I) gave largely 1-phenylcyclohexene, whereas the *trans* isomer (II) led to 3-phenylcyclohexene. The subsequent preparation, by other means, of pure 3-phenylcyclohexene and measurement of its refractive index,[6,7] however, invalidated the earlier conclusion with respect to the product composition from the *trans* isomer (II). We have therefore reinvestigated the products of the *trans* isomer (II) by analysis with the now readily available tools of ultraviolet and infrared spectroscopy and mass spectrometry. At the same time we reinvestigated briefly the products of dehydration of the *cis* isomer (I) as well as those of the pyrolysis of the 2-phenylcyclohexyl methyl sulfites, III and IV since these products had also been deemed to be mixtures of 1- and 3-phenylcyclohexene on the basis of refractive index only.[4,5]



H_5C_6 OR

I, R=H

III, R=OSO_2CH_3



H_5C_6

II, R=H

IV, R=OSO_2CH_3

Our results confirm (and, in one minor respect, extend) the findings of Schaeffer and Collins[3]—obtained by the entirely different technique of isotope dilution— that dehydration of *trans*-2-phenylcyclohexanol (II) (but not of the *cis* isomer I) leads to extensive ring contraction. Ring contraction, though to a lesser extent, also occurred in the pyrolysis of the *trans* methyl sulfite IV but not with *cis*-2-phenylcyclohexyl methyl sulfite (III).

Results. Dehydration of *trans*-2-phenylcyclohexanol with 85% phosphoric acid[5] gave a hydrocarbon fraction whose refractive index (1.5493–

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(2) (a) From the Ph.D. thesis of J. W. McCoy. (b) Present address: Department of Chemistry, University of Pennsylvania, Philadelphia 4, Pa.

(3) H. J. Schaeffer and C. J. Collins, *J. Am. Chem. Soc.*, **78**, 124 (1956).

(4) G. Berti, *J. Am. Chem. Soc.*, **76**, 1213 (1954).

(5) C. C. Price and J. V. Karabinos, *J. Am. Chem. Soc.*, **62**, 1159 (1940).

(6) E. R. Alexander and A. Mudrak, *J. Am. Chem. Soc.*, **72**, 1810 (1950).

(7) A. Berlande, *Compt. rend.*, **213**, 437 (1941).

TABLE I

PROPERTIES OF REFERENCE HYDROCARBONS

Compound	B.P., °C.	Mm.	n_D^{20}	λ, mμ	ϵ_{EtOH}	Ref.
1-Phenylcyclohexene	124–127	14–15	1.5692	—	—	9
	128	16	1.5645 (25°)	247	12,000[a]	10
	82	1	1.5660 (25°)	—	—	11
			1.5690	246	12,120	12
			1.5664 (25°)	248	12,170[b]	13
			1.5692	247	12,940	14
3-Phenylcyclohexene	235	atm.	1.5440 (26°)	—	—	7
	76–79	2	1.5448	—	—	6
			1.5448	—	—	3
			1.5444	253	653	14
			1.5417 (25°)	248	232	13
	118–119	19	1.5449	248	775[b]	c
Phenylcyclohexane	105–115	10–15	1.5249	—	—	9
	111–113	13	1.5237 (25°)	—	—	14
	107	13	1.5255[b]	—	—	c
Benzalcyclopentane	108–118	8	(1.5518)[d]	—	—	3
	86	1.9	1.5752	248	17,150[b]	c
1-Benzylcyclopentene	113–117	18	1.5355–1.5510[e]	—	—	9
	103–107	11	1.5367	—	—	3
	108–109	14	1.5363	248	750[b]	c
Benzylcyclopentane			1.5170–1.5245[f]	—	—	9
	70–72	5	1.5200	—	—	15
	103–104	12.5	1.5178[b]	—	—	c
1,3-Endoethylene-1,2,3,4-tetrahydronaphthalene (V)	117	25	—	—	—	16
	115	15	—	—	—	17
	108–108.5	13.5	1.5555[b]	248	200[b]	c

[a] In cyclohexane. [b] Data used in calculations, see text. [c] This work. [d] Only 66% purity claimed for this sample. [e] At temperatures ranging from 17.5 to 23°. [f] At temperatures ranging from 17 to 21°.

1.5498) was considerably different from that (1.5553) previously observed.[5,8] Estimation of the composition of this material—assuming it to be a binary mixture of 1- and 3-phenylcyclohexane—on the basis of refractive index and ultraviolet extinction coefficient at 252 mμ (*cf.* Table I) led to inconsistent results. Moreover, the infrared spectrum of the dehydration product showed numerous bands not present in either 1- or 3-phenylcyclohexene. On the assumption that part of the material might have suffered ring contraction (*cf.* ref. 15), it was hydrogenated and the infrared spectrum of the hydrogenated material was recorded and compared with the spectra of pure phenylcyclohexane and benzylcyclopentane. Both hydrocarbons were clearly present. Mass spectrometric analysis of the hydrogenated material indicated it to be *ca.* 35% phenylcyclohexane and 65% benzylcyclopentane. Moreover, the presence of benzalcyclopentane in the dehydration product prior to hydrogenation was suggested by the isolation of benzaldehyde from an ozonolysis reaction.

Careful inspection of the mass spectrum of the hydrogenated product disclosed a very large residual peak at mass 129 not present in the mass spectrum of either phenylcyclohexane or benzylcyclopentane. This peak also occurred in the spectrum of the product before hydrogenation. Since 1,3-endoethylene-1,2,3,4-tetrahydronaphthalene (V) is reported to be obtained in the cyclization of the olefin resulting from dehydration of 1-benzylcyclopentanol,[17] and since this hydrocarbon might well have a large mass peak at mass 129, due to loss of

(8) Calculated from the refractive indices of hydrocarbon standards and the composition of the products reported in ref. 5.

(9) G. Egloff, "Physical Constants of Hydrocarbons," Reinhold Publishing Corp., New York, N. Y., Vol. III (1946), pp. 265, 276.

(10) A. C. Cope, F. S. Fawcett, and G. Munn, *J. Am. Chem. Soc.*, **72**, 3399 (1950).

(11) R. C. Carlin and H. P. Landerl, *J. Am. Chem. Soc.*, **75**, 3969 (1953).

(12) R. T. Arnold and P. N. Richardson, *J. Am. Chem. Soc.*, **76**, 3649 (1954).

(13) J. Weinstock and F. G. Bordwell, *J. Am. Chem. Soc.*, **77**, 6706 (1955).

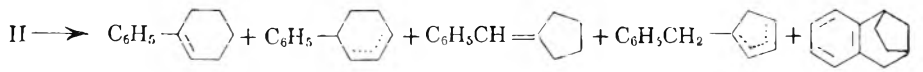
(14) R. Y. Mixer and W. G. Young, *J. Am. Chem. Soc.* **78**, 3379 (1956).

(15) D. V. Nightingale and M. Maienthal, *J. Am. Chem. Soc.*, **72**, 4823 (1950).

(16) W. Baker and W. G. Leeds, *J. Chem. Soc.*, 974 (1948).

(17) L. H. Groves and G. A. Swan, *J. Chem. Soc.*, 871 (1951).

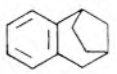
TABLE II



V

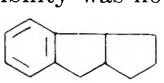
This work:	20%	13%	17%	46%	4%
Ref. 3	21%	15%[a]	*Ca.* 20%	(32%)[b]	[c]

[a] 9% of 3-phenylcyclohexene and 6% of 4-phenylcyclohexene. [b] This figure refers to 1-benzylcyclopentene only. [c] Not analyzed for.



V

the ethylene bridge subsequent to ionization in the mass spectrometer chamber, the presence of V in the dehydration product of II was suspected, especially since phthalic anhydride (in small yield) was isolated from the permanganate oxidation of the product mixture obtained in the dehydration of II. The mass spectrum of a synthetic sample of compound V[16] does, indeed, have an unusually intense peak at mass 129 and mass spectral analysis of the mixture obtained in the dehydration of II followed by hydrogenation showed it to consist of 33.5% phenylcyclohexane, 62.6% benzylcyclopentane, and 3.9% V. Assuming this composition there were still small residual peaks at mass 41 and 65. It is possible that these may be due to very small quantities of other isomers, such as 3,4-benzo[3.3.0]bicyclooctane (VI) but this possibility was not explored further.



VI

In any case, a synthetic mixture of the above composition (33.5:62.6:3.9) agreed well with the hydrogenation product in refractive index (1.5213 *vs.* 1.5217) and infrared spectrum.

Complete calculation of the composition of the dehydration mixture of II from ultraviolet and refractive index data was unfortunately not feasible, since the data were not sufficiently mathematically independent to allow a sensitive calculation. The approximate benzalcyclopentane content of the mixture was therefore estimated as 17% by comparison of the 11.61μ infrared band of the product mixture with that of synthetic mixtures of varying benzalcyclopentane content. It follows that the benzylcyclopentene content of the mixture must be 46%, since the total benzylcyclopentane after reduction amounts to 63% (*vide supra*). The distribution of the phenylcyclohexene fraction as between conjugated and unconjugated isomer can then be calculated from the ultraviolet data (Table I, marked values) to be 20% 1-phenylcyclohexene and 13% 3-phenylcyclohexene.[18]

It is of interest to compare out data with those of Schaeffer and Collins.[3] Since these investigators have shown that 4-phenylcyclohexene as well as 3-phenylcyclohexene is present in the dehydration mixture of II, and since neither of these isomers would be expected to have strong ultraviolet absorption, it is evident that our purported analysis of 3-phenylcyclohexene (based on UV data) is, in fact, an analysis of unconjugated (combined 3- and 4-)phenylcyclohexene. Similarly, our analysis of benzylcyclopentene (which is based on the difference between total material giving benzylcyclopentane on hydrogenation and benzalcyclopentane as analyzed by infrared) is, in fact, an analysis for total unconjugated (1-, 3-, and 4-)benzylcyclopentene.[19] Taking these facts into account our analysis and that of Schaeffer and Collins[3] are summarized in Table II. It is evident that the two sets of data are in good agreement, except in the case of benzylcyclopentene. However, in this case our figure, as explained above, refers to total benzylcyclopentene whereas that of Schaeffer and Collins[3] refers to 1-benzylcyclopentene only. Since the data of Schaeffer and Collins account for only about 88% of the distilled material, and of the missing 12%, only 4% are accounted for by V, the discrepancy would disappear if the mixture contained about 11 ± 3% of 3- and 4-benzylcyclopentene. In any case, our mass spectral analysis shows convincingly that the dehydration mixture contains 63% of material reducible to benzylcyclopentane.

Dehydration of *cis*-2-phenylcyclohexanol (I) with 85% phosphoric acid gave a hydrocarbon mixture whose refractive index (1.5637–41) was in good agreement with earlier findings (1.5644[5,8]). Hydrogenation of this product led to material which, according to mass spectrometric analysis, contained 97.4% phenylcyclohexane and 2.6% benzylcyclopentane, indicating that very little ring contraction had occurred in the dehydration of I. Schaeffer and Collins[3] report that the dehydration product contains 88% 1-phenylcyclohexene and 2% 3-phenylcyclohexene leaving open the question of the remaining 10% of material. It is

(18) The infrared spectrum of the product closely resembled that of a synthetic mixture containing 20% 1-phenylcyclohexene, 13% 3-phenylcyclohexene, 17% benzalcyclopentane, 46% 1-benzylcyclopentene, and 4% V.

(19) There is an implicit assumption here that 3- and 4-benzylcyclopentene do not absorb appreciably at 11.61μ, the band used for analyzing benzalcyclopentane. The general consistency of our results, both internally and with those of ref. 3 suggests that this assumption is sound.

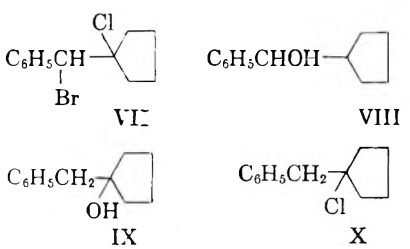
evident that not all this material is a product of ring contraction.

The finding of ring contraction in the dehydration of *trans*-2-phenylcyclohexanol (II) suggested a reexamination of the pyrolysis of *cis*- and *trans*-2-phenylcyclohexyl methyl sulfite (III and IV),[4] since the possibility of ring contraction was not previously considered in the analysis of the products of this reaction. Pyrrolysis of the *cis* isomer (III) gave a hydrocarbon fraction boiling at 115–130°/15 mm. The refractive index of the product (1.5583) was substantially lower than that (1.5625) reported earlier.[4] The discrepancy may be due to the fact that in the previous investigation[4] the reaction product was distilled over sodium at atmospheric pressure, since we were able to show (see Experimental) that 3-phenylcyclohexene, one of the components of the pyrolysis mixture, is not stable under such conditions.[20] Hydrogenation of the pyrolysis product of III gave material which, according to mass spectrometric analysis contained 98.3% phenylcyclohexane and 1.7% benzylcyclopentane, proving substantial absence of ring contraction. The pyrolysis product, according to refractive index and ultraviolet absorption (ϵ_{252} = 7,140) contained 57% 1-phenylcyclohexene and 43% 3-phenylcyclohexene. (Calculated for this composition: n_D^{20} 1.5585, ϵ_{252} 7,140; assuming n_D^{20} 1.5692, ϵ_{252} 12,000 for 1-phenylcyclohexene, n_D^{20} 1.5444, ϵ_{252} 700 for 3-phenylcyclohexene.) This finding changes the previous data[4] only qualitatively.

In contrast, hydrogenation of the pyrolysis product of *trans*-2-phenylcyclohexyl methyl sulfite IV gave a product which, according to mass spectrometric analysis, was 78.6% phenylcyclohexane and 21.4% benzylcyclopentane. Here, evidently, ring contraction had taken place (though to a lesser extent than in the phosphoric acid dehydration of alcohol II) and the previous analysis of the pyrolysis product[4] is therefore not valid. A complete analysis of this product was not attempted in the present investigation.

Synthesis of reference hydrocarbons. 1-Phenylcyclohexene, 3-phenylcyclohexene, and 1-benzylcyclopentene were prepared by methods described in the literature,[6,7,21] and the properties of two of the reaction products are shown in Table I to be in good agreement with those reported by other investigators. Considerable difficulties were encountered in the synthesis of benzalcyclopentane. The best sample of benzalcyclopentane obtained in this investigation resulted from the dehalogenation of phenyl(1-chlorocyclopentyl)bromoethane (VII) with zinc; this sample was analytically pure and had n_D^{20} 1.5752; ϵ_{252} 18,400. Successive fractions of this material did not differ in boiling point or refractive index. Slightly impure benzalcyclopentane (n_D^{20} 1.5655) was obtained by the Chugaev reaction of cyclopentyl phenyl carbinol (VIII); this material appeared to contain some sulfur-containing by-products but its infrared spectrum was very similar to that of the material described above.

Other likely procedures failed to yield benzalcyclopentane.[22] Dehydration of 1-benzylcyclopentanol (IX) with iodine and with oxalic acid gave the unconjugated isomer 1-benzylcyclopentene, which was also the major product of the dehydrohalogenation of 1-benzylcyclopentyl chloride (X) with triethanolamine. This preference for formation of the nonconjugated isomer is surprising. It must be due to the preference for an endocyclic bond over an exocyclic one,[23] since dehydration of benzyl diethyl carbinol, $C_6H_5CH_2COH(C_2H_5)_2$ and dehydrohalogenation of the corresponding chloride, $C_6H_5CH_2CCl(C_2H_5)_2$, give the conjugated olefin 1-phenyl-2-ethyl-2-butene, $C_6H_5CH{=}C(C_2H_5)_2$.[24]



Other preparations of benzalcyclopentane which failed are dehydrohalogenation of cyclopentylphenylchloromethane, $C_6H_5CHClC_5H_9$ with boiling pyridine (quaternization appeared to occur), and with boiling aqueous triethanolamine [cyclopentyl phenyl carbinol (VIII) resulted]; dehydration of cyclopentyl phenyl carbinol (VIII) with potassium hydrogen sulfate or phosphoric acid (complex mixtures resulted); and dehydration of 1-benzylcyclopentanol IX with hot solid potassium hydroxide. The latter procedure yielded toluene in almost mole-per-mole yield, apparently as the result of a base-induced cleavage. The other product of the assumed cleavage, cyclopentanone, was probaly resinified by the potassium hydroxide. It is known that treatment of benzyl dimethyl carbinol,

(20) Berti's crude product had about the same refractive index (1.5580[4]) as our product. Similarly, our pyrolysis product from the *trans*-sulfite IV had n_D^{20} 1.5550, in fair agreement with Berti's product prior to distillation (n_D^{20} 1.5560) but in poor agreement with his distilled product (n_D^{20} 1.5598). H. Pines and M. Kolobielski, *J. Am. Chem. Soc.*, **79**, 1698 (1957) have recently shown that 1-phenylcyclohexene undergoes disproportionation and dehydrogenation when heated above 200° with sodium-benzylsodium.

(21) Y. I. Denisenko, *Ber.*, **69**, 1668 (1936); L. Piaux, *Compt. rend.*, **199**, 1127 (1934).

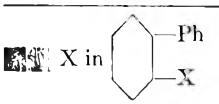
(22) Difficulties in the preparation of benzalcyclopentane are also reported in ref. 3.

(23) *Cf.* H. C. Brown, *J. Org. Chem.*, **22**, 439 (1957).

(24) A. Klages, *Ber.*, **37**, 1724 (1904); K. Auwers and F. Eisenlohr, *J. prakt. Chem.*, [2] **82**, 94 (1910). Unfortunately the structural evidence for the product is not convincing. See also J. M. Lamberti and P. H. Wise, *J. Am. Chem. Soc.*, **75**, 4787 (1953).

TABLE III

ELIMINATION FROM 2-PHENYL-SUBSTITUTED CYCLOHEXYL COMPOUNDS

 X in	Stereo-isomer	Method	Products % 1-Phenyl[a]	3-Phenyl[a]	Ring Contr.	Ref.
OH	*cis*	H_3PO_4	88[3]	2[3]	3[b]	3, *b*
OH	*trans*	H_3PO_4	17,[b] 21[3]	9[c]	63[b]	3, *b*
OAc	*cis*	Pyrol.	7	93	0	6
OAc	*trans*	Pyrol.	86.5	13.5	0	6
OCS_2CH_3	*cis*	Pyrol.	0–4	96–100	0	6
OCS_2CH_3	*trans*	Pyrol.	88	12	0	6
OSO_2CH_3	*cis*	Pyrol.	57	43	<2	*b*
OSO_2CH_3	*trans*	Pyrol.	[d]	[c]	21	*b*
NH_2	*trans*	HNO_2	~0	~0	~100	15
$N^+(CH_3)_3$	*cis*	OH, Δ	100	0	0	12
$N^+(CH_3)_3$	*trans*	OH, Δ	100	0	0	12, 13
$O \leftarrow N(CH_3)_2$	*cis*	Pyrol.	9	91	0	26
$O \leftarrow N(CH_3)_2$	*trans*	Pyrol.	85	15	0	26

[a] -cyclohexene. [b] This work. [c] Also 6% 4-phenylcyclohexene.[3] [d] Combined yield of phenylcyclohexenes: 79%.

$C_6H_5CH_2COH(CH_3)_2$ with hot potassium hydroxide yields toluene and acetone.[25]

Discussion. The mechanism of dehydration of *trans*-2-phenylcyclohexanol (II) with phosphoric acid has been adequately presented by Schaeffer and Collins[3] who were able, by radiochemical means, to ascertain the extent of phenyl migration in this reaction. The results of several recent studies of elimination from 2-phenyl-substituted cyclohexyl compounds are summarized in Table III.

The reactions may be divided into four classes, *viz.:* (1) Reactions which proceed stereospecifically (or nearly so) with *cis* elimination; in this class are the pyrolysis of acetate,[6] xanthates,[6] tertiary amine oxides,[26] and the *trans* isomer of 2-phenylcyclohexyltrimethylammonium hydroxide.[12,13] Where two products of *cis* elimination are possible, the conjugated 1-phenylcyclohexene is preferred over the unconjugated 3-phenylcyclohexene by a ratio of about 85–88 to 12–15. (2) Reactions which appear to be stereospecific with *trans* elimination; the acid-catalyzed dehydration of *cis*-2-phenylcyclohexanol seems to be in this category, since it gives *ca.* 88% of the conjugated 1-phenylcyclohexene.[3] (3) Reactions of low stereospecificity but not involving ring contraction, such as the pyrolysis of *cis*-2-phenylcyclohexyl methyl sulfite. (4) Reactions involving ring contractions. Here are found the pyrolysis of *trans*-2-phenylcyclohexyl methyl sulfite, the acid-catalyzed dehydration of *trans*-2-phenylcyclohexanol and the reaction of *trans*-2-phenylcyclohexylamine with nitrous acid,[15] with the extent of ring contraction increasing in the order given. These data suggest that as the ionic character of the transition state increases (from what may be essentially an ion pair in the pyrolysis of the sulfite[4,27] to an almost free solvated carbonium ion in the nitrous acid reaction), the amount of ring contraction also increases. The large amount (43%) of unconjugated product (3-phenylcyclohexene) resulting in the pyrolysis of *cis*-2-phenylcyclohexyl methyl sulfite may also be explained on the basis of an ion-pair mechanism, since the methyl sulfite part of the ion pair may have a tendency to abstract an adjacent proton on the same side of the molecule (*i.e.*, *cis*) and in the *cis* isomer, a hydrogen *cis* to the methyl sulfite group is available only at position 3 (*cf.* Fig. 1).

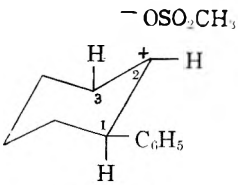


FIGURE 1

EXPERIMENTAL[28]

cis-2-Phenylcyclohexanol (I), m.p. 40–42° (lit.[4] 40–42°) was prepared by Raney nickel hydrogenation of *o*-phenylphenol at 100–110° and 2000–2200 p.s.i.[5]

trans-2-Phenylcyclohexanol (II). Equilibration of commercial mixed 2-phenylcyclohexanol with aluminum isopropoxide[29] was found to be a more convenient route to this isomer than the previously published procedure.[6] Mixed 2-phenylcyclohexanol (417 g., Matheson, Co., Inc.) was equilibrated by boiling with 2700 ml. of anhydrous isopropyl alcohol containing 167 g. aluminum isopropoxide and 9 ml. acetone at reflux for 90 hr. After 2 l. of solvent was distilled, the residue was poured into 3.5 l. of water containing 300 ml. hydrochloric acid. The organic layer was separated, the aqueous layer extracted with ether, and the combined

(25) D. Sontag, *Ann. chim.*, [11] **1**, 384 (1934).

(26) A. C. Cope and C. L. Bumgardner, *J. Am. Chem. Soc.*, **79**, 960 (1957).

(27) C. C. Price and G. Berti, *J. Am. Chem. Soc.*, **76**, 1207, 1211 (1954).

(28) Elementary analyses by Micro-Tech Laboratories, Skokie, Ill. Infrared analyses by Mr. D. Sweeney on a Perkin-Elmer Model 21 double-beam instrument and by Mr. Rolland Ro on a Baird double-beam instrument. Mass spectra by Mr. George W. Young on a Consolidated Model 21-103A mass spectrometer.

(29) *Cf.* W. G. Dauben, G. J. Fonken and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956). We thank Professor Dauben for communicating this method to us in advance of publication.

TABLE IV

PHYSICAL DATA ON PRODUCT MIXTURES FROM DEHYDRATION OF *cis*- AND *trans*-2-PHENYLCYCLOHEXANOLS

Expt. No.	Alcohol Dehydrated	Dehydration Method	Yield, %	Boiling Range, °C.	Press., Mm.	n_D^{20}	ϵ_{252}	ϵ_{248}
1	*cis*	H_3PO_4	88	115–130	16	1.5641	9400	10,000
2	*cis*	H_3PO_4	89	115–130	16	1.5637	—	—
3	*trans*	H_3PO_4	85	105–117	12	1.5493	5880	5,830
4	*trans*	H_3PO_4	87	109–12[illegible]	13	1.5498	5990	—
5	*cis*	Berti[4]	90	115–130	15	1.5583	7140	7480
6	*trans*	Berti[4]	80	116–132	15	1.5550	6950	7040

organic material washed with dilute acid and water, dried, and distilled. After two recrystallizations the *trans*-alcohol melted at 56–57° (lit.[6] 56–57.5°).

Dehydration by phosphoric acid. The procedure was that reported earlier,[5] involving gentle boiling under reflux with an equal volume of phosphoric acid for 4 hr. After dilution with water, extraction with ether, washing with water and drying, the olefin mixtures were distilled through a modified Claisen flask and then redistilled at reduced pressure from sodium. The properties of the products are summarized in Table IV.

Ozonization of 7.9 g. of the dehydration product from the *trans*-alcohol and phosphoric acid followed by distillation gave 0.5 g. of material boiling below 105° (13 mm.), which gave a precipitate with 2,4-dinitrophenylhydrazine. The hydrazone, after recrystallization from ethanol, had a melting point of 237–238°, undepressed on admixture with authentic benzaldehyde 2,4-dinitrophenylhydrazone. None of the cyclopentanone derivative could be isolated, even by alumina chromatography, although the procedure used readily separated a synthetic mixture of the dinitrophenylhydrazones of cyclopentanone and benzaldehyde.

Oxidation of 5 g. of the same mixture of olefins by boiling with aqueous potassium permanganate, followed by filtration and precipitation with acid yielded 2.1 g. of mixed acids, m.p. 120–180°. This was redissolved in a minimum amount of 10% potassium hydroxide. Reacidification precipitated *benzoic acid*, m.p. 119–121°. Continuous extraction of the mother liquor with ether gave 250 mg. of acid. After repeated sublimation and bicarbonate washing, *phthalic anhydride*, m.p. 129–130°, was obtained. Its identity was confirmed by mixed melting point and infrared spectra.

Berti dehydration.[4] The alcohols were converted to their methyl sulfite esters by treatment with methyl chlorosulfinite in pyridine and ether at −5°. The crude esters, *cis*-2-phenylcyclohexyl methyl sulfite (94%), n_D^{20} 1.5320 (lit.[4] 1.5313), and *trans*-2-phenylcyclohexyl methyl sulfite (89%), m.p. 46–48° (lit.[4] m.p. 48–50°), were pyrolyzed without purification and the olefins produced redistilled *in vacuo* over sodium to give material with properties as reported in Table III.

1-Phenylcyclohexene was prepared by heating 1-phenylcyclohexanol (from cyclohexanone and phenylmagnesium bromide), m.p. 60–61° (lit.[11] 62°) with an equal weight of potassium acid sulfate at 140–150° for 0.5 hr. The olefin was twice redistilled. Diagnostic infrared bands[30] were found at 9.44, 10.86, 12.44, 13.48, and 15.27μ (lit.[11] 10.86, 12.42, and 13.44μ).

3-Phenylcyclohexene was prepared both by the Chugaev procedure from *cis*-2-phenylcyclohexanol[6] (b.p. 118–119°/19 mm., n_D^{20} 1.5449) and by reaction of 3-bromocyclohexene[31] with phenylmagnesium bromide[7] (b.p. 114.5–115°/15 mm., n_D^{20} 1.5450). To obtain the low refractive index observed, which agrees with that reported by Alexander and Mudrak[6] and Schaeffer and Collins,[3] it appears important to distill at diminished pressure. Berlande[7] and Berti,[4] who distilled at atmospheric pressure, obtained material of somewhat higher refractive index, possibly due to thermal isomerization. The diagnostic infrared bands[30] of 3-phenylcyclohexene are at 11.23, 11.37, 12.70, 13.86, and 14.88μ (lit.[14] 11.17, 11.33, 12.67, 13.79, and 14.81μ).

1-Benzylcyclopentene (*A*) 1-Benzylcyclopentanol (IX, from cyclopentanone and benzylmagnesium chloride[3]), m.p. 59.5–61° (lit.[3] 58–60°) was dehydrated by heating with oxalic acid.[21] The material boiled at 108–109°/14 mm. and had n_D^{20} 1.5363. The material absorbed in the infrared at 9.32, 9.70, and 10.40μ. Diagnostic bands of benzalcyclopentane (see below) were absent. The same material, b.p. 102–104°/11.5 mm., n_D^{20} 1.5360, was obtained by dehydration of IX with iodine. (*B*) The carbinol IX was converted to the corresponding chloride by shaking with concentrated hydrochloric acid. Dehydrohalogenation with triethanolamine gave material boiling at 103–120°/12 mm., n_D^{20} 1.5362–1.5484. The infrared spectrum indicated that this material was principally 1-benzylcyclopentene.

Benzalcyclopentane (*A*) Crude 1-chloro-1-benzylcyclopentane (X, 208 g.) was brominated in boiling carbon tetrachloride by adding bromine dropwise under illumination by a tungsten projector lamp. The residue of crude α-(1-chlorocyclopentyl)benzyl bromide (VII) left after distillation of the solvent was added dropwise to a well stirred slurry of 150 g. of zinc powder in 1 l. of boiling ethanol. The exothermic reaction required occasional cooling. After addition was completed, another 50 g. of zinc was added and the mixture stirred for 8 hr. Dilution with an equal volume of saturated aqueous calcium chloride, extraction with ether, washing with water, drying and distillation gave 110 g. (65% from 1-benzylcyclopentanol) of crude olefin, b.p. 115–119°/12 mm.

Attempted distillation from sodium at 14 mm. appeared to lead to rearrangement to benzylcyclopentene, since the distillate had n_D^{20} 1.5360. However, distillation over sodium at 1.9 mm. gave material of constant boiling point (86°) and refractive index (n_D^{25} 1.5752).

Anal. Calcd. for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 90.94; H, 8.94.

The sample crystallized when cooled to −20°.

(*B*) Cyclopentylphenylcarbinol (VIII) was prepared in poor yield by the reaction of cyclopentylmagnesium bromide with benzaldehyde.[15] Much benzyl alcohol and cyclopentene were formed also. The desired carbinol boiled at 142–143.5°/13 mm., n_D^{20} 1.5412 (lit.[15] b.p. 110–112°/5 mm., n_D^{20} 1.5412). Application of the Chugaev procedure to this carbinol gave somewhat impure benzalcyclopentane, b.p. 122–123°/14.5 mm., n_D^{20} 1.5655 which did not crystallize at −20° and contained some sulfurous by-product. Nevertheless, the infrared spectrum of this sample was very similar to that of the sample from the above dehalogenation reactions. Diagnostic bands in the infrared are found at 9.84, 10.99, and 11.61μ.

1,3-Endoethylene-1,2,3,4-tetrahydronaphthalene (V) was pre-

(30) By "diagnostic infrared bands" are meant absorption bands which occur in the given compound but not in any of its isomers looked for in the product mixture.

(31) K. Ziegler, A. Spaeth, E. Schaaf, W. Schumann, and E. Winkelmann, *Ann.*, **551**, 80 (1942).

pared from benzene and cyclopentene-1-carboxylic acid[32] as described in the literature.[16] The material boiled at 108–108.5°/13.5 mm. and had n_D^{20} 1.5555. Diagnostic infrared peaks are found at 9.05, 9.45, 9.62, 10.20, 10.35, 10.56, 12.95, and 13.86μ.

Benzylcyclopentane was prepared by hydrogenation of benzylcyclopentene over Raney nickel catalyst at 44 p.s.i. and room temperature; b.p. 103–104°/12.5 mm., n_D^{20} 1.5178. The compound has a sharp absorption peak at 9.69μ and lesser peaks at 9.27 and 11.04μ.

Phenylcyclohexane was purified by fractionation of commercial material (Eastman) through a 24-inch helix-packed column, b.p. 107°/13 mm., n_D^{20} 1.5255. Diagnostic infrared peaks are found at 9.35, 9.94, 10.03, 11.29, and 11.58μ.

Hydrogenation of reaction products. The reaction products of runs 2, 4, 5, and 6 (Table III) were hydrogenated over Raney nickel at 32–45 p.s.i. at room temperature. The hydrogenated products had the following properties:

Run 4. B.p. 104–105°/13 mm., n_D^{20} 1.5217.

Run 5. B.p. 111–113°/15 mm., n_D^{20} 1.5261.

Run 6. B.p. 107–108°/14 mm., n_D^{20} 1.5240.

The distilled hydrogenation products were analyzed mass spectrometrically,[33] using the 92-peak for benzylcyclopentane (B), 104 for phenylcyclohexane (P) and (in run 4) 129 for 1,3-endoethylene-1,2,3,4-tetrahydronaphthalene (V). The results were as follows:

Run 2. 2.6% B, 97.4% P.

Run 4. 62.6% B, 33.5% P, 3.9% V (n_D^{20} calcd.[34] 1.5218. Found: 1.5217).

Run 5. 1.7% B, 98.3% P (n_D^{20} calcd.:[34] 1.5254. Found: 1.5261).

Run 6. 21.4% B, 78.6% P (n_D^{20} calcd.:[34] 1.5239. Found: 1.5240).

The infrared spectrum of the hydrogenation product of run 4 was compared with that of a synthetic mixture of the indicated composition and there was good agreement in the relative intensity of the peaks.

NOTRE DAME, IND.

(32) Prepared by Mr. Anthony T. Tu by saponification of the ester obtained according to the method developed by the Rev. Conrad Pillar in these laboratories and described by R. L. Kronenthal and E. I. Becker, *J. Am. Chem. Soc.*, 79, 1095 (1957).

(33) For a brief review with references see: E. L. Eliel, Th. J. Prosser and G. W. Young, *J. Chem. Ed.*, 34, 72 (1957).

(34) Using the marked values in Table I.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS UNIVERSITY]

Correlation of Ultraviolet Absorption Spectra with Structure of α,β-Unsaturated Acids and Derivatives[1]

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A correlation between the structure and ultraviolet absorption spectra of α,β-unsaturated acids and derivatives has been developed from data found in the literature. For alicyclic and acyclic types each added alkyl substituent at the olefinic double bond produces a bathochromic shift of *ca.* 8–10 mμ. For alicyclic acids a 5-mμ shift is obtained with any exocyclic double bond and each endocyclic double bond in a five- or seven-membered ring. Other structural features which affect the value of the absorption maximum in these compounds are discussed briefly, including hetero atom substitution at the olefinic double bond and extended conjugation. Examples of the utility of the correlation with respect to structure elucidation are presented.

The position and intensity of the ultraviolet region K-band absorption have been found valuable as an aid to structure elucidation, in particular for such compounds as α,β-unsaturated ketones,[3,4] aldehydes,[5] nitroölefins[6] and conjugated dienes.[3c,4] However, no summary correlation between structure and ultraviolet absorption maxima of α,β-unsaturated acids and derivatives has appeared, although their characteristic absorption region (205–230 mμ) is well recognized. Certain workers have noted, in limited series of compounds, the bathochromic displacements produced by increasing substitution at the olefinic double bond,[7–11] and the correlation between ultraviolet absorption and structure in a small group of alicyclic acids.[11,12] The present paper correlates the available ultraviolet spectra of α,β-unsaturated acids and deriva-

(1) Presented at the 132nd National Meeting of the AMERICAN CHEMICAL SOCIETY, New York, N. Y., September, 1957.

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(3) (a) A. E. Gillam and E. S. Stern, *An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry*, Edward Arnold, Ltd., London, 1954. (b) R. B. Woodward, *J. Am. Chem. Soc.*, 63, 1123 (1941); (c) R. B. Woodward, *J. Am. Chem. Soc.*, 64, 72 (1942); (d) R. B. Woodward, *J. Am. Chem. Soc.*, 64, 76 (1942); (e) L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 815 (1941).

(4) L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd Edition, Reinhold, N. Y., 1949, pp. 184–98.

(5) L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 565 (1943).

(6) E. A. Braude, E. R. H. Jones, and G. G. Rose, *J. Chem. Soc.*, 1104 (1947).

(7) (a) H. E. Ungnade and I. Ortega, *J. Am. Chem. Soc.*, 73, 1564 (1951). (b) H. E. Ungnade and I. Ortega, *J. Am. Chem. Soc.*, 74, 6313 (1952).

(8) J. Cason, N. L. Allinger, and D. E. Williams, *J. Org. Chem.*, 18, 842 (1953).

(9) E. A. Braude, *Ann. Repts. on Progr. Chem.* (*Chem. Soc. London*) 42, 105 (1945).

(10) L. J. Andrews, S. J. Cristol, S. L. Lindenbaum, and W. G. Young, *J. Am. Chem. Soc.*, 67, 715 (1945).

(11) E. R. H. Jones, G. H. Mansfield, and M. C. Whiting, *J. Chem. Soc.*, 4073 (1956).

(12) O. H. Wheeler, *J. Am. Chem. Soc.*, 78, 3216 (1956).

tives with their structure, employing several representative examples.

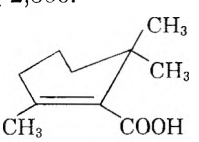
CORRELATION OF SPECTRA

Acyclic acids. Table II summarizes the reported ultraviolet spectra of most acylic α,β-unsaturated acids and esters of known structure. An acid and its corresponding methyl or ethyl ester or amide generally absorb at the same wave length.[13-16] ± 1 mμ, although the esters may often absorb at a slightly higher value and usually have a slightly larger extinction coefficient (in ethanol solvent). Those acids having a single α-substituent absorb at or below 208 mμ, whereas the β-substituted components have an average $\lambda_{max.}$ of 208 mμ.[17] The numerous α,β-disubstituted acids have an average absorption maximum of 216 mμ while the β,β-disubstituted compounds absorb at a slightly higher wave length, 218 mμ (average).[18,19] Thus the average value of $\lambda_{max.}$ for a disubstituted acid is 217 $\pm$ 5 mμ[17b] and it may be concluded that an average bathochromic shift of 10 mμ is produced upon addition of the second alkyl group. The parent compound, acrylic acid, is estimated to have a $\lambda_{max.}$ of *ca.* 197 mμ.

Relatively few spectra of completely (α, β, β-) substituted unsaturated acids have been reported. However, it is clear from the available data that these compounds have an absorption maximum averaging *ca.* 8 mμ higher than the corresponding disubstituted acid, *i.e.*, 225 $\pm$ 5 mμ. The lowered extinction coefficients and somewhat lower than expected $\lambda_{max.}$ observed with these compounds suggest some steric strain in the excited state.

Alicyclic acids. The spectra of alicyclic α,β-unsaturated acids and esters are summarized in Table III. A correlation between angle strain (and ring size) and ultraviolet spectra has been developed by Schubert and Sweeney for alicyclic α,β-unsaturated ketones.[20] As pointed out more recently by Jones, Mansfield, and Whiting[11] and by Wheeler[12] the spectra of alicyclic α,β-unsaturated acids are also evidently dependent upon ring size.

Ring strain in the unsubstituted five-and seven-membered *endocyclic* ring compounds shifts the absorption maximum to *ca.* 222 mμ from the value of 216 $\pm$ 5 mμ observed with the unstrained 1-cyclohexene-1-carboxylic acids. Similarly, the 2-alkyl substituted strained compounds absorb at 230 $\pm$ 5 mμ and the cyclohexene acids at 224 $\pm$ 5 mμ. Thus, an additional alkyl substituent produces a bathochromic shift of 8 mμ in each series. A slightly lowered extinction coefficient is noted with the non-planar cyclohexenecarboxylic acids, due probably to some inhibition of resonance. An extreme example is β-cyclogeranic acid (I), which is completely alkylated in the 2 and 6 positions (ϵ_{max}^{206} 3,400) and has the spectrum of a simple tetrasubstituted alkene;[21] 1,2-dimethylcyclohexene, for example, has ϵ_{max}^{208} 2,500.[21f]



I

$\epsilon_{max.}^{206}$ 3,400

(13) J. L. H. Allen, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 1862 (1955).

(14) U. Eisner, J. A. Elvidge, and E. P. Linstead, *J. Chem. Soc.*, 1372 (1953).

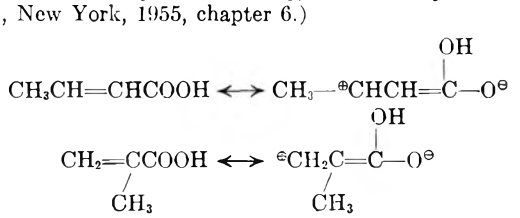
(15) (a) Wheeler[12] discusses the similarity of acid, amide, and nitrile spectra: *cf.* (b) S. Dev., *J. Indian Chem. Soc.*, **33**, 769 (1956), and (c) R. Heilmann, J. Bonnier, and G. de Gaudemaris, *Compt. rend.*, **244**, 1787 (1957). The nitriles appear to absorb at wave lengths *ca.* 3–9 mμ less than the corresponding acids, depending on the degree of alkyl substitution.

(16) The following few exceptions have been noted: (a) 4-ethyl-2-methyl-2-octenoic and 4-heptyl-2-methyl-2-undecenoic acids [J. Cason and K. L. Rinehart, Jr., *J. Org. Chem.*, **20**, 1591 (1955)]; (b) α-cyanocrotonic acid[10]; (c) 3-carboxy-2,3,4-trimethylbutenolide [D. E. Ames, R. E. Bowman, and T. F. Grey, *J. Chem. Soc.*, 375 (1954)].

(17) (a) Readings below 210 mμ may be difficult with certain instruments; *cf.* ref. 3a, p. 98 and G. Eglinton, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 2873 (1952). (b) 2,6-Dienoic and 5-hydroxy-2-enoic acids in certain cases absorb at somewhat higher wave lengths, suggesting some interaction between the α,β-olefinic acid grouping and the remote double bond or hydroxyl group, possibly leading to stabilization of an excited state; *cf.* R. C. Cookson and N. S. Wariyar, *J. Chem. Soc.*, 2303 (1956).

(18) The *trans* isomers have a measurably higher extinction coefficient than the corresponding *cis* compounds; for an interesting application see R. Adams and B. L. Van Duuren, *J. Am. Chem. Soc.*, **75**, 4631 (1953).

(19) The 2-mμ bathochromic shift of the absorption maxima of the β and β,β-substituted acids relative to the corresponding α and α,β-substituted compounds has been noted previously in other instances; *cf.* E. R. H. Jones, G. H. Whitham, and M. C. Whiting, *J. Chem. Soc.*, 1865 (1954) and ref. 4, p. 190. The β substituent is evidently more effective than the α in stabilizing the excited state, thus lowering the transition energy and increasing $\lambda_{max.}$ (For an excellent discussion of the principles of electronic spectra applied to resonance problems see G. W. Wheland, "*Resonance in Organic Chemistry*," John Wiley and Sons, Inc., New York, 1955, chapter 6.)



(20) W. M. Schubert and W. A. Sweeney, *J. Am. Chem. Soc.*, **77**, 2297 (1955).

(21) (a) A. Caliezi and H. Schinz [*Helv. Chim. Acta*, **35**, 1637 (1952)] report end absorption at 220 mμ (log ϵ 3.3) for I and β-cyclofarnesylic acid, a similar compound. For pertinent discussions of other examples see: (b) W. G. Dauben and P. D. Hance, *J. Am. Chem. Soc.*, **75**, 3352 (1953); (c) E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 3331 (1955); (d) E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955); (e) D. J. Cram and N. L. Allinger, *J. Am. Chem. Soc.*, **78**, 5275 (1956); (f) O. H. Wheeler and J. L. Mateos, *J. Org. Chem.*, **21**, 1110 (1956).

An *exocyclic* double bond in conjugation with a carboxyl group generally produces a bathochromic shift of *ca.* 5 mμ above the value of the similarly substituted acyclic compound. Although it has been shown that in one series of exocyclic compounds[12] the value of $\lambda_{max.}$ may depend upon ring size, a limited amount of other previously reported data do not indicate this to be a generally significant effect.[22,23] An average value of 223 ± 5 mμ for unsubstituted exocyclic acids would therefore appear to be an acceptable and useful one until more data are accumulated. The data on α-substituted exocyclic acids are somewhat limited and reveal rather small bathochromic shifts due to the added group; there also appears to be a general lowering of the magnitude of the extinction coefficient.[24] However, in the absence of appreciable steric hindrance (as indicated by a value of $\epsilon_{max.}$ > *ca.* 10,000) a slightly larger bathochromic shift per alkyl group might occur, leading to an average value of 230±5 mμ (for examples, see discussion below). When steric inhibition is small there is but little effect on the absorption maximum, although the value of $\epsilon_{max.}$ may be lowered to some extent.[25]

The above correlation between structure and ultraviolet absorption maxima for relatively unhindered α, β-unsaturated acyclic and alicyclic acids and esters is summarized in Table I. A *relatively* low value of ϵ_{max} may suggest a degree of substitution greater than that indicated by the λ_{max} value. Also, special structural features must be considered (see paragraphs below and ref. 17b).

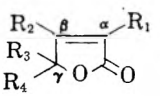
TABLE I

CALCULATION OF ULTRAVIOLET SPECTRA OF ACYCLIC AND ALICYCLIC α,β-UNSATURATED ACIDS AND ESTERS

Substitution	λ_{max} ± 5 Mμ
α or β	208
α,β or β,β	217[a]
α,β,β	225[a,b]

[a] Add 5 mμ for any exocyclic double bond or an endocyclic double bond in a five- or seven-membered ring compound. [b] A somewhat lower value may be found in hindered molecules, accompanied by a *relatively* lower extinction coefficient.

Lactones. α,β-Unsaturated lactones have not been included in the above correlation since their absorption maxima, although related to structure in the same general manner as summarized in Table I, reveal certain exceptions. The butenolides (and pentenolides) without α or β alkyl substituents frequently show only strong end absorption to *ca.* 210–214 mμ[14,26a]; on the other hand, several have

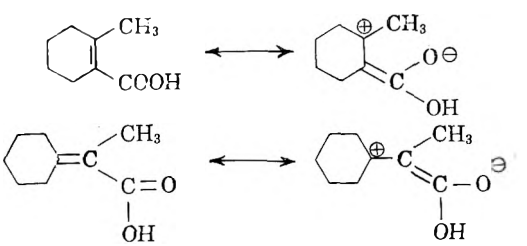


maxima at *ca.* 214 mμ.[14,26,b,c,28] Approximately 200 β-substituted steroid butenolides have been reported having λ_{max} 217 ± 5 mμ (ϵ_{max} 10,000–20,000)[29,30]. α,β-Dialkyl α,β-unsaturated lactones have a maximum in the region 215–230 mμ (ϵ_{max} 10,000–15,000) apparently depending on the groups in the γ position.[16c] Two α-methyl β-substituted steroid butenolides (λ_{max} 222 and 227 mμ) show the expected bathochromic shift from the corresponding unsubstituted compounds (217 mμ).[31] The addition of an α substituent apparently does not always produce the shift, however.[32]

(22) Cyclohexylideneacetic acid itself has a lower λ_{max} (220 mμ as determined in the present work) than cyclopentylidene and cycloheptylideneacetic acids (224 mμ; ref. 12), although its ring-substituted derivatives have higher values (223–225 mμ; see Table III). Unfortunately, the data on ring-substituted cyclopentylidene and cycloheptylideneacetic acids are very limited. A more intensive study of this group of compounds would be desirable.

(23) The conclusions of Wheeler[12] and H. C. Brown, J. H. Brewster, and H. Shechter [*J. Am. Chem. Soc.*, **76**, 467 (1954)] would predict a relatively lower λ_{max} for cyclohexylideneacetic acid than for the corresponding strained cyclopentylidene compound.

(24) In the case of α-substituted exocyclic acids the added alkyl substituent would not be expected to stabilize the excited state to the degree of a β-substituent in an endocyclic acid. This conclusion becomes readily apparent if one compares the two transitions involved.



(25) For more detailed discussions see (a) E. A. Braude and W. F. Forbes, *J. Chem. Soc.*, 3776 (1955); (b) W. F. Forbes and W. A. Mueller, *Can. J. Chem.*, **34**, 1347 (1956); (c) R. B. Turner and D. M. Voitle, *J. Am. Chem. Soc.*, **73**, 1403 (1951).

(26) (a) L. J. Haynes and E. R. H. Jones, *J. Chem. Soc.*, 954 (1946). (b) A. R. Pinder, *J. Chem. Soc.*, 2236 (1952); (c) A. R. Pinder, *J. Chem. Soc.*, 1577 (1956).

(27) R. E. Bowman and J. F. Cavalla, *J. Chem. Soc.*, 1171 (1954).

(28) D. P. Langlois and H. Wolff, *J. Am. Chem. Soc.*, **70**, 2624 (1948).

(29) L. Dorfman [*Chem. Revs.*, **53**, 47 (1953)] lists about 70 of these compounds. Reichstein and co-workers (in *Helv. Chim. Acta*, 1952–1956) list about 100 more (25 references); other workers list *ca.* 30 more compounds therein.

(30) However, β-cyclohexylbutenolide has λ_{max} 208–210 mμ, log ϵ_{max} 4.1–4.3; (a) J. Fried, R. G. Linville, and R. C. Elderfield, *J. Org. Chem.*, **7**, 362 (1942). (b) G. R. Clemo and W. Cocker, *J. Chem. Soc.*, 30 (1946).

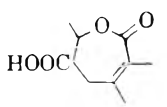
(31) L. Ruzicka, Pl. A. Plattner, and H. Heusser, *Helv. Chim. Acta*, **27**, 1173 (1944).

Functionally substituted acids. Other structural features in addition to the degree of alkyl substitution about the olefinic double bond which produce bathochromic shifts of the absorption maximum will be discussed only briefly here. One factor is the presence of hetero atoms ("auxochromes") attached to the ethylenic linkage.[33,34] In α,β-unsaturated acids and esters the shifts vary from 15 to 80 mμ depending on the nature of the hetero atom. For example, an α-chlorine, bromine, or alkoxyl group produces a shift of 15–20 mμ and a lowering of the absorption intensity in most instances, whereas the same substituent in the β position causes a similar shift accompanied by a slight increase in $\epsilon_{max.}$[35–38] The "auxochromic" shifts are also observed with α,β-unsaturated lactones.[37]

As expected, extended conjugation also shifts the absorption maximum.[10,38] For example, acyclic 2,4-dienoic acids, such as sorbic acid, absorb at 259 ± 5 mμ; $\epsilon_{max.}$ *ca.* 20,000–25,000;[13,14,37e,38–40a–e] *cis-trans* isomerism affects the position of this maximum as well as the value of $\epsilon_{max.}$[13,40a] An added alkyl substituent in these molecules generally produces a bathochromic spectral shift of *ca.* 5–8 mμ.[39,40a–c] Few alicyclic dienoic acid spectra have been reported, but their observed λ_{max} are in rough agreement with the calculated values.[38d,40d–h,41f] Cinnamic acid and its α and β-alkyl derivatives have two strong bands near 215 and 265–275 mμ.[41,42] Here, the alkyl substitution often appears to produce a hypsochromic shift of the long wave length band which has been attributed to steric inhibition of resonance.[42] In certain ring substituted cinnamic acids the two principal absorption bands appear at somewhat longer wave lengths.[43] The conjugative effect of a cyclopropyl group is observed with 3-(2-carboxy-3-methylcyclopropyl)propenoic acid (ϵ_{max}^{229} 19,400)[40c] and chrysanthemum dicarboxylic acid ($\epsilon_{max}^{236–238}$ 15,600).[40b] In these compounds a bathochromic shift of *ca.* 8 mμ is noted for the added methyl group.

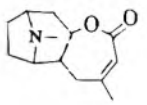
The alicyclic non-conjugated 1,4-dienoic acids such as 1,4-cyclohexadiene-1-carboxylic acid[11,44] (IV) have two principal bands near 200 and 230 mμ (the latter often weak, $\epsilon_{max.}$ <4,000). The long wave length band excitation state has been recognized as not due to the >C=C(COOH)– system,[11] and may possibly be pictured as a "semi-cyclobutadiene" type stabilization. This may be thought of as involving some π orbital overlap in the excited state, a condition permitted in the boat form of the

(32) For example, an α,β-dimethylheptenolide, II, [R. Adams and M. Gianturco, *J. Am. Chem. Soc.*, **79**, 166 (1957); spectrum measured in this laboratory on sample generously provided by Dr. Adams] absorbs at a lower wave length than the β-methylheptenolide alkaloid, dioscorine, III.[26] NOTE ADDED IN PROOF: The lactone ring in dioscorine is now believed to be six-, rather than seven-membered [A. R. Pinder, *Chemistry & Industry*, 1240 (1957)]. Thus, compound II has no prototype with which to be directly compared, although its absorption maximum may be considered somewhat low relative to substituted five- and six-membered lactones.



II

$\epsilon_{max.}^{214}$ 14,000



III

$\epsilon_{max.}^{217}$ 16,100

(33) K. Bowden, E. A. Braude, and E. R. H. Jones, *J. Chem. Soc.*, 948 (1946).

(34) F. E. Bader, *Helv. Chim. Acta*, **36**, 215 (1956).

(35) L. N. Owen, *J. Chem. Soc.*, 385 (1945).

(36) L. N. Owen and M. U. S. Sultanbawa, *J. Chem. Soc.*, 3089, 3098, 3105 (1949).

(37) (a) H. Mohler and H. Lohr, *Helv. Chim. Acta*, **21**, 485 (1938); (b) E. Shaw, *J. Am. Chem. Soc.*, **68**, 2510 (1946); (c) E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.*, 1423 (1949); (d) D. T. Mowry, *J. Am. Chem. Soc.*, **72**, 2535 (1950); (e) H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 3628 (1950); (f) J. H. Ford, A. R. Johnson, and J. W. Hinman, *J. Am. Chem. Soc.*, **72**, 4529 (1950); (g) H. H. Wasserman and F. M. Precopio, *J. Am. Chem. Soc.*, **74**, 326 (1952); (h) L. A. Duncanson, *J. Chem. Soc.*, 1207 (1953); (i) T. A. Geisman, *J. Am. Chem. Soc.*, **75**, 4008 (1953); (j) R. N. Lacey, *J. Chem. Soc.*, 832 (1954); (k) A. Stabursvik, *Acta Chem. Scand.*, **8**, 525 (1954).

(38) (a) A. Smakula, *Angew. Chem.*, **47**, 657 (1934); (b) K. W. Hausser, R. Kuhn, A. Smakula, and M. Hoffer, *Z. physik. Chem.*, **B29**, 371 (1935); (c) K. W. Hausser, R. Kuhn, A. Smakula, and A. Deutsch, *Z. physik. Chem.*, **B29**, 378 (1935); (d) E. R. H. Jones, D. G. O'Sullivan, and M. C. Whiting, *J. Chem. Soc.*, 1415 (1949); (e) A. Crossley and T. P. Hilditch, *J. Chem. Soc.*, 3353 (1949); (f) V. Petrov and O. Stephenson, *J. Chem. Soc.*, 1310 (1950); (g) J. A. Elvidge, R. P. Linstead, and P. Sims, *J. Chem. Soc.*, 1793 (1953); (h) E. R. H. Jones, B. L. Shaw, and M. C. Whiting, *J. Chem. Soc.*, 3212 (1954); (i) L. Crombie and M. Manzoor-i-Khuda, *Chemistry & Industry*, 409 (1956).

(39) E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 3324 (1955).

(40) (a) J. A. Elvidge, R. P. Linstead, and J. F. Smith, *J. Chem. Soc.*, 1026 (1952); (b) S. H. Harper, K. C. Sleep, and L. Crombie, *Chemistry & Industry*, 1538 (1954); (c) S. H. Harper and H. W. B. Reed, *J. Chem. Soc.*, 779 (1955); (d) G. Wendt, *Ber.*, **74**, 1242 (1941); (e) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **31**, 1067 (1948); (f) M. W. Cronyn and J. E. Goodrich, *J. Am. Chem. Soc.*, **74**, 3331 (1952); (g) H. Schmid and W. Bencze, *Helv. Chim. Acta*, **36**, 1468 (1953); (h) E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 607 (1954).

(41) (a) A. Smakula and A. Wasserman, *Z. Physik. Chem.*, **A155**, 353 (1931); (b) M. Ramart-Lucas and M. R. Trivédi, *Bull. soc. chim. France*, (4) **53**, 178 (1933); (c) M. Ramart-Lucas, *Bull. soc. chim. France*, (5) **1**, 719 (1934); (d) M. Ramart-Lucas, J. Hoch, and M. Grumez, *Bull. soc. chim. France*, (5) **16**, 447 (1949); (e) J. D. Roberts, G. B. Kline, and H. E. Simmons, Jr., *J. Am. Chem. Soc.*, **75**, 4765 (1953); (f) R. H. Burnell and W. I. Taylor, *J. Chem. Soc.*, 3636 (1954).

(42) G. Tsatsas, *Bull. soc. chim. France*, (5) **14**, 1011 (1947).

(43) (a) R. F. Patterson and H. Hibbert, *J. Am. Chem. Soc.*, **65**, 1862 (1943); (b) S. Wawzonek, S. C. Wang, and P. Lyons, *J. Org. Chem.*, **15**, 593 (1950); (c) I. A. Pearl and D. L. Beyer, *J. Org. Chem.*, **16**, 216 (1951); (d) E. L. Bennett and E. Hoerger, *J. Am. Chem. Soc.*, **74**, 5975 (1952); (e) W. Baker and C. S. Howes, *J. Chem. Soc.*, 119 (1953).

(44) S. L. Emerman and J. Meinwald, *J. Org. Chem.*, **21**, 375 (1956) report $\lambda_{max.}^{235}$, $\epsilon_{max.}$ 2500 for compound IV.

1,4-cyclohexadiene ring (IVa). A methyl group at the double bond (V) produces no change in the long wave length absorption maximum, as might be expected, since it is "out of plane" of the envisioned stabilization interaction.[11,45]

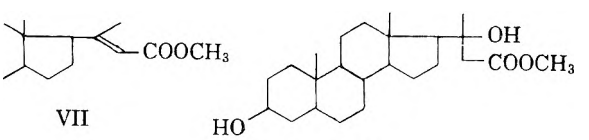
DISCUSSION

Up to the present time, the principal use of the ultraviolet spectra of α,β-unsaturated acids and esters has been simply to establish the presence of the $-C=\overset{|}{C}COOH$ system. Examples are found in the structure work on the *Senecio* acids by Adams and co-workers,[46] the many terpene acids studied by Schinz and co-workers,[47] and such compounds as masticadienoic acid,[48] pseudosantonin,[21b,30b] shikimic acid,[49] and Feist's acid.[50]

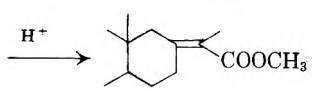
Rather limited use has been made of the value of $\lambda_{max.}$ to determine the degree of substitution about the olefinic double bond of α,β-unsaturated acids. Noteworthy is the work by Cason and co-workers on phthienoic (mycolipenic) acid, $\epsilon^{217}_{max.}$ 12,000.[51] A study of several model compounds aided in reaching the correct conclusion that the acid is α,β-disubstituted.[52–54] In another study, the structure of the alkaloid dioscorine III[28b,c,32] was found to be in better agreement with its observed $\lambda_{max.}$ (217 mμ) than the originally proposed structure, VI.[55] The work on the structure of helvolic acid is also illustrative.[21e]

There appear to be few cases in which the spectral data are in serious disagreement with the reported structures, aside from a few sterically hindered compounds (see also ref. 17b). However, attention will be directed to two apparently erroneous formulas which merit discussion here. The bromination of 4-bromo-2,4-hexadienoic acid has been reported[56] to yield 4,4,5-tribromo-2-hexenoic acid ($\epsilon^{221}_{max.}$ 7,000; hexane), whereas the structure 2,4,5-tribromo-2-hexenoic acid appears to be in better agreement with the observed spectrum.[57,58]

The absorption maxima of the reported methyl $\Delta^{20,22}$-3β-hydroxynorallocholenate (partial structure VII, reported λ_{max} 231 mμ, log ϵ4.2) and the corresponding $\Delta^{5,6}$ isomer (from graph, λ_{max} 228–230 mμ, log ϵ4.4) are in disagreement with their assigned structures,[59] for which a value of *ca.*

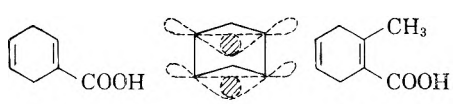


VII VIII



X

(45) A similar situation exists in bicyclo[2.2.1]-2,5-heptadiene-2-carboxylic acid and its 3-methyl derivative (λ^{229}_{max}, ϵ 3,700 and 231, ϵ 3,800, respectively; ref. 11).



IV IVa V

$\epsilon^{236}_{max.}$ 2,100 $\epsilon^{236}_{max.}$ 2,550

(46) The absence of two olefinic bonds in conjugation with the carboxyl group was deduced from the spectrum of mikanecic acid (*cf.* ref. 32 and earlier papers in this series for other examples).

(47) Numerous papers in *Helv. Chim. Acta*, 1948–1956; *cf.* Table III.

(48) D. H. R. Barton and E. Seoane, *J. Chem. Soc.*, 4150 (1956).

(49) (a) I. I. Salamon and B. D. Davis, *J. Am. Chem. Soc.*, **75**, 5567 (1953); (b) R. Grewe and A. Bokranz, *Ber.*, **88**, 49 (1955).

(50) (a) M. G. Ettlinger and F. Kennedy, *Chemistry & Industry*, 166 (1956); (b) A. T. Bottini and J. D. Roberts, *J. Org. Chem.*, **21**, 1169 (1956); *cf.* the spectrum of methyl cyclopropene-1-carboxylate (ref. 36, p. 3101).

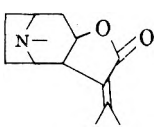
(51) J. Cason and G. Sumrell, *J. Biol. Chem.*, **192**, 405 (1951).

(52) Ref. 8 and 16a and (a) J. Cason and G. Sumrell, *J. Org. Chem.*, **16**, 1181 (1951); (b) J. Cason, N. L. Allinger, and C. F. Allen, *J. Org. Chem.*, **18**, 857 (1953); (c) J. Cason, N. L. Allinger, and G. Sumrell, *J. Org. Chem.*, **18**, 850 (1953); (d) J. Cason and M. J. Kalm, *J. Org. Chem.*, **19**, 1836 (1954).

(53) S. Ställberg-Stenhagen, *Arkiv Kemi*, **6**, 537 (1954).

(54) A. S. Bailey, N. Polgar, and R. Robinson, *J. Chem. Soc.*, 3031 (1953).

(55) The originally proposed structure VI [K. Gorter, *Rec. trav. chim.*, **30**, 161 (1911)] was altered to the heptenolactone III in agreement with spectral and chemical evidence.[26b,c,32] The absorption maximum (217 mμ) also agrees with a hexenolactone structure. See NOTE ADDED IN PROOF, ref. 32.



VI

(56) O. Dann, *Ber.*, **80**, 427, 435 (1947).

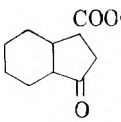
(57) Dann[56] reports 4,5-dibromo-2-hexenoic acid (ϵ^{208}_{max} 10,900; hexane) and 4,5,6,7-tetrabromo-2-octenoic acid (ϵ^{208}_{max} 9,100; hexane or alcohol), whereas 2-bromocrotonic and 2-bromo-2-pentenoic acids absorb at 228 mμ, ϵ_{max} 7000 and 6500, respectively (alcohol) (ref. 33 and B. J. P. Alles and M. U. S. Sultanbawa, *J. Chem. Soc.*, 3472 (1956)). One would expect the spectrum of 4,4,5-tribromo-2-hexenoic acid to have greater resemblance to the former two compounds than the latter (*i.e.*, have a λ_{max} at, or slightly above, 208 mμ). On the other hand, if a γ-*gem* dibromo group should have an unexpectedly large stabilizing effect on the α,β-unsaturated acid structure, it would be necessary to reconsider Dann's structure.

(58) It seems likely that the starting compound [most likely 4-bromo-2,4-hexadienoic acid; *cf.* C. K. Ingold, G. J. Pritchard, and H. G. Smith, *J. Chem. Soc.*, 79 (1934)] undergoes 1,4-addition followed by a double bond shift to the α,β-position; see experimental section of Dann's paper[56] for pertinent details.

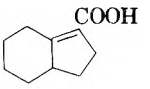
(59) (a) L. Ruzicka, Pl. A. Plattner, and J. Patalki, *Helv. Chim. Acta*, **25**, 425 (1942). (b) L. Ruzicka, Pl. A. Plattner, and J. Patalki, *Helv. Chim. Acta*, **28**, 1360 (1945).

218–219 mμ would be expected. These compounds were obtained from their respective hydroxy esters (*e.g.*, VIII) by treatment with acetic anhydride (48 hr. reflux) or, in one instance, with potassium acid sulfate (180–190°, 1 hr.). It appears likely that in each case the dehydration product is more reasonably expressed as X (partial structure) obtained by way of two rearrangements (expected λ_{max} 230 ± 5 mμ).[60,61]

A final example of the utility of the ultraviolet absorption maximum for structure elucidation is found in the case of the "obscure" tetrahydro-



XIII



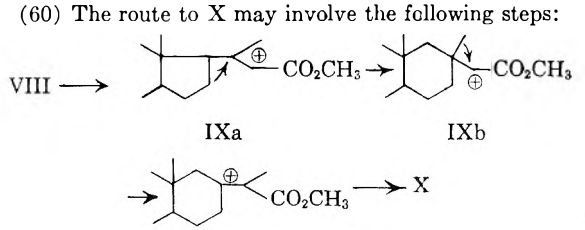
XIV

TABLE II

ULTRAVIOLET SPECTRA OF ACYCLIC α,β-UNSATURATED ACIDS AND ESTERS[a]

Compound[b]	λ_{max}, mμ[a,c]	ϵ_{max}[d,e]
A. α-Substituted		
Methyl acrylate	≤210	—[7a]
Methyl methacrylate	208	—[7a,64]
2-Ethylpropenoic	208W	6,770[65]
Itaconic	≤206	(≥ 8,000)[19]
α-Methylenesuccinic	≤206	(≥ 8,000)[19]
α-Methyleneglutaric	≤206	(≥ 8,000)[19]
α-Methyleneadipic	≤210	(≥ 8,000)[19,66]
α-Methylenepimelic	≤206	(≥ 8,000)[19]
2-Methylenedodecanoic	208	8,150[8]
B. β-Substituted		
Crotonic, *trans*	205	14,000[13,19,21c,37a,38a,b,56,69]
Crotonic, *trans*	208H,W	13,000[38a,b,56,67,68,71]
Crotonic, *cis*	205.5	13,500[13]
Fumaric	208W	14,000[38a,67,70,71]
Maleic	210W	13,000[38a,67,70,71]
2-Pentenoic	209W	12,200[65]
Glutaconic	204	13,500[38a]
2-Hexenedioic	205	13,900[38a]
4,5-Dibromo-2-hexenoic	208H	10,900[56]
4,5,6,7-Tetrabromo-2-octenoic	208	9,100[56]
Ethyl 2-nonenoate	210N	14,250[52a]

(60) The route to X may involve the following steps:

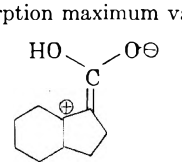


For analogous acid catalyzed ring expansion-rearrangements *cf.* (a) N. Kizhner, *J. Russ. Phys. Chem. Soc.*, **42**, 1211 (1910); (b) N. Kizhner, *J. Russ. Phys. Chem. Soc.*, **43**, 1149 (1911); (c) H. Meerwein, *Ann.*, **417**, 255 (1918); (d) W. K. Conn and A. Schneider, *J. Am. Chem. Soc.*, **76**, 4578 (1954).

(61) The formation of X would explain the very poor yield of difficultly purifiable $\Delta^{20,22}$-3β-21-dihydroxynorallocholenic acid lactone (XI) (λ_{max} *ca.* 219 mμ) obtained by selenium dioxide or *N*-bromosuccinimide oxidation of the dehydration product of VIII (*cf.* ref. 4, p. 560 and ref. 59). The yields appear to be extremely small (*cf.* experimental sections, ref. 59) and to result, at least in the case of the selenium dioxide reaction, by way of some prior equilibration of X to VII (during 2 hr. reflux with aqueous acetic acid which was present) followed by oxidation. The yield of XI obtained using *N*-bromosuccinimide is claimed to be less than 10%, although the only products reported in the experimental section[59b] were recovered starting material (32%) and a conjugated diene lactone (λ_{max}. 273, log ε 4.35) assigned the structure $\Delta^{16,17;20,22}$-3β-acetoxy-21-hydroxynorallocholadienic acid (23–21)-lactone (XII) (less than 7% yield).

(62) (a) D. W. Mathieson, *J. Chem. Soc.*, 3251 (1953); (b) the bromo acid, prepared from hexahydroindane-1-carboxylic acid, was not isolated, but is presumably the 1-bromo compound.

(63) A trisubstituted acid with the double bond exocyclic to a six membered ring and endocyclic to a five membered ring would be expected to have a λ_{max} of 235 ± 5 mμ. The decrease in strain energy in passing from the ground state of XIV to the excited state (XIVa) would contribute to the rather high absorption maximum value.



XIVa

indanecarboxylic acid obtained by Mathieson[62a]. This acid (m.p. 126.5–127°, ϵ_{max}^{234} 12,000) obtained as one product of the Clemmensen reduction of XIII and the sole product of dehydrobromination of bromohexahydroindane-1-carboxylic acid,[62b] probably has the structure XIV, in agreement with the expected absorption value.[63]

TABLE II (*Continued*)

Compound[b]	λ_{max}, mμ[a,c]	ϵ_{max}[d,e]
2-Dodecenoic	208	13,480[52c]
5-Methyl-2-hendecenoic	210	13,160[52c]
5-Methyl-2-tridecenoic	210	13,900[8]
2-Pentadecenoic	210N	(30,000)[72]
2-Heptadecenoic	210N	(30,000)[72]
2-Heptadecenoic	213H	(16,000)[68]
2-Octadecenoic, *trans*	213H	(20,000)[73]
2-Octadecenoic, *cis*	213H	(13,000)[73]
2-Hexacosenoic	210	13,600[52c]
Ethyl 5-hydroxy-2-pentenoate	$\leqslant$213	$\geqslant$ 9,500[26a]
Ethyl 5-hydroxy-2-hexenoate	$\leqslant$215	$\geqslant$ 10,000[26a]
4-(1-Hydroxycyclohexyl)-2-butenoic	211	13,580[76]
Methyl 4-(1-hydroxy-4-methylcyclohexyl)-2-butenoate	212	13,060[76]
4-(1-Hydroxy-2-methylcyclohexyl)-2-butenoic	213	14,400[76]
2,6-Nonadienoic	215	(10,000)[74]
7-Methyl-2,6-octadienoic	218	(8,000)[75]
5-Hydroxy-5-phenyl-2-pentenoic	217	18,000[38d]
C. α,β-Disubstituted		
Tiglic (*trans* 2-methyl-2-butenoic)	213	12,500[12,18,53,65,77–79]
Angelic (*cis* 2-methyl-2-butenoic)	216	9,000[18,53,65,77–79]
2-Cyanocrotonic	215	9,700[10]
Methyl 2-cyanocrotonate	220	8,400[10]
Methyl 4-hydroxy-2,4,4-trimethyl-2-butenoate	217	8,500[39]
Methyl 2-ethyl-2-hexenoate	219	12,100[80]
Ethyl 3-carbethoxy-5-methyl-3-hexenoate	213H	11,400[81]
Longenecic	214	8,130[69]
2,4,6-Trimethyl-2-heptenedioic	216	(9,100)[82]
Senecic, *trans* (intergerrinecic)	214	9,021[18]
Senecic, *trans* (intergerrinecic)	218	9,333[83,86]
Senecic, *cis*	215	5,000[18,83]
Senecic, *cis*	218.5W	4,950[86]
Isatenecic, *trans* (retronecic)	218	9,400[83,86]
Isatenecic, *cis*	215	4,500[83]
Usaramoensenecic, *cis*	215	5,977[18]
Dimethyl 2,7-dimethyl-2,6-octadienoate	217M	22,000[84]
4-Ethyl-2-methyl-2-octenoic	219H	14,000[16a]
Ethyl 4-ethyl-2-methyl-2-octenoate	216H	13,400[16a]
2,4,8-Trimethyl-2-nonenoic	217M	(11,200)[85]
Methyl 2,5,9-trimethyl-2-decenoate	218M	(8,300)[85]
Methyl 2-carbomethoxy-4,8-dimethyl-2-nonenoate	219M	(3,800)[85]
Ethyl 4-isopropyl-2-methyl-2-octenoate	217H	13,200[87]
Ethyl 4-*tert*-butyl-2-methyl-2-octenoate	218H	12,860[87]
2-Methyl-2-dodecenoic	218H	11,330[52d]
Ethyl 3-carbethoxy-3-tridecenoate	213.5H	10,200[81]
2,5-Dimethyl-2-tridecenoic	217.5	12,700[52b]
Ethyl 3-carbethoxy-3-pentadecenoate	213H	10,100[81]
2,4,6-Triethyl-5-propyl-2-heptenedioic	218	16,300[88]
2,5-Dimethyl-2-heptadecenoic	216	12,200[52b]
4-Heptyl-2-methyl-2-hendecenoic	219H	13,800[16a]
Ethyl 4-heptyl-2-methyl-2-hendecenoate	216H	12,800[16a]
Glyceryl 1,2-*bis*-2-methyl-2-octadecenoate	218M	(22,400)[89]
Glyceryl 1,3-*bis*-2-methyl-2-octadecenoate	216M	(27,600)[89]
2-Methyl-2-octadecenoic	215M	(13,000)[89,90]
Methyl 2-methyl-2-octadecenoate	218M	(11,800)[90]
2-Methyl-2-eicosenoic	218M,H	13,500[52d,90]
2,4-Dimethyl-2-eicosenoic	214M	(11,800)[90]
2,4-Dimethyl-2-heneicosenoic	216	12,600[53]
2,5-Dimethyl-2-heneicosenoic	218	13,000[53]
2,4-Dimethyl-2-docosenoic	216M	(13,500)[90]
Phthienoic (2,4,6-trimethyl-2-tetracosenoic)	217H	12,000[51,54,91]
2,4-Dimethyl-2-heptacosenoic	218H	14,550[52d]
2-Methyl-2-octacosenoic	217H	14,000[52d]
Masticadienoic	214	12,500[48]
Masticadienolic	212	12,100[48]
Isomasticadienoic	212	15,000[48]
D. β,β-Disubstituted		
3-Methyl-2-butenoic	216	12,000[7b,12,21c]
3-Methyl-2-butenoic	219W	10,400[65]

TABLE II (*Continued*)

Compound[b]	λ_{max} mμ[a,c]	ϵ_{max}[d,e]
4-Hydroxy-3-methyl-2-butenoic	219	13,460[36]
Ethyl 5-carboxy-3-methyl-2-pentenoate	216	13,000[92]
3-Methyl-2,6-heptadienoic	220	(12,500)[74]
3-Methyl-7(6?)-hydroxy-2-octenoic	218	(6,300)[74]
3-Methyl-2-nonenoic	219	12,070[51,52a]
3,7-Dimethyl-2-octenoic	218M	(11,000)[85,93]
Ethyl 6-isopropyl-3-methyl-2,6-heptadienoate	218	(8,300)[94]
Ethyl ϵ-methylgeranate	218	(11,300)[94]
Ethyl 3,5,5-trimethyl-2,6-heptadienoate	223N	(11,500)[95]
Ethyl ϵ-ethylgeranate	220	(10,000)[96]
Diethyl 3,8-dimethyl-2,8-decadiendioate	218	28,500[92]
Farnesylic	220	(8,000)[21a]
Ethyl α,β-dihydro-α-ionylideneacetate	220	(12,600)[21a,97]
Agathenedicarboxylic	220	(16,000)[38a]
E. α,β,β-Trisubstituted		
2,3-Dimethyl-2-butenoic	221	9,700[21c,41d]
Methyl 2-cyano-3-methyl-2-butenoate	230	11,100[10]
Ethyl 2-cyano-3-methyl-2-pentenoate	232	12,200[10]
Ethyl 3-carbethoxy-4-methyl-3-pentenoate	219.5H	9,200[81]
Ethyl 3-carbethoxy-4-methyl-3-hexenoate	218H	6,960[81]
Ethyl 3-carbethoxy-4,5-dimethyl-3-hexenoate	219.5H	7,890[81]
Ethyl 2,3-dimethyl-5-carbethoxy-6-one-2-heptenoate	225	4,270[32,80]
Ethyl 2,3-dimethyl-5-carbethoxy-6-ol-2-heptenoate	223.5	4,000[32,80]
Methyl isopolyporenate	226	8,000[99]
Methyl isopolyporenate diacetate	226	8,900[99]
Methyl b-oxopolyporenate	226	9,200[99]
Methyl a,b-dioxopolyporenate	226	9,400[99]

[a] Solvent is 95% ethanol unless otherwise indicated; W, water; H, hexane or similar hydrocarbon; M, methanol; N, no solvent listed. The values in water or hexane are equal to or up to *ca.* 3 mμ higher than the values reported in ethanol. [b] If the spectra of both an acid and its ester are reported, only the former is recorded here, unless the values differ by more than 2 mμ. Also, if values reported for the same compound by different workers disagree by more than 2 mμ, each is recorded. [c] If an absorption range is reported, an average value is recorded here. [d] Values in parentheses were calculated from the reported log ϵ value. Data from several workers for the same compound are averaged to give the value recorded. [e] Superscripts refer to references in text or at end of table.

(64) F. T. Wall, R. E. Florin, and C. J. Delbecq, *J. Am. Chem. Soc.*, **72**, 4769 (1950).

(65) E. Bueding, *J. Biol. Chem.*, **202**, 505 (1955).

(66) L. N. Owen and A. G. Peto, *J. Chem. Soc.*, 1146 (1956).

(67) H. Ley and H. Wingchen, *Ber.*, **67**, 501 (1934).

(68) I. I. Rusoff, J. R. Platt, H. B. Klevens, and G. O. Burr, *J. Am. Chem. Soc.*, **67**, 673 (1945); solvent iso-octane, heptane, or ethanol.

(69) R. Adams, T. R. Govindachari, J. H. Looker, and J. D. Edwards, Jr., *J. Am. Chem. Soc.*, **74**, 700 (1952), report 211–213 ± 3 mμ for crotonic acid (ethanol).

(70) A. Wasserman and A. Smakula, *Z Physik. Chem.*, **A155**, 366 (1931).

(71) N. A. Sörensen, *Ann.*, **546**, 57 (1941).

(72) W. M. Lauer, W. J. Gensler, and E. Miller, *J. Am. Chem. Soc.*, **63**, 1153 (1941).

(73) G. S. Meyers, *J. Am. Chem. Soc.*, **73**, 2100 (1951).

(74) R. Helg, F. Zobrist, A. Lauchenauer, K. Brack, A. Caliezi, D. Stauffacher, E. Zweifel and H. Schinz, *Helv. Chim. Acta*, **39**, 1269 (1956).

(75) R. Helg and H. Schinz, *Helv. Chim. Acta*, **35**, 2406 (1952).

(76) A. S. Dreiding and R. J. Pratt, *J. Am. Chem. Soc.*, **75**, 3717 (1953).

(77) A. S. Dreiding and R. J. Pratt, *J. Am. Chem. Soc.*, **76**, 1902 (1954).

(78) R. E. Buckles, G. V. Mock, and L. Locatell, Jr., *Chem. Revs.*, **55**, 659 (1955).

(79) A. Castille, *Bull. classe sci. Acad. roy. Belg.*, (5) **16**, 811 (1930).

(80) A. T. Nielsen, this paper.

(81) C. G. Overberger and C. W. Roberts, *J. Am. Chem. Soc.*, **71**, 3618 (1949); the authors question the purity of the trisubstituted esters.

(82) R. Anliker, D. Dvornik, K. Gubler, H. Heusser, and V. Prelog, *Helv. Chim. Acta*, **39**, 1785 (1956).

(83) M. Kropman and F. L. Warren, *J. Chem. Soc.*, 700 (1950).

(84) E. Buchta and H. Schlesinger, *Ann.*, **598**, 1 (1956).

(85) P. C. Jocelyn and N. Polgar, *J. Chem. Soc.*, 132 (1953).

(86) E. C. Leisegang, *J. S. African Chem. Inst.*, **3**, 73 (1950).

(87) K. L. Rinehart, Jr., and L. J. Dolby, *J. Org. Chem.*, **22**, 13 (1957).

(88) A. T. Nielsen, *J. Am. Chem. Soc.*, **79**, 2524 (1957).

(89) G. I. Fray, N. Polgar, and R. Robinson, *J. Chem. Soc.*, 3031 (1953).

(90) A. S. Bailey, N. Polgar, F. E. G. Tate, and A. Wilkinson, *J. Chem. Soc.*, 1547 (1955).

(91) C. Asselineau, J. Asselineau, S. Ställberg-Stenhagen, and E. Stenhagen, *Acta Chem. Scand.*, **10**, 479, 1035 (1956).

(92) R. P. Linstead, J. C. Lunt, B. C. L. Weedon, and B. R. Shephard, *J. Chem. Soc.*, 3621 (1952).

(93) R. Heilmann and R. Glenat, *Bull. soc. chim. France*, 1586 (1955).

(94) H. Favre and H. Schinz, *Helv. Chim. Acta*, **35**, 1627 (1952).

(95) K. Brack and H. Schinz, *Helv. Chim. Acta*, **34**, 2009 (1951).

(96) W. Surber and H. Schinz, *Helv. Chim. Acta*, **37**, 1239 (1954).

(97) A. Caliezi and H. Schinz, *Helv. Chim. Acta*, **33**, 1129 (1950).

(98) (a) L. Ruzicka, E. Bernhold and A. Tallichet, *Helv. Chim. Acta*, **24**, 223 (1941); (b) L. Ruzicka and G. Dalma, *Helv. Chim. Acta*, **22**, 1516 (1939).

(99) T. G. Halsall, R. Hodges, and E. R. H. Jones, *J. Chem. Soc.*, 3019 (1953).

TABLE III

ULTRAVIOLET SPECTRA OF ALICYCLIC α,β-UNSATURATED ACIDS AND ESTERS[a]

Compound	λ_{max}, mμ	ϵ_{max}
A. Unsubstituted Endocyclic		
Cyclopentene-1-carboxylic	222	10,500[11,12]
Dehydronorcedrenedicarboxylic	222	(16,000)[100-102]
Cyclohexene-1-carboxylic	217	10,000[7a,11,12,15b,103]
4,5-Dibromo-1-cyclohexene-1-carboxylic	212	10,000[44]
Shikimic (3,4,5-trihydroxy-1-cyclohexene-1-carboxylic)	214	(8,500)[49a]
Methyl 2,6-dimethyl-5,6-dihydro-1,2-pyran-3-carboxylate	212.5N	(8,000)[34]
3,5,5-Trimethyl-1(6?)-cyclohexene-1-carboxylic	217	9,500[40b]
4-Vinyl-1-cyclohexene-1,4-dicarboxylic	215	11,000[104]
5-Methyl-1-cyclohexene-2,3,4-tricarboxylic	220M	6,600[105]
Cycloheptene-1-carboxylic	222	9,900[12,15b,106]
Tetrahydrothujic (4,4-dimethyl-1-cycloheptene-1-carboxylic)	223	(10,000)[107]
Cyclooctene-1-carboxylic	218	12,100[108]
B. Substituted Endocyclic		
2-Methyl-1-cyclopentene-1-carboxylic	231	10,500[11,109]
2-Carboxymethyl-1-cyclopentene-1-carboxylic	228	(10,000)[40g]
2-Methyl-bicyclo[2.2.1]-1-octene-1-carboxylic	234	8,100[11]
2-Methyl-5-(1-carboxyisopropyl)-1-cyclopentene-1-carboxylic	225N	(10,000)[110]
5-Butyl-2-carboxymethyl-1-cyclopentene-1-carboxylic	229	(10,000)[40g]
2-Butyl-5-(1-carboxy-2-hydroxyethyl)-1-cyclopentene-1-carboxylic	232	(10,500)[40g]
2-Methyl-1-cyclohexene-1-carboxylic	218	(9,500)[7a]
2-Methyl-1-cyclohexene-1-carboxylic	225	9,200[11]
Methyl 2-methyl-3,4,5-trihydroxycyclohexene-1-carboxylate	221M	(6,600)[49b]
Cyclolavandulylic (2,4,4-trimethyl-1-cyclohexene-1-carboxylic)	225	(8,900)[111]
β-Cyclogeranic (2,6,6,-trimethyl-1-cyclohexene-1-carboxylic)	206	(3,400)[21a,80]
β-Bicyclosesquilavandulylic	228	(8,300)[112]
C. Unsubstituted Exocyclic		
Cyclopentylideneacetic	224	12,500[12]
$\Delta^{5;17,20}$-Pregnadien-3-ol-20-carboxylic, *trans*	222	(12,500)[114,115]
$\Delta^{5;17,20}$-Pregnadien-3-ol-20-carboxylic, *cis*	224	(11,000)[116]
Cyclohexylideneacetic	220	14,000[12,21b,80,117]
4,4-Dimethylcyclohexylideneacetic	225	(2,000)[122]
1-Carboxymethylene-6-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalene-2-carboxylic	225	(16,000)[118]
Dioxocassaic	223	(16,000)[98b,119]
Cycloheptylideneacetic	224	12,600[12]
Methyl 2-carbomethoxymethylcycloheptylideneacetate	232	(17,800)[120]
D. Substituted Exocyclic		
$\Delta^{5;17,20}$-3-Acetoxy-20-methylpregnadiene-20-carboxylic	224N	—[116]
Methyl tetrahydrohelvolate	219.5	8,500[21e]
Methyl octahydrohelvolate	222	7,900[21e]
Methyl hexahydropyrohelvolate	220	7,450[21e]
α-Cyanocyclohexylideneacetic	235	(12,500)[121]
Ethyl α-carbethoxymethylcyclohexylidene acetate	220H	5,050[81]
Methyl α-(4-methylcyclohexylidene)propionate	225	8,220[21b]
2,3,4,4a,5,6,7,8-Octahydronaphthalene-1-carboxylic	219	(9,400)[7a]
Ethyl α-cyano-(2-cyclohexylcyclohexylidene)acetate	235	(10,000)[121]
4-(1-Carboxyvinyl)-1,2,3,4,4a,4b,5,6,7,8,10,10a-decahydrophenanthrene-9-carboxylic	225	9,400[113]

[a] See footnotes a–e of Table II.

(100) Pl. A. Plattner, G. W. Kusserow, and H. Kläui, *Helv. Chim. Acta*, **25**, 1345 (1942).

(101) G. Stork and R. Breslow, *J. Am. Chem. Soc.*, **75**, 3291 (1953).

(102) G. Stork and F. H. Clarke, Jr., *J. Am. Chem. Soc.*, **77**, 1072 (1955).

(103) E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 2014 (1950).

(104) E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 3238 (1956).

(105) D. Craig and J. J. Shipman, *J. Am. Chem. Soc.*, **74**, 2005 (1952).

EXPERIMENTAL

All measurements were performed using a Cary Recording Quartz Spectrophotometer, model 11 M S. Solutions were prepared with 95% ethanol. The author wishes to thank Messrs. Raymond J. Shuba and Peter R. Segatto for obtaining the spectral data.

Samples of ethyl 2,3-dimethyl-5-carbethoxy-6-one-2-heptenoate, ethyl 2,3-dimethyl-5-carbethoxy-6-ol-2-heptenoate and 5-carboxy-2,3-dimethyl-6-hydroxy-2-heptenoic acid 1,6-lactone were generously provided by Prof. Roger Adams.[32] The sample of β-cyclogeranic acid was kindly furnished by Dr. William J. Houlihan and recrystallized from petroleum ether, m.p. 94°; reported[40d] m.p., 93–94°.

Cyclohexylideneacetic acid was prepared by the procedure of Wallach; rectangular prisms from petroleum ether, m.p. 92–93°.[40e,123]

Methyl 2-ethyl-2-hexenoate. A solution of 2-ethyl-2-hexenoic acid (Carbide) (100 g., 0.70 mole), 700 ml. of methanol and 50 ml. of concentrated sulfuric acid was allowed to stand at *ca.* 3° (refrigerator) for one week. The excess methanol was removed *in vacuo* at 30°, water added, and the ester separated, washed with sodium bicarbonate solution, water and dried. Distillation gave 84 g. (77%) of ester, b.p. 77–78° (15 mm.), n_D^{20} 1.4444.[124]

NEW BRUNSWICK, N. J.

(106) E. A. Braude, W. F. Forbes, and E. A. Evans, *J. Chem. Soc.*, 2202 (1953).
(107) J. Gripenberg, *Acta Chem. Scand.*, **5**, 995 (1951).
(108) A. C. Cope, M. Burg, and S. W. Fenton, *J. Am. Chem. Soc.*, **74**, 173 (1952).
(109) G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 3052 (1953).
(110) Pl. A. Plattner, A. Fürst, A. Eschenmoser, W. Keller, H. Kläui, St. Meyer, and M. Rosner, *Helv. Chim. Acta*, **36**, 1845 (1953).
(111) W. Kuhn and H. Schinz, *Helv. Chim. Acta*, **35**, 2008 (1952).
(112) W. Kuhn and H. Schinz, *Helv. Chim. Acta*, **35**, 3395 (1952).
(113) E. R. H. Jones, T. Y. Shen, and M. C. Whiting, *J. Chem. Soc.*, 763 (1951); the structure of this compound was not established.
(114) H. Heusser, K. Eichenberger, and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 1088 (1950).
(115) J. Romo and A. Romo de Vivar, *J. Am. Chem. Soc.*, **79**, 1118 (1957).
(116) D. H. Hey, J. Honeyman, and W. J. Peal, *J. Chem. Soc.*, 185 (1954).
(117) D. D. E. Newman and L. N. Owen, *J. Chem. Soc.*, 4713 (1952).
(118) R. Rüegg, J. Dreiding, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **33**, 889 (1950).
(119) L. G. Humber and W. I. Taylor, *J. Chem. Soc.*, 1044 (1955).
(120) Pl. A. Plattner, A. Fürst, and K. Jirasek, *Helv. Chim. Acta*, **29**, 730 (1946).
(121) P. Bagchi, F. Bergmann, and D. K. Banerjee, *J. Am. Chem. Soc.*, **71**, 989 (1949).
(122) Ch. A. Vodoz and H. Schinz, *Helv. Chim. Acta*, **33**, 1040 (1950); the authors suggest the presence of some β,γ-isomer in the sample.
(123) Wallach, *Ann.*, **365**, 261 (1909), reports m.p. 91–92°.
(124) M. Häusermann, *Helv. Chim. Acta*, **34**, 1482 (1951) reports b.p. 66–69° (10 mm.), n_D^{21} 1.4403.

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION OF HUMBLE OIL AND REFINING COMPANY]

Ozonolysis of Cyclohexene in Methanol

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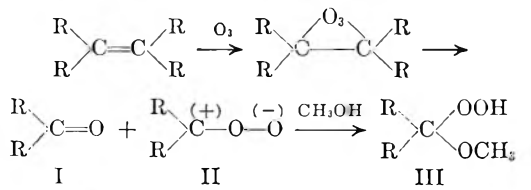
The ozonolysis of cyclohexene in methanol yields polymers of the expected methoxy hydroperoxide. Whenever an aldehyde is formed along with an alkoxyhydroperoxide during ozonolyses in alcohol solvents, it is to be expected that the two will interact.

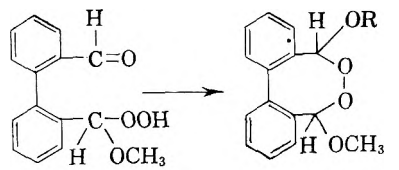
Criegee and co-workers[2–4] have shown that ozonolysis of olefins cleaves the double bond to produce an aldehyde or ketone (I) and a zwitterion (II). If the solvent is methanol, the zwitterion (II) reacts with the solvent to produce a methoxy hydroperoxide (III). Until recently all of the cases studied using methanol as solvent were those in which I was a ketone.



A compound which during ozonolysis would yield an aldehyde as fragment I is phenanthrene. The initial product from the ozonolysis of phenanthrene in methanol is the methoxy hydroperoxide IV.[5] It was isolated, however, in the form of the cyclic hemiperacetal Va, produced by addition of the hydroperoxy group to the carbonyl group of IV.[5b] When kept in solution at room temperature the hemiperacetal reacted further with the solvent to form the peracetal Vb. It is of interest to determine whether such interactions are general during ozo-

(1) For reprints of this paper, address the author at the Department of Chemistry, The University of Texas, Austin, Tex.
(2) R. Criegee and G. Wenner, *Ann.*, **564**, 9 (1949).
(3) R. Criegee and G. Lohaus, *Ann.*, **583**, 6 (1953).
(4) R. Criegee and G. Lohaus, *Ann.*, **583**, 12 (1953).
(5) (a) P. S. Bailey, *J. Am. Chem. Soc.*, **78**, 3811 (1956). (b) P. S. Bailey and S. B. Mainthia, Results to be published shortly.

nolysis, or whether the situation in compound IV is unique.



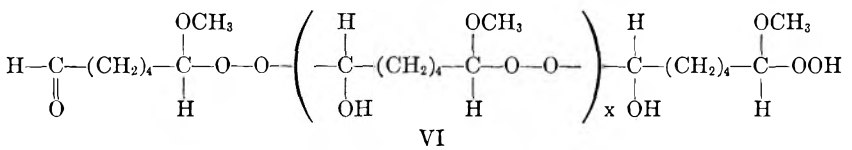
IV V a) R = H b) R = CH_3

A simpler compound with a double bond similar to that of the 9,10 bond of phenanthrene is cyclohexene. Criegee and coworkers[6] have ozonized cyclohexene in inert solvents and have obtained a 6% yield of a monomeric ozonide. The rest was largely a polymeric peroxidic material. Three patents have been issued for the ozonolysis of cyclohexene in methanol.[7,8] The peroxidic ozonolysis product was analyzed but no structure was assigned to it. It was described as a complex mixture of monomeric alkoxy peroxides and hydroperoxides.

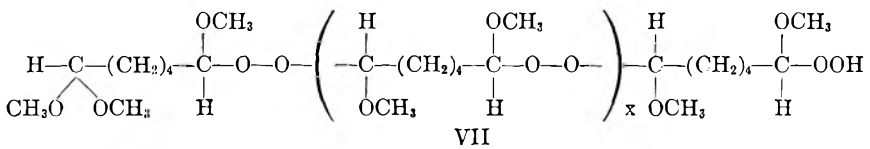
In the present work the ozonolysis of cyclohexene in methanol has been repeated and the product has been shown to be a mixture of polymeric peroxides of types VI and VII and/or methylated products intermediate between VI and VII. These are produced by an *inter*molecular interaction of the hydroperoxy and aldehyde groups of the methoxy hydroperoxide (VIII). This is to be contrasted with the *intra*molecular interaction found in the case of the hydroperoxide (IV) from ozonolysis of phenanthrene. This difference in behavior of the two hydroperoxides is to be expected on the basis that the two interacting groups in IV are in close proximity, whereas they are not in VIII. It appears that compounds which yield an aldehyde as fragment I do not give simple alkoxy hydroperoxides as final products upon ozonolysis in alcohols as solvents. Instead, hemiperacetals and peracetals from intermolecular or intramolecular interactions generally will be produced. An exception is the ozonolysis of 1,2-dibenzoylethylene. The aldehyde fragment, phenylglyoxal, forms acetals with the solvent preferentially.[9]

Structure VI is entirely in the hemiperacetal form. Structure VII was produced by reaction of VI with methanol, whereby the aldehyde group was converted to an acetal group and the hemiperacetal groups were converted to peracetal groups. When the cold reaction mixture from the ozonolysis of cyclohexene was evaporated immediately, and was kept cold during the evaporation, the residue was found to be rich in VI. When, however, the reaction mixture was allowed to stand for a period of time at room temperature before evaporation, the residue was found to be rich in VII.

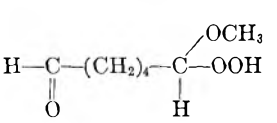
These products could not be separated and purified. Decomposition, resulting in loss of the peroxidic function, occurred during attempted distillation. The mixtures were sufficiently characterized, however, by elemental analyses, cryoscopic molecular weight determinations, methoxyl group determinations, infrared spectra, and decomposition to adipic acid by hydrogen peroxide in formic acid solution.



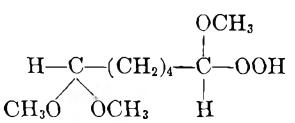
VI



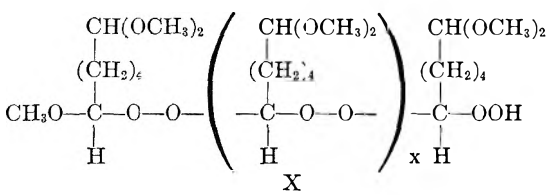
VII



VIII



IX



X

Hydrogen peroxide in basic solution gave only a trace of adipic acid. The fact that a high yield (85%) was obtained in formic acid is excellent evi-

(6) R. Criegee, G. Blust, and G. Lohaus, *Ann.*, **583**, 2 (1953).

(7) (a) R. E. Foster and H. E. Schroeder (to E. I. du Pont de Nemours and Co., Inc.) U. S. Patent **2,657,240** (Oct. 27, 1953). (b) E. I. du Pont de Nemours and Co., Inc., British Patent **713,344** (Aug. 11, 1954).

(8) E. E. Fisher (to E. I. du Pont de Nemours and Co., Inc.) U. S. Patent **2,733,270** (Jan. 31, 1956).

(9) P. S. Bailey and S. S. Bath, *J. Am. Chem. Soc.*, **79**, 3120 (1957).

TABLE I

ANALYTICAL DATA FOR PEROXIDIC PRODUCTS

	Sirup from Immed. evap.	Sirup from Evap. after 1 hr.	Sirup from Evap. after 4 days	Theor. for Structure VI (x = 1)	Theor. for Structure VII (x = 1)	Theor. for Structure IX
% C	50.67, 50.42	50.88, 50.74	51.94, 51.74	51.84	53.55	51.90
% H	9.15, 9.07	8.98, 9.09	9.14, 9.26	8.70	9.35	9.68
% O		38.0, 37.4		39.46	37.10	38.42
% Active O		7.44, 7.31		9.86	8.56	7.68
% OCH_3	26.30, 25.95	36.21, 36.02	41.51, 40.92	19.14	38.75	44.71
Mol. Wt.		402,[a] 584[b]	393[a]	486	561	208
Infrared Spectrum	Strong OH band at 2.95μ Medium C=O band at 5.8μ	Strong OH band at 3μ Weak C=O band at 5.75μ	Strong OH band at 3μ Weak C=O band at 5.75μ			

[a] Molecular weight determination by boiling point elevation of benzene. Performed by Miss Jennie M. Chenet of Humble. [b] Molecular weight determination cryoscopically in benzene—probably more accurate, since less chance of decomposition at the lower working temperature. Performed by Mr. S. B. Mainthia of University of Texas.

dence for the peracetal formulation, which would be readily hydrolyzed under acidic conditions. The high methoxyl group content also speaks for this formulation. Only one other possible polymeric peroxide (X) would have such a high methoxyl group content. Not being a peracetal, however, it would not be expected to be hydrolyzed and oxidized to adipic acid in so high a yield.

The infrared spectra showed a strong hydroxyl band at 3μ, an extremely weak carbonyl band at 5.8 μ and no band at 9.4–9.6 μ, the region which both Criegee[10] and Briner[11] and their co-workers have found to be characteristic of ozonides.

The molecular weight determinations indicated that the polymers (VI and VII) were primarily trimeric. It is to be noted, however, that in the case of the sample which had stood for four days before evaporation of the solvent, the methoxyl group content is so high that one must assume the presence of considerable amounts of the completely methoxylated monomer IX. If this is so, it is reasonable to assume that the mixtures are composed of monomers (VIII and/or IX), dimers, and polymers (VI and/or VII) in which "x" varies from 1 to 4 or 5. The analytical data are summarized in Table I.

EXPERIMENTAL

The ozone source was a Welsbach T-23 laboratory ozonator. Oxygen dried to a dewpoint of −60° or below was employed. The ozonolysis flask was essentially a tube with the gas inlet at the bottom, a sealed-in fritted disc just above the inlet, and the outlet near the top. The cyclohexene was Phillips Pure (99%) grade.

The peroxidic ozonolysis products. A stream of oxygen containing approximately 6% ozone by weight was passed through a solution of 4.1 g. (0.05 mole) of cyclohexene and 50 ml. of anhydrous methanol at a rate of approximately 20 liters per hour and a temperature of approximately −70°. The ozone was completely absorbed until one mole per mole of cyclohexene had reacted, after which the gas stream released iodine in the potassium iodide trap adjoining the ozonolysis flask.

In one case the methanol was immediately evaporated from the cold solution at 0.5 mm. pressure, using a Rinco rotary evaporator. The residue was a clear, very viscous sirup weighing 8.9 g. In two other cases the reaction mixture was allowed to stand for 1 hr. and for 4 days before evaporation. The residual sirups were less viscous and weighed 9.5 g. and 9.9 g., respectively. All three samples strongly oxidized iodide ion to iodine and slowly released oxygen from lead tetraacetate. The latter is a weak, but positive, test for a hydroperoxide.[12] Analytical data is summarized in Table I.

In another experiment an attempt was made to purify the sirup by fractional distillation at 0.5 mm. The clear distillate (b.p. 90–118°) gave only weak peroxide tests with sodium iodide. Throughout the distillation gas evolution occurred from the sirup in the still. Attempts were then made, on a fresh batch of the sirup, to prepare crystalline derivatives, such as an oxime, a semicarbazone, and a 2,4-dinitrophenylhydrazone involving the carbonyl group and a 3,5-dinitrobenzoate and benzoate involving the hydroperoxy group. In each case loss of the peroxidic property occurred. Under the alkaline conditions necessary for oxime and semicarbazone preparations no crystalline material was obtained, indicating that the aldehyde group was involved in acetal formation.

Conversion to adipic acid. The ozonolysis was carried out on a 0.05 mole sample and the methanol evaporated as described in the preceding experiments. The peroxidic residue (9.1 g.) was dissolved in 35 ml. of 90% formic acid and 17 ml. of 30% hydrogen peroxide was added. Upon gentle warming a vigorous reaction set in (Caution!). After the spontaneous reaction had ceased (30–45 min.) the reaction mixture was refluxed for 30 min., after which time it gave a negative peroxide test with sodium iodide. The mixture was cooled and the initial crop of adipic acid was filtered off. The filtrate was evaporated and the residue was washed with ether and separated by filtration. The total yield of adipic acid melting at 147–150° was 6.2 g. (85% based on cyclohexene). From the filtrates 0.3 g. of acidic material melting at 135–140° was obtained. The rest was an oil.

(10) R. Criegee, A. Kerckow, and H. Zinke, *Chem. Ber.*, **88**, 1878 (1955).

(11) E. Briner and E. Dallwigk, *Compt rend.*, **243**, 630 (1956); *Helv. Chim. Acta.*, **39**, 1446 (1956).

(12) R. Criegee, *Fortschr. Chem. Forsch.*, **1**, 536 (1950).

Acknowledgment. The author wishes to thank the Humble Oil and Refining Company for inviting him to their Baytown laboratories for the summer of 1956 and placing their research facilities at his disposal. He is especially grateful to Mr. J. A. Anderson, Jr., and Dr. J. T. Horeczy, in whose sections he worked, for facilitating many things; Doctors E. M. Amir and R. H. Perry for sharing their laboratory with him, and Messrs. E. J. Hoffman and R. L. Heinrich for sharing their office with him.

BAYTOWN, TEX.

[CONTRIBUTION FROM COATES CHEMICAL LABORATORIES, LOUISIANA STATE UNIVERSITY]

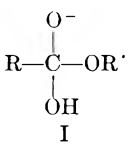
Solvolyses of Some Sterically Hindered Aliphatic Esters[1]

JAMES G. TRAYNHAM AND MERLE A. BATTISTE[2]

Received June 5, 1957

Solvolyses, mainly in alkaline solutions, of several methyl, isopropyl, and *s*-octyl branched aliphatic esters have been studied. Even when the normal reaction path through an addition intermediate (I) was severely hindered, evidence for the alternate path (alkyl-oxygen fission) was not obtained.

Alkaline hydrolyses of primary and secondary alkyl esters usually occur by acyl-oxygen fission,[3] probably through an addition intermediate (I).[4]



I

With tertiary alkyl,[5] allyl,[6] and diarylcarbinyl[7] esters, alkyl-oxygen fission[8] occurs predominantly or exclusively. For these systems the alternative mode of fission has been attributed to ion formation.[3] A bimolecular displacement reaction, however, leads to alkyl-oxygen fission in the hydrolysis of β-lactones.[9] Even with methyl esters under conditions that mask the usual reaction, slow alkyl-oxygen fission has been observed.[10]

With two modes of fission possible (by three paths: acyl-oxygen, alkyl-oxygen by ionization, and alkyl-oxygen by displacement), the difference in energy requirements in each case will control the course of the reaction. With saturated primary and secondary alkyl esters, the addition intermediate appears to be favored energetically. In other systems, the formation of relatively stable carbonium ions or relief of strain in a small ring compound appear to be favored over the addition intermediate. When normal acyl-oxygen fission merely regenerates reactants (*e.g.*, methyl benzoate and methoxide in anhydrous methanol[11]), alkyl-oxygen fission, much less favored but not prohibitively so, occurs slowly.

In several types of reactions, including hydrolysis of certain aromatic esters, steric factors have been found to outweigh all other factors in controlling the reaction course among several alternatives. Thus in olefin-forming eliminations with highly-branched alkyl derivatives, the less-substituted olefin predominates.[10] And highly-hindered aromatic esters which are not hydrolyzed by the usual procedure quickly respond, through acylium ion formation, to treatment with concentrated sulfuric acid.[12] The effects of extensive branching on the rates of esterification and hydrolysis have been examined in some detail.[13] We though it of interest to examine the importance of steric factors in controlling the course of the hydrolysis reaction with aliphatic esters.

The change in mode of fission as the alkyl group is changed from primary to tertiary may arise in part from an increase in energy requirements for formation of the addition intermediate (I). Formu-

(1) Taken from the M.S. thesis of M. A. Battiste, Louisiana State University, August, 1956. Presented in part at the Southwide Chemical Conference, Memphis, Tenn., December 7, 1956.

(2) University research assistant, 1955–56.

(3) For excellent reviews, see C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, p. 752 ff, Cornell University Press, Ithaca, N. Y., 1953; and J. Hine, *Physical Organic Chemistry*, p. 266 ff, McGraw-Hill Book Co., Inc., New York, N. Y., 1956.

(4) M. L. Bender, *J. Am. Chem. Soc.*, **73**, 1626 (1951).

(5) C. A. Bunton, A. E. Comyns, J. Graham, and J. R. Quayle, *J. Chem. Soc.*, 3817 (1955).

(6) H. W. J. Hills, J. Kenyon, and H. Phillips, *J. Chem. Soc.*, 576 (1936); J. Kenyon, S. M. Partridge, and H. Phillips, *J. Chem. Soc.*, 207 (1937); M. P. Balfe, H. W. J. Hills, J. Kenyon, H. Phillips, and B. C. Platt, *J. Chem. Soc.*, 556 (1942).

(7) M. P. Balfe, M. A. Doughty, J. Kenyon, and R. Poplett, *J. Chem. Soc.*, 605 (1942); M. P. Balfe, A. Evans, J. Kenyon, and K. N. Nandi, *J. Chem. Soc.*, 803 (1946).

(8) A. G. Davies and J. Kenyon, *Quart. Revs.* (*London*), 9, 203 (1955).

(9) W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1264 (1937); F. A. Long and M. Purchase, *J. Am. Chem. Soc.*, **72**, 3267 (1950).

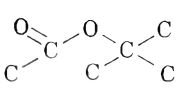
(10) J. P. Bunnett, M. M. Robison, and F. C. Pennington, *J. Am. Chem. Soc.*, **72**, 2378 (1950).

(11) H. C. Brown and I. Moritani, *J. Am. Chem. Soc.*, **77** 3623 (1955).

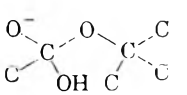
(12) M. S. Newman, *J. Am. Chem. Soc.*, **63**, 2431 (1941).

(13) See M. S. Newman, in *Steric Effects in Organic Chemistry*, ed. by M. S. Newman, pp. 205–225, John Wiley and Sons, Inc., New York, N. Y., 1956.

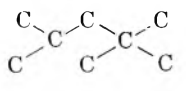
las II–V illustrate the relationship between *t*-butyl acetate, its addition intermediate and hydrocarbons of similar structure. Homomorphs[14] of di-*t*-butylmethane (V) have been shown to be appreciably strained. Although oxygen is smaller than methyl (and II and III are not properly regarded as true homomorphs of IV and V, respectively), the in-



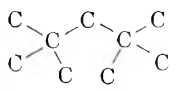
II



III



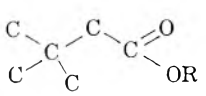
IV



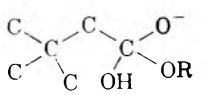
V

crease in strain in going from II to III is probably quite similar to that for the transition IV to V. At least it seems reasonable that a significant contribution to the difference in energy requirements for the two modes of fission with such branched esters may arise from the unfavorable strain in the addition intermediate leading to acyl-oxygen fission. By considering changes in steric interaction accompanying changes in hybridization of the carbonyl carbon, Taft[15a] has described similar conclusions about the role of steric effects in the formation of the addition intermediate.

Strained structures may be obtained with nontertiary alkyl esters when the acid chain rather than the alkyl chain is branched (formulas VI and VII).



VI



VII

In order to evaluate the importance of this strain in promoting alkyl-oxygen fission, we have studied solvolyses, mainly in alkaline solutions, of several *s*-octyl, methyl, and isopropyl esters prepared from branched aliphatic acids. The acids chosen were trimethylacetic, *t*-butylacetic and diisopropylacetic acids. Both racemic and optically active esters were solvolized under a variety of conditions: hydroxide in aqueous alcohol, methoxide in anhydrous methanol, 2-propoxide in anhydrous 2-propanol, and dilute acid in aqueous methanol or acetone. Normal acyl-oxygen fission would give alcohol with complete retention of configuration, alkyl-oxygen fission by ionization would give alcohol or ether with inversion and extensive racemization, and alkyl-oxygen fission by displacement would give alcohol or ether with inversion of configuration.

In nearly all experiments only alcohol with complete retention of configuration was obtained. In one early experiment, based on the expectation that the *s*-octyl *t*-butylacetate would be more resistant to hydrolysis than it proved to be, concentrated alkali in slightly aqueous 2-propanol was employed and the product alcohol was appreciably racemized (15% loss of activity). However these same conditions racemized (−)2-octanol no less extensively. Under no conditions was ether obtained and in no other experiment was the rotation of product 2-octanol significantly different from that of starting 2-octanol. With *s*-octyl diisopropylacetate, saponification in anhydrous methanol proceeded to a maximum of 12% after 20 days refluxing. Despite this extremely slow rate, we were unable to detect any methyl *s*-octyl ether (which would have indicated alkyl-oxygen fission). Even when conditions were chosen which would mask the normal path—*i.e.*, alkoxide in anhydrous alcohol with the corresponding alkyl ester—no ether nor carboxylate could be detected in the resulting reaction mixtures. These results clearly indicate that even when bimolecular attack at the carbonyl carbon is severely hindered and the rate of acyl-oxygen fission is unusually slow, alkyl-oxygen fission in these substituted acetates is still highly unfavored.

The occurrence of alkyl-oxygen fission by displacement in the reaction of methoxide with methyl benzoate,[10] in contrast to its absence in our experiments with methyl *t*-butylacetate, may result from the greater electron-withdrawing influence of phenyl over alkyl. The slightly greater electron depletion at the methyl carbon in the benzoate may well facilitate nucleophilic attack at that carbon sufficiently to account for the contrasting observations. Strong support for this suggestion is found in the data of Hammett and Pfluger[15b] on the reaction of trimethylamine with methyl esters to give quaternary ammonium salts by alkyl-oxygen fission.

$$RCO_2CH_3 + N(CH_3)_3 \longrightarrow RCO_2^- + N(CH_3)_4^+$$

The order of rates of these reactions parallels the order of acid strengths (*e.g.*, benzoate faster than acetate), providing evidence that electron-withdrawal in R increases the rate of alkyl-oxygen fission. Somewhat more direct support is derived from a single preliminary experiment in our laboratory which we hope to extend and report in detail later. Methyl trifluoroacetate, in which electron-withdrawing effects in the acid chain are essentially maximum, reacted with methoxide in refluxing anhydrous methanol to give a rather rapid evolution of gas, presumed to be methyl ether.

The lower susceptibility of secondary carbons (compared with primary carbons) to nucleophilic displacements would make such reactions even less

(14) H. C. Brown, G. K. Barbaras, H. L. Berneis, W. H. Bonner, R. B. Johannesen, M. Grayson, and K. L. Nelson, *J. Am. Chem. Soc.*, **75**, 1 (1953).

(15a) R. W. Taft, Jr., in *Steric Effects in Organic Chemistry*, ed. by M. S. Newman, p. 597, John Wiley and Sons, Inc., New York, N. Y., 1956.

(15b) L. P. Hammett and H. L. Pfluger, *J. Am. Chem. Soc.*, **55**, 4079 (1933). We are grateful to Referee II for pointing out the pertinence of this reference to our discussion.

TABLE I

PHYSICAL PROPERTIES OF ACIDS, ACID CHLORIDES, AND ESTERS

Compound	B.P., (Mm.) °C.	n_D^{20}	d_4^{20}	α_D^{20}
Trimethylacetic acid	82–85 (20)	...	...	...
Trimethylacetyl chloride	104–105	1.4142	1.003	...
s-Octyl trimethylacetate	92–93 (11)	1.4172	0.842	−8.85°[a]
		1.4175		+10.53°[b]
Methyl trimethylacetate	98–99	1.3894	0.850	...
Isopropyl trimethylacetate	68–69 (104)	1.3888	0.830	...
t-Butylacetic acid	98–99 (25)	1.4110	0.915	...
t-Butylacetyl chloride	68–71 (100)	1.4229	0.964	...
s-Octyl *t*-butylacetate	114 (10)	1.4247	0.848	−6.25°[a]
				+7.49°[b]
Methyl *t*-butylacetate	124–126	1.3994	0.870	...
Isopropyl *t*-butylacetate	82–83 (69)	1.4025	0.838	...
Diisopropylacetic acid	108 (12)	1.4264	...	...
Diisopropylacetyl chloride	88–89 (54)	...	...	...
s-Octyl diisopropylacetate	137 (12)	1.4333	...	+7.81°[b]
Methyl diisopropylacetate	72–74 (34)	1.4159	...	...

[a] From (−)2-octanol, α_D^{20} −6.45°. [b] From (+)2-octanol, α_D^{20} +7.88°.

likely among the *s*-octyl and isopropyl esters studied here.

The differences in energy requirements of the alternative modes of reaction for unbranched aliphatic esters are greater then than the steric strains imposed on the addition intermediate among the esters included in this study. A tentative inference is that, although steric factors do indeed play a significant role in determining the *rates* of normal ester hydolyses, polar factors seem to play the predominant role in determining the *course* of the reactions of esters of primary and secondary alcohols in basic solution.

EXPERIMENTAL[16]

Preparation of materials. Trimethylacetic acid and *t*-butylacetic acid were obtained (in 82% and 85% yields) by hypobromite oxidation[17] of pinacolone and methyl neopentyl ketone,[18] respectively. Diisopropylacetic acid was prepared in 50% yield by hydrolysis of diisopropylcyanoacetic acid with concentrated HCl in a sealed tube heated at 160–170° for 14–18 hr.[19] The diisopropylcyanoacetic acid[20] (m.p. 95.5–97.5°) was obtained by alkaline hydrolysis of the ethyl ester[20] [b.p. 85–87° (3 mm.), n_D^{20} 1.4350, d_4^{20} 0.953] which was prepared[20] in 61–77% yield from ethyl cyanoacetate and isopropyl bromide or iodide.

The acids were converted to the corresponding acid chlorides (66–90% yields) with excess thionyl chloride. Heating the acid chloride with the appropriate alcohol, followed by the usual work-up, gave esters in good yields. The physical properties of these compounds are described in Table I.

Anhydrous methanol was prepared from reagent grade alcohol and magnesium turnings.[21] Anhydrous 2-propanol was prepared by distilling reagent grade alcohol from calcium metal.[21]

2-octanol was resolved in the customary manner;[22] b.p. 91° (18 mm.), n_D^{20} 1.4260, d_4^{20} 0.821, α_D^{20} −6.45° and +7.88°.

Solvolysis experiments. (*A*) *Hydroxide in aqueous alcohol.* *1. Methanol.* A solution was prepared by dissolving 5.18 g. (0.024 mole) of (+)*s*-octyl trimethylacetate in 60 ml. of aqueous 90% methanol which was 0.75*M* in sodium hydroxide. After being refluxed for 4 days, the mixture was diluted with water and extracted with petroleum ether (b.p. 60–70°). Drying and distilling gave 2.9 g. (93%) of (+)2-octanol; n_D^{20} 1.4261, α_D^{20} +7.86°.

Similar treatment of 6.10 g. (0.027 mole) of (+)*s*-octyl *t*-butylacetate led to 3.13 g. (90%) of (+)2-octanol; n_D^{20} 1.4262, α_D^{20} +7.82°. From the alkaline aqueous solution, *t*-butylacetic acid was obtained in 96% yield.

Hydrolysis of 5.13 g. (0.020 mole) of (+)*s*-octyl diisopropylacetate under similar conditions was attempted, but after 13 days refluxing only traces of 2-octanol could be isolated. Analysis of the product fractions by use of refractive indices indicated that the extent of hydrolysis did not exceed 5%.

2. 2-Propanol. A sample of (−)*s*-octyl *t*-butylacetate was added to about 4 times its volume of an alkaline solution prepared by dissolving potassium hydroxide (27% by wt.) in slightly aqueous 98% 2-propanol. The solution was refluxed for 41 hr. Dilution with water, extraction with petroleum ether, and distillation gave (−)2-octanol in 88% yield; n_D^{20} 1.4260, α_D^{20} −5.30°.

(*B*) *Methoxide in anhydrous methanol.* To a solution prepared by dissolving about 0.1 g.-atom of sodium in 60 ml. of anhydrous methanol was added about 0.05 mole of ester. The solution was protected by drying tubes from atmospheric moisture while being refluxed for an appropriate time (48 hr. unless specified otherwise). It was then cooled, acidified with dilute sulfuric acid, and diluted with water to dissolve all salts. The mixture was extracted twice with petroleum ether (b.p. 30–40°).[23] The combined organic material was washed with dilute carbonate solution, dried over

(16) All optical rotations were measured with pure liquids in 1-dm. jacketed tubes.

(17) A. H. Homeyer, F. C. Whitmore, and V. H. Wallingford, *J. Am. Chem. Soc.*, 55, 4209 (1933).

(18) Prepared by procedure of W. A. Mosher and J. C. Cox, Jr., *J. Am. Chem. Soc.*, 72, 3701 (1950).

(19) J. von Braun and F. Fischer, *Ber.*, 66, 101 (1933). The sealed tube was not specified by these authors but was found necessary in our experiments.

(20) F. C. B. Marshall, *J. Chem. Soc.*, 2754 (1930).

(21) A. I. Vogel, *Practical Organic Chemistry*, 3rd ed., pp. 169–70, Longmans, Green and Co., New York, N. Y., 1956.

(22) A. W. Ingersoll, *Org. Reactions*, II, 400 (1944). Only slightly more than 0.5 mole of brucine was used for each mole of *s*-octyl hydrogen phthalate in the resolution step.

(23) Methanol formed azeotropes with some of the esters and had to be excluded from the organic extract as much as possible. Petroleum ether was better than ethyl ether as the extracting solvent for this reason.

potassium carbonate, and distilled. In no experiment was any methyl *s*-octyl ether found. (The ether was prepared independently from methyl iodide and sodium *s*-octoxide; b.p. 78–82° (42 mm.), n_D^{21} 1.4108.)

The aqueous carbonate solution was acidified to permit isolation of any organic acid. No significant amount of acid could be found in these experiments.

1. (−)*s-Octyl trimethylacetate* gave a 57% yield of methyl trimethylacetate (n_D^{20} 1.3894) and a 92% yield of (−)2-octanol (α_D^{20} −6.46°, n_D^{20} 1.4260).

2. (−)*s-Octyl t-butylacetate* gave a 61% yield of methyl *t*-butylacetate (n_D^{20} 1.3996) and a 93% yield of (−)2-octanol (α_D^{20} −6.44°, n_D^{20} 1.4255). The infrared spectrum of the alcohol indicated slight contamination by ester.

3. *s-Octyl diisopropylacetate*, even after 20 days, was recovered in 88% yield. Small amounts (less than 0.2 g.) of methyl diisopropylacetate and 2-octanol were also obtained.

4. *Methyl t-butylacetate* was recovered unchanged after 14 days refluxing. No attempt to trap methyl ether was made, but no *t*-butylacetic acid could be detected.

(*C*) *2-Propoxide in 2-propanol.* A solution prepared from 0.18 g.-atom of sodium metal, 275 ml. of anhydrous 2-propanol, and 0.13 mole of isopropyl *t*-butylacetate was refluxed for 5 days while being protected from atmospheric moisture. From the organic material extracted from the acidified mixture, no isopropyl ether nor *t*-butylacetic acid could be obtained. The unreacted ester was recovered.

(*D*) *Acid hydrolyses. 1.* (+)*s-Octyl trimethylacetate* (5.32 g., 0.025 mole) was dissolved in 60 ml. of aqueous 90% methanol which was 0.6*M* in HCl. The solution was refluxed for 4 days, diluted with water, and extracted with petroleum ether. The extract was washed with dilute carbonate solution and with water. Drying and distillation gave, in addition to about 6% recovery of *s*-octyl ester, a 12% yield of methyl trimethylacetate[24] and a 90% yield of (+)2-octanol (α_D^{20} +7.88°, n_D^{20} 1.4257).

2. (+)*s-Octyl t-butylacetate* (6.2 g., 0.027 mole) was treated in a similar fashion. There were obtained about 7% recovery of starting ester, 76% yield of methyl *t*-butylacetate and 83% yield of (+)2-octanol (α_D^{20} +7.77°, slight recemization).

3. When a solution of (+)*s-octyl diisopropylacetate* (4.7 g., 0.018 mole) in 60 ml. of aqueous 90% acetone, 0.6*M* in HCl, was refluxed for 12 days, no detectable reaction occurred.

Acknowledgment. We have appreciated helpful discussions with Dr. Harold Shechter about this study before experiments were begun, and with Dr. H. C. Brown and Dr. Samuel Siegel near its completion.

BATON ROUGE, LA.

(24) Some loss resulting from the difficulty of cleanly separating ester and petroleum ether may account for this low yield.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

1,5-Diaryl-2,3-pyrrolidinediones. VIII. Synthesis and Structure Proof

WALTER L. MEYER[1] AND WYMAN R. VAUGHAN

Received April 26, 1957

1,5-Diphenyl-2,3-pyrrolidinedione (XI) has been synthesized and its structure has been proven. This material was found to be identical with the previously unidentified thermal decarboxylation product of 1,5-diphenyl-4-carbethoxy-2,3-pyrrolidinedione, and distinctly different from the substance previously assigned this structure, which is now known to be 5-phenyl-3-anilino-2(5*H*)-furanone.

Many reports of 1,5-diaryl-2,3-pyrrolidinediones as the products of the reaction of a benzylideneaniline with pyruvic acid or of a benzylidenepyruvic acid with an aromatic amine have appeared in the literature since Schiff and Gigli[2] first reported 1,5-diphenyl-2,3-pyrrolidinedione itself. Although the formulation of these compounds has been accepted almost without question,[3] several curious aspects of their chemical behavior[4] and dissimilarities in properties and infrared spectra between these and 2,3-pyrrolidinediones with other types of substitution[4–6] suggested that a critical examination of the structure of the supposed 1,5-diaryl-2,3-pyrrolidinediones was in order.[7,8]

Previous investigators[9,10] have attempted degradative studies on the presumed 1,5-diphenyl-2,3-pyrrolidinedione (I) without conclusive results.

(1) National Science Foundation Predoctoral Fellow, 1954–1957. Abstracted from a portion of the Ph.D. dissertation of Walter L. Meyer, University of Michigan, 1957.

(2) R. Schiff and L. Gigli, *Ber.*, **31**, 1306 (1898).

(3) *Cf.*, however, K. Garzarolli-Thurnlackh, *Monatsh.*, **20**, 480 (1899).

(4) (a) W. R. Vaughan and L. R. Peters, *J. Org. Chem.*, **18**, 393 (1953); (b) W. R. Vaughan and L. R. Peters, *J. Org. Chem.*, **18**, 405 (1953); (c) W. R. Vaughan and D. I. McCane, *J. Org. Chem.*, **20**, 143 (1955); (d) W. R. Vaughan, *J. Org. Chem.*, **20**, 1619 (1955).

(5) (a) P. L. Southwick and L. L. Seivard, *J. Am. Chem. Soc.*, **71**, 2532 (1949); (b) P. L. Southwick and R. T. Crouch, *J. Am. Chem. Soc.*, **75**, 3413 (1953); (c) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).

(6) (a) R. Schiff and C. Bertini, *Ber.*, **30**, 601 (1897); (b) L. J. Simon and A. Conduché, *Ann. chim. phys.*, [8] **12**, 5 (1907).

(7) For a preliminary report on the results of this study see W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 93 (1957).

(8) Since the publication of our preliminary report,[7] results of a study which reached the same conclusions have appeared, see H. H. Wasserman and R. C. Koch, *Chemistry & Industry*, 428 (1957).

(9) H. Bücherer and R. Russischwili, *J. Prakt. Chem.*, **128**, 89 (1930).

(10) S. Bodforss, *Ann.*, **455**, 41 (1927).

Thus it was determined that for a structure proof of I, unequivocal synthesis offered the most promising procedure.

For synthesis of the 2,3-pyrrolidinedione structure (Chart I), the starting materials of choice were the butyrolactams (II). Since a convenient procedure was available for the preparation of 1-phenyl-2-pyrrolidinone (IIb) from available starting materials,[11] pilot experiments on the introduction of a 3-keto function were carried out on this model.

For the introduction of functionality at the 3-position of the pyrrolidinone ring, the base-catalyzed formylation of an activated methylene position with ethyl formate was utilized. In spite of the weak activating influence of the amide carbonyl,[12] low yields of a crude semi-solid substance having properties expected of the desired 1-phenyl-3-hydroxymethylene-2-pyrrolidinone (III) could be obtained from this reaction. Although we were unable to purify this product, *O*-acyl derivatives were readily prepared and purified, serving

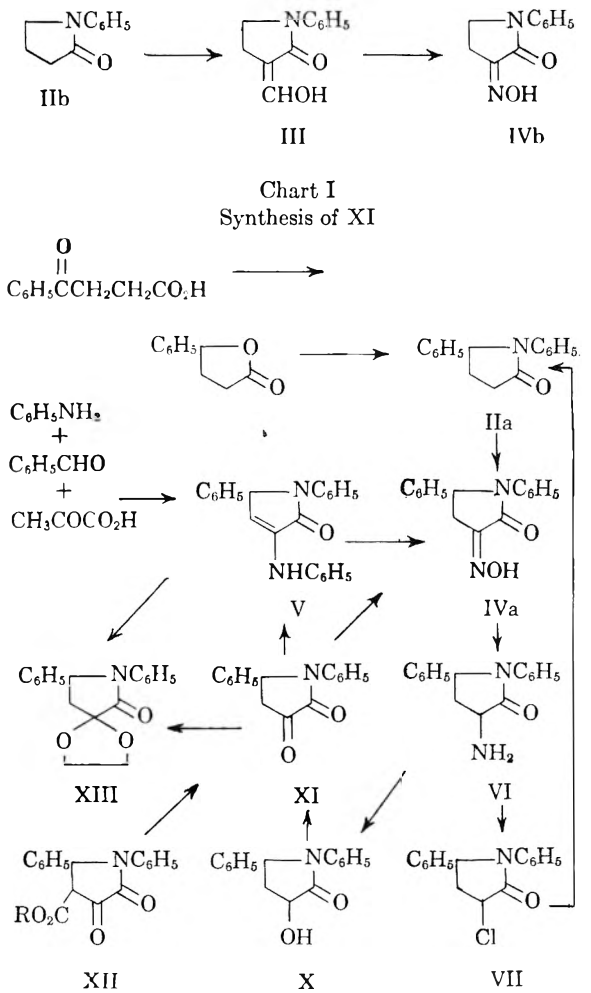


Chart I
Synthesis of XI

(11) E. Späth and J. Lintner, *Ber.*, 69, 2727 (1936).

(12) Other reagents designed to attack the 3-methylene group of IIb, *e.g.*, selenium dioxide, bromine, or amyl nitrite, failed to react, indicating the lactam methylene group to be very inactive.

further to characterize the hydroxymethylene compound (III).

Nitrosation of crude III at the reactive α-position with simultaneous cleavage of the formyl group afforded the 2,3-pyrrolidinedione-3-oxime (IVb). With the 1-phenyl compound, either aqueous nitrous acid or ethanolic amyl nitrite and base produced this conversion. In contrast to the hydroxymethylene compound III, 1-phenyl-3-oximino-2-pyrrolidinone (IVb) is a high-melting stable material, readily purified. However, even under the most fruitful reaction conditions employed, the yield of this oxime was very poor, 8.4% from the lactam IIb. Since all attempted hydrolysis experiments on IVb failed, attention was turned to the 1,5-diphenyl series, from which larger amounts of the corresponding oxime were available.

For the synthesis of 1,5-diphenyl-2-pyrrolidinone (IIa), γ-phenyl-γ-butyrolactone was conveniently prepared on a large scale by sodium borohydride reduction of β-benzoylpropionic acid. Application of our modified technique for reaction of a lactone with aniline afforded good yields of the desired lactam IIa.

In view of the difficulties encountered in the isolation and purification of the 1-phenyl-3-hydroxymethylene compound, reaction conditions were modified in such a manner as to obviate the isolation of the 1,5-diphenyl analog. Following the formylation step, the crude mixture was treated with sufficient alcohol to hydrolyze any excess sodium hydride, and butyl nitrite was added to effect the nitrosation. In this manner there was obtained a low yield of 1,5-diphenyl-3-oximino-2-pyrrolidinone (IVa). On treatment with acetic acid and acetic anhydride, an acetate, which was easily reconverted to the parent oxime, was readily obtained.

Bodforss[10] reported the preparation of an oxime by treatment of 1,5-diphenyl-3-anilino-2(5*H*)-pyrrolone (the pyrrolidinedione anil, V) with hydroxylamine hydrochloride and sodium ethoxide. His oxime was assigned the structure IVa, assuming replacement of the anil by oxime. However, Bodforss reported a rather ill-defined melting behavior for his material, which was incompletely characterized, whereas the IVa obtained in this work melted quite sharply with decomposition in a very reproducible manner. On repetition of Bodforss' procedure with some modification, we found it possible to obtain his oxime in excellent yields on a large scale. This material was found to be identical with the IVa produced by the formylation-nitrosation route, apparently confirming the structure assignment.

In view of the excellent yields in the oximation of V, and the ready availibility of V from pyruvic acid, benzaldehyde, and aniline,[13] there was at

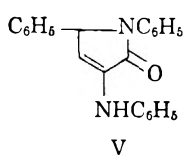
(13) W. R. Vaughan, *J. Org. Chem.*, 20, 1613 (1955).

hand a useful synthetic route to IVa. Although extensive research was undertaken toward its hydrolysis to the ketone, many common and several obscure methods for oxime cleavage being attempted, we were unable to find suitable conditions for this conversion. It would seem that 3-carbonyl derivatives of 1,5-diphenyl-2,3-pyrrolidinedione are extremely resistant to hydrolysis, for although the anil V may be converted to an ethylene ketal, it likewise has resisted cleavage; and the derived ethylene ketal is similarly unaltered under various hydrolytic conditions.

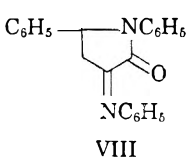
Catalytic hydrogenation of the oxime IVa over a platinum catalyst in acetic acid gave good yields of the primary amine VI. This amine, on treatment with nitrosyl chloride, smoothly afforded 1,5-diphenyl-3-chloro-2-pyrrolidinone (VII), which on catalytic hydrogenolysis in alcoholic base over palladium on calcium carbonate[14] yielded 1,5-diphenyl-2-pyrrolidinone (IIa). The identity of this substance with the sample previously prepared was confirmed by mixture melting point and identity of the infrared spectra of the two samples.

Thus it is assured that the pyrrolidinone skeleton has not been altered in any of the intermediates II through VII, and at the same time the structure IVa is confirmed.

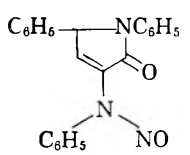
The arguments may now be extended to the anil V. Since this substance contains a replaceable anilino group, in the oxidation state of the anil, which is replaced by hydroxylamine to yield IVa, the anil function must also be at the 3-position of the lactam ring. Only two possible formulations allow this, V and VIII; and



V



VIII



IX

the infrared spectrum, as pointed out by Vaughan,[13] is inconsistent with VIII, since it contains a strong sharp absorption at 3300 cm.$^{-1}$ (NH).

Bodforss[10] reported the conversion of the anil to a derivative by treatment with sodium nitrite in hot glacial acetic acid. For unexplained reasons he postulated this compound to be a nitro derivative, although the sole analytical figure reported, (nitrogen) is in better agreement with the nitroso derivative. Since it was insoluble in sodium hydroxide, he postulated the "nitro" group to have entered one of the aromatic rings. The derivative was described as a yellow compound of melting point 143°.

We have been unable to duplicate this result. Rather, when the anil was subjected to Bodforss' conditions, a red mononitroso derivative (IX) which melted with decomposition at 271–272° was obtained.[15] The nitroso derivative is transparent in the high frequency (3000-4000 cm.$^{-1}$) region of the infrared, but otherwise has a spectrum which resembles that of the anil V. Thus it must be formulated as the *N*-nitroso derivative, chemically confirming the presence of an NH function in V. It was not found possible to obtain a positive Liebermann test for the *N*-nitroso group of IX, although the formation of the various colors characteristic of the test may easily have been masked by the intense color of IX itself. Thus both chemical and physical evidence demand an NH group in the anil, and the formulation of Vaughan[13] (V) is confirmed.

On treatment of the hydrochloride of VI with aqueous sodium nitrite, VI afforded the corresponding alcohol X in nearly quantitative yield.[16] Under rigidly controlled conditions, similar to those of Bruce[17] for the oxidation of dihydrocholesterol, chromic acid in aqueous acidic solution oxidized the alcohol in benzene solution to a ketonic product. This substance, the pyrrolidinedione XI, was difficult to separate from starting material and a second contaminant, but the characteristic nature of its infrared spectrum (as described below) and the preparation of pure derivatives, an anil identical with the intermediate V (of proven structure) and an ethylene ketal (*vide infra*) served for its characterization.

The formation of these derivatives confirms the hypothesis drawn from the infrared spectrum that the oxidation product is 1,5-diphenyl-2,3-pyrrolidinedione (XI). They demonstrate the presence of a ketonic carbonyl group in the material by their very formation, and the position of this new carbonyl must be *3*, since V has been shown to have the anil function at the *3* position.

1,5-Diphenyl-4-carbethoxy-2,3-pyrrolidinedione (XII) is known to decarboxylate on heating in nitrobenzene, but the organic product of this pyrolysis was not identified.[4c] This substance has now been isolated and purified, and was found to have an infrared spectrum similar to that of the XI obtained by oxidation of X.[18] We have determined

(14) M. Busch and H. Stöve, *Ber.*, **49**, 1063 (1916).

(15) Since it was found in the present work that at lower reaction temperatures significant amounts of anil were recovered, lowering the melting point and decreasing the intensity of the color of the product, it is suspected that Bodforss' material was the same as ours, but highly contaminated with unreacted anil.

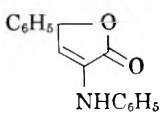
(16) A compound for which the structure X was offered was reported by Wasserman and Koch, *cf.* ref. 8, who oxidized it to what appears to be XI. While their compound melted 50° above our X, we have found our X and that of Wasserman and Koch to have *very similar* (but not identical) infrared spectra and to be monomeric. It is possible that they are epimers.

(17) W. F. Bruce, *Org. Syntheses*, **Coll. Vol. II**, 139 (1943).

(18) A pure product from the thermal decomposition of XII was first obtained by Mrs. I. S. Covey in independent work in these laboratories. We are indebted to Mrs. Covey for communication of her results and observations to us prior to publication. [W. R. Vaughan and I. S. Covey, paper in preparation].

that this "decarbethoxylation"[19] product of XII is in fact 1,5-diphenyl-2,3-pyrrolidinedione (XI). A sample of XI prepared in this manner readily affords an anil (V), an oxime (IVa), and an ethylene ketal (XIII). The first two of these derivatives are identical with our synthetic intermediates of proven structure, confirming the assignment of structure XI to the ketone; and the ethylene ketal XIII is identical with that obtained from the oxidation product XI. This confirms the structure of XIII as assigned and the identity of the two samples of XI.

1,5-Diphenyl-2,3-pyrrolidinedione (XI) exhibits properties expected of a compound of its structure. The infrared spectrum contains strong carbonyl absorptions at 1760 and 1700 cm.$^{-1}$, and no evidence of any (enolic) hydroxyl group. The compound gives no color reaction with aqueous or alcoholic ferric chloride solution and affords carbonyl derivatives with great ease, in complete analogy with the other authentic 2,3-pyrrolidinediones examined by Southwick.[5b,c] It bears no similarity to the material formerly assigned this structure, which on consideration of the evidence of Meyer and Vaughan[7] is now known to be 5-phenyl-3-anilino-2(5*H*)-furanone (XIV). Thus this



XIV

must be considered the first *true* 1,5-diaryl-2,3-pyrrolidinedione not containing other substituents which has been prepared (*cf.* ref 8).

The pyrrolidinedione XI apparently also exhibits the aldol dimerization behavior observed by Southwick for his simple 1-substituted compounds.[5c] Such a dimer is presumed to be the contaminant in the XI produced by the chromic acid oxidation of the alcohol X, from consideration of the infrared spectrum of the crude oxidation product. Although it was not purified and analyzed in the course of this work, the spurious bands in the infrared agree quite well with those reported by Southwick for the 1,1′-disubstituted-2,4′,5′-trioxo-3-hydroxy-3,3′-bipyrrolidines,[5c] and a high melting compound with a similar spectrum is obtained in the thermal preparation of XI from the β-keto ester XII if the solution is too concentrated or the thermal treatment is prolonged. Further work on this presumed dimer will be reported at a later date.

(19) This curious thermal "decarbethoxylation" of XII appears to be similar to the thermal decarbomethoxylation of *dl*-3-ethylenedioxy-16-carbomethoxy-5-androsten-17-one reported by W. S. Johnson, B. Bannister, R. Pappo, and J. E. Pike, *J. Am. Chem. Soc.*, **78**, 6354 (1956). Additional observations concerning this reaction will be published separately, W. R. Vaughan and I. S. Covey, paper in preparation.

EXPERIMENTAL

All melting and boiling points are uncorrected. Infrared spectra, unless otherwise noted, were obtained from Nujol mulls by means of a Perkin-Elmer Model 21 Infrared Spectrophotometer. Microanalyses are by Spang Microanalytical Laboratory, Ann Arbor, Mich.

1-Phenyl-2-pyrrolidinone (IIb). The method of Späth and Lintner[11] was modified for the preparation of IIb. A mixture of 86 g. (1.0 mole) of γ-butyrolactone (General Aniline and Film Corp.) and 165 ml. of aniline was heated at reflux with azeotropic removal of water for 3 days. After this period, 17 ml. (95%) of water had been collected and the pot temperature reached 220°. The mixture was distilled at reduced pressure, the fraction boiling 195–200°/21 mm. being collected as IIb. In this manner there was obtained 137 g. (85%) of product which solidified in the receiver. On recrystallization from petroleum ether (b.p. 60–75°) or ethyl acetate, the compound melts at 68–69° (reported[11] 68–69°).

1-Phenyl-3-hydroxymethylene-2-pyrrolidinone (III). The procedure of Tracy and Elderfield[20] for the formylation of γ-ethoxypropylmethyl ketone was modified for this reaction. In a four-neck, round-bottom flask, fitted with a mercury sealed stirrer, dropping funnel, reflux condenser, and inlet for dry nitrogen, was placed 100 ml. of dry toluene and 4.6 g. (0.10 g.-atom) of a 50% dispersion of sodium in toluene.[21] Under a dry nitrogen atmosphere with cooling in ice there was added dropwise a solution of 16.1 g. (0.100 mole) of IIb and 18 ml. of ethyl formate in 50 ml. of toluene. After the addition was complete, the mixture was allowed to rise to room temperature and was stirred for 12 hr. The tan gelatinous suspension was poured onto a mixture of ice and 5% hydrochloric acid, the layers were separated, and the aqueous layer was extracted twice with ether. After washing the combined organic layers three times with 100 ml. portions of 5% sodium bicarbonate solution, they were dried with Drierite and the solvent was removed at reduced pressure to leave 17.0 g. of a yellow oil. The oil gave a blue-green color with ferric chloride and was instantly oxidized by 1% potassium permanganate solution, but on distillation it was found to consist mainly of starting material. No procedure was found for purifying III. In one experiment it was separated from the starting lactam with dilute sodium hydroxide, which allowed isolation of a crude sample of III. This gave the above described positive tests with ferric chloride and potassium permanganate, and an infrared spectrum which contained strong absorptions at 3160, 1700, 1645, and 1620 cm.$^{-1}$ was obtained. This sample was also found incapable of purification. However, derivatives were prepared from the crude yellow oil as follows:

Acetate. A sample of the oil was treated with 5 ml. of acetic anhydride and heated on the steam bath for 1.5 hr. Cooling and partial evaporation produced fine white cottony needles of 1-phenyl-3-acetoxymethylene-2-pyrrolidinone. After several recrystallizations from methanol, the material melted at 162.0–162.5°.

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.67; N, 6.06. Found: C, 67.53; H, 5.69; N, 6.11.

Benzoate. A 3.0 g. sample of the oil was dissolved in a few ml. of pyridine and treated with benzoyl chloride. After warming on the steam bath for 30 min., the solution was cooled, methanol was added, and 0.6 g. (12% based on IIb) of the benzoate of III was filtered off; m.p. 182–184°. After two recrystallizations from ethanol, the analytical sample was obtained as white cottony needles, m.p. 183.0–183.5°.

Anal. Calcd. for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.16; N, 4.78. Found: C, 73.75; H, 5.23; N, 4.69.

(20) A. H. Tracy and R. C. Elderfield, *J. Org. Chem.*, **6**, 63 (1941).

(21) The sodium dispersion had an average particle size 6μ; this reagent was kindly supplied by the Ethyl Corp., Detroit, Mich.

1-Phenyl-3-oximino-2-pyrrolidinone (IVb). The preparation of III was carried out as described above to the point of hydrolysis. After the 12 hr. reaction period, there was added to the gelatinous suspension a solution of 11.7 g. (0.100 mole) of amyl nitrite (Merck & Co., Inc., U.S.P.) in toluene. After stirring an additional 4 hr., the mixture was poured onto ice. The layers were separated and the organic layer washed with two 200-ml. portions of 5% sodium hydroxide solution. The combined aqueous layers were acidified with hydrochloric acid and extracted with benzene. The solution was dried with Drierite and the solvent was evaporated in an air stream. After one recrystallization of the residue from ethanol there was obtained 1.6 g. (8.4%) of IVb, m.p. 200–205° dec. Three further recrystallizations produced white needles of analytical purity, m.p. 210.5–212.0° dec.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30; N, 14.73. Found: C, 63.31; H, 5.36; N, 14.79.

This compound could also be obtained by treatment of a basic aqueous solution of the crude hydroxymethylene compound III with sodium nitrite, followed by slow acidification.

The oxime IVb is soluble in 5% sodium hydroxide solution, produces no color with ferric chloride, and gives a negative test with Tollens' reagent. It dissolves in concentrated sulfuric acid affording a yellow solution which turns blood-red immediately on addition of concentrated nitric acid (Bodforss'[10] test for the pyrrolidinedione anil). It was not hydrolyzed by ethanolic-aqueous hydrochloric acid.

γ-Phenyl-γ-butyrolactone. To a filtered solution of 89 g. (0.50 mole) of crude β-benzoylpropionic acid[22] in 500 ml. of ethanol was added slowly with stirring a solution of 30 g. (0.79 mole) of commercial sodium borohydride (Metal Hydrides Inc.) in 500 ml. of ethanol. Following the addition, the reaction mixture was stirred at room temperature for 3 hr. After acidification with 10% hydrochloric acid, most of the ethanol was distilled off at atmospheric pressure on the steam bath. The resulting mixture was cooled to room temperature, extracted with benzene, and the benzene extracts dried with Drierite. The benzene was removed at reduced pressure on the steam bath and the residue distilled at 106–113°/0.5 mm. (reported 171–172°/11 mm.,[23] 123°/2 mm.[24]). This yielded 68.2 g. (84%) of product which solidified and melted at 34–36° (reported[24] 38°) and was sufficiently pure for further use.

1,5-Diphenyl-2-pyrrolidinone (IIa). The preparation of IIa was carried out by the procedure devised for the synthesis of IIb. A mixture of 68.2 g. (0.421 mole) of γ-phenyl-γ-butyrolactone and 80 ml. of aniline was refluxed with azeotropic removal of water for 3 days, 4.5 ml. of water being collected. When no further azeotroping occurred, excess aniline was distilled at water pump pressure and the residue dissolved in benzene. After washing thoroughly with 10% hydrochloric acid, the benzene solution was dried with Drierite and evaporated to dryness in an air stream. The crystalline residue was recrystallized from ethyl acetate to yield 61.5 g. (62%) of IIa. Two further recrystallizations from ethyl acetate or isopropyl alcohol yielded 52.0 g. (52%) of white product, m.p. 110–112°.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.99; H, 6.37; N, 5.90. Found: C, 81.11; H, 6.41; N, 5.98.

1,5-Diphenyl-3-anilino-2(5H)-pyrrolone (V). The procedure of Vaughan[13] was used for the reaction between benzaldehyde, aniline, and pyruvic acid to produce V.

1,5-Diphenyl-3-oximino-2-pyrrolidinone (IVa). (a) *From 1,5-Diphenyl-2-pyrrolidinone* (IIa). A one-liter, four-neck, round-bottom flask was fitted with a reflux condenser, dropping funnel, mercury sealed stirrer, and thermometer, charged with 100 ml. of sodium dried reagent benzene and 2.0 g. (0.085 mole) of sodium hydride, and filled with a dry nitrogen atmosphere. While stirring and passing through a slow stream of dry nitrogen, there was added at room temperature a solution of 6.3 g. (0.0085 mole) of ethyl formate (dried over phosphoric anhydride and redistilled, b.p. 53.0–53.2°) in 25 ml. of dry benzene. The resulting suspension was warmed to 55–60°, and a solution of 10.0 g. (0.0422 mole) of IIa in 125 ml. of dry benzene was added dropwise over a 1-hr. period. Following this addition, the reaction mixture was stirred at 55–60° under dry nitrogen for 24 hr.

After cooling the mixture to 6°, 20 ml. of absolute ethanol was added dropwise and the temperature was allowed to rise to about 25° with stirring to decompose residual sodium hydride. A solution of 4.4 g. (0.043 mole) of *n*-butyl nitrite[25] in 25 ml. of benzene was added and the mixture was then stirred for 8 hr. at 40–50°. After cooling to 10°, 100 ml. of water was added, the resulting mixture was stirred for 15 min., poured into a separatory funnel, and the layers were separated. The organic phase was washed with two 50-ml. portions of 10% sodium hydroxide. The combined aqueous phase and basic wash solutions were cooled, treated with Norit, filtered, and acidified with hydrochloric acid. The resinous yellow-orange suspension was cooled in the refrigerator overnight and then filtered. Recrystallization from ethanol produced 0.50 g. (4.5%) of IVa which melted at 219–222° dec. after darkening near 210°. After two further recrystallizations from ethanol, there was obtained analytically pure product in the form of white needles, m.p. 229–230° dec. (heated at 3°/min. after immersion in the bath at 200°).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.30; H, 5.39; N, 10.53.

The benzene layer, after being washed with sodium hydroxide solution, was dried with Drierite and evaporated under an air stream. This produced 7.7 g. (77%) of starting material, identified by melting point and infrared spectrum.

(b) *From 1,5-diphenyl-3-anilino-2(5H)-pyrrolone* (V). This procedure is essentially that of Bodforss.[10] To a refluxing solution of sodium ethoxide prepared from 17.0 g. (0.739 g.-atom) of sodium and 800 ml. of absolute alcohol was added with stirring 42.0 g. (0.610 mole) of hydroxylamine hydrochloride. After stirring at reflux for 20 min., 40.0 g. (0.122 mole) of V was added. The suspension was stirred and refluxed for 18 hr. and then filtered while hot, affording 41.0 g. of inorganic salts. An equal volume of water was added to the filtrate, and after chilling in the refrigerator for 3 hr., this was filtered from a trace of insoluble material through a pad of Celite on a sintered glass funnel. The clear solution was acidified with glacial acetic acid and cooled for 1.5 hr. The copious white precipitate was filtered and washed with 50% ethanol to yield 24.4 g. of IVa. By chilling the filtrate overnight, an additional 2.5 g. was obtained. The total yield of nearly pure material by this procedure was 26.9 g. (82.9%), m.p. 230–231° dec. (reported[10] darkening at 195°, liquefaction by 245°). The analytical sample was recrystallized twice from ethanol, m.p. 230–231° dec. (heated at 3°/min. after immersion in the bath at 200°), and m. p. 238–240° dec. (heated at 16°/min.).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.12; H, 5.31; N, 10.51.

This product has an infrared spectrum identical with that of the compound obtained by procedure (a), the main absorptions being at 3180 (broad), 1695, and 1660 $cm.^{-1}$ On admixture of the two samples there is no depression of the melting point (mixture m.p. 229–230° dec., heated at 3°/min. after immersion in the bath at 200°).

An acetate was prepared with acetic anhydride and acetic acid, m.p. 190–192° dec. (heated at 8°/min.) after three recrystallizations from ethanol.

(22) L. F. Somerville and C. F. H. Allen, *Org. Syntheses*, **Coll. Vol. II**, 81 (1943).

(23) N. H. Cromwell, P. L. Creger, and K. E. Cook, *J. Am. Chem. Soc.*, **78**, 4412 (1956).

(24) I. Heilbron, *Dictionary of Organic Compounds*, Oxford University Press, New York, 1953, Vol. 2, p. 809.

(25) W. A. Noyes, *Org. Syntheses*, **Coll. Vol. II**, 108 (1943).

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.23; N, 9.09. Found: C, 70.16; H, 5.31; N, 9.09.

Samples of this acetate prepared from the IVa obtained by procedures (a) and (b) were identical, having an undepressed mixture m.p. and superimposable infrared spectra.

A sample of the acetate was treated with sodium methoxide in methanol. After filtration, dilution with water, and acidification, the oxime IVa was obtained and identified by m.p. and infrared spectrum.

1,5-Diphenyl-3-amino-2-pyrrolidinone (VI). A 2.0 g. (0.0075 mole) sample of the oxime IVa was hydrogenated in 100 ml. of glacial acetic acid with 100 mg. of platinum dioxide (Baker & Co., Inc.) and 43 p.s.i.g. of hydrogen. After shaking for 3 days, the catalyst was filtered off and the tan filtrate was evaporated nearly to dryness in an air stream. Approximately 150 ml. of water and 5 ml. of hydrochloric acid were added to dissolve most of the oil. Three extractions with 50 ml. portions of benzene removed all non-basic material, and after filtration of the aqueous solution 20% potassium hydroxide was added until the mixture was basic. The suspension was cooled to 0° and extracted with a total of 200 ml. of benzene in three portions. The benzene was dried with magnesium sulfate and evaporated to dryness in an air stream. This left 1.6 g. (85%) of white crystalline VI, which after one recrystallization from ethyl acetate-petroleum ether (b.p. 60–75°) melted at 139–142°. Two further recrystallizations produced white plates of analytically pure material, m.p. 140.5–142.0°.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.17; H, 6.39; N, 11.11. Found: C, 76.13; H, 6.31; N, 11.01.

A hydrochloride was prepared and recrystallized from aqueous hydrochloric acid, m.p. 243–245° dec.

Anal. Calcd. for $C_{16}H_{17}ClN_2O$: C, 66.55; H, 5.93; Cl, 12.28; N, 9.70. Found: C, 66.47; H, 6.04; Cl, 12.25; N, 9.74.

1,5-Diphenyl-3-chloro-2-pyrrolidinone (VII). A 0.5 g. (2.0 mmole) sample of VI was dissolved in 50 ml. of chloroform and cooled to the freezing point in a Dry Ice–acetone bath. To this was added a solution of nitrosyl chloride in chloroform until the yellowish color persisted for some time. After a few minutes shaking, colorless needles started to precipitate, and after 4 hr. a clear yellow solution was obtained. The solvent was evaporated in an air stream, leaving a tan oil. This was dissolved in 25 ml. of benzene and passed through a small chromatographic column packed with alumina. Elution was continued with benzene. The first 100 ml. to come through the colum was collected and evaporated to dryness. The yellowish crystals were recrystallized from carbon tetrachloride-petroleum ether (b.p. 60–75°) to yield 0.26 g. (48%) of VII as fine white needles, m.p. 95–99°. Two further recrystallizations gave the analytical sample, m.p. 102.5–103.5°.

Anal. Calcd. for $C_{16}H_{14}ClNO$: C, 70.73; H, 5.19; Cl, 13.05; N, 5.16. Found: C, 70.73; H, 5.24; Cl, 13.09; N, 5.20.

1,5-Diphenyl-2-pyrrolidinone (IIa). A 220-mg. (0.81 mmole) sample of crude VII was dissolved in 50 ml. of absolute alcohol. To this solution was added 3.2 ml. of a solution of 170 mg. of 85% potassium hydroxide in 100 ml. of absolute ethanol (0.82 mmole of KOH) and 1 g. of a palladium on calcium carbonate catalyst.[14] The suspension was stirred at room temperature under one atmosphere of hydrogen for 6 hr., until the reduction had stopped and 88% of the theoretical amount of hydrogen had been absorbed. The catalyst was filtered and washed with ethanol and the solvent evaporated in an air stream. The residue was taken up in 10 ml. of benzene, dried with magnesium sulfate, filtered, and the solution again evaporated to dryness. The total yield of crude product from evaporation of the benzene was 180 mg. (94%). Recrystallization of the residue from isopropyl alcohol yielded 20 mg. (10%) of IIa, m.p. 107–110°. Infrared spectra of this material and the authentic sample were identical, and on admixture the m.p. was undepressed.

1,5-Diphenyl-3-(phenylnitrosamino)-2(5H)-pyrrolone (IX). The conditions of Bodforss[10] were modified for the nitrosation.[26] To a stirred suspension of 2.0 g. (0.0061 mole) of 1,5-diphenyl-3-anilino-2(5*H*)-pyrrolone (V) in 50 ml. of hot acetic acid on the steam bath was added dropwise over a 20 min. period of solution of 0.5 g. (0.0072 mole) of sodium nitrite in 10 ml. of water. On addition of the first drop, the reaction mixture became deep yellow, and by the end of addition it was deep red. Complete solution occurred near the end of addition, and shortly afterward red needles began to precipitate from the solution. The heating was maintained for 10 min. after the end of addition and the mixture was then allowed to reach room temperature over a 2-hr. period. The suspension was chilled and the solid filtered off. In this manner there was obtained 0.4 g. (18%) of IX. An analytical sample was prepared by four recrystallizations from acetic acid, fine bright red needles, m.p. 271–272° dec.

Anal. Calcd. for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.84. Found: C, 74.42; H, 4.72; N, 11.84.

The infrared spectrum of this material was transparent in the high frequency region, the only absorptions above 1600 cm.$^{-1}$ (except the weak CH band at 3040 cm.$^{-1}$ observed in a hexachlorobutadiene mull) being at 1655 and 1692 cm.$^{-1}$

1,5-Diphenyl-3-hydroxy-2-pyrrolidinone (X). A solution of 2.0 g. (0.0079 mole) of 1,5-diphenyl-3-amino-2-pyrrolidinone (VI) in 73.5 ml. (0.00793 mole) of 0.1083 *N* hydrochloric acid (or an equivalent amount of the solid amine hydrochloride) was diluted to 300 ml. and filtered. Over a period of 3 days there was added a solution of 0.65 g. (0.0094 mole) of sodium nitrite in 50 ml. of water. White crystals were slowly deposited, and bubbles of gas slowly evolved. After 2 more days, 1.6–2.0 g. (80–100%) of X was filtered off. This melted at 140–145°, with prior shrinking, to form a red melt. Three recrystallizations from isopropyl alcohol-water gave the analytical sample, m.p. 148–150°, with shrinking at 145°.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53, Mol. Wt., 253. Found: C, 75.78; H, 5.89; N, 5.54, Mol. Wt., 255, 258 (f.p. in camphor).

A benzoate was prepared by the use of benzoyl chloride and pyridine, m.p. 181–185°. After several recrystallizations from methanol, m.p. 188–189°.

Anal. Calcd. for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.17; H, 5.43; N, 3.92.

1,5-Diphenyl-2,3-pyrrolidinedione (XI). (a) *From* X. The chromic acid oxidation of the alcohol X was carried out in a manner similar to that used by Bruce[17] for the oxidation of dihydrocholesterol. A solution of 1.0 g. (4.0 mmoles) of X in 20 ml. of benzene was shaken with a solution of 0.3 g. (3.0 mmoles) of chromium trioxide in 30 ml. of water containing 2.0 ml. of sulfuric acid and 2.0 ml. of acetic acid for 24 hr. At the end of this period, the layers were separated and the aqueous layer was washed with 50 ml. of benzene. The combined benzene solutions were dried with magnesium sulfate, treated with Norit, filtered, and evaporated in an air stream. A small amount of toluene was added to the resulting sirup and the crystalline material was filtered. The infrared spectrum of this product contained strong sharp absorption bands at 1760 and 1700 cm.$^{-1}$ in addition to weaker bands from a contaminant. It melted at 159–162°, but could not be completely purified by recrystallization from any solvent tried nor by chromatography on alumina. It was characterized as the following derivatives:

Anil (V). Treatment of an ethanolic solution of the product with aniline produced white crystals after a day at room temperature, m.p. 215–217° dec. after recrystallization from ethanol. This had an infrared spectrum identical with authentic V, and on admixture there was no depression of m.p.

Ethylene ketal (XIII). The oxidation product was refluxed in benzene containing ethylene glycol and methane-

(26) The product obtained by Bodforss in this manner was not well characterized.

sulfonic acid for 4 hr., the solution was dried with sodium carbonate, and chromatographed on alumina. The second 25-ml. fraction to come through the column on elution with benzene was evaporated and the solid was fractionally crystallized from ethanol. After one further recrystallization from ethanol, the solid melted at 143–146°, and on admixture with an authentic sample of the ketal (*vide infra*) this was undepressed. The infrared spectrum of this sample and that of the authentic ketal were identical.

(b) *From 1,5-diphenyl-4-carbethoxy-2,3-pyrrolidinedione* (XII). This procedure is due to the research of Covey.[18] A solution of 1.0 g. (0.0031 mole) of 1,5-diphenyl-4-carbethoxy-2,3-pyrrolidinedione (XII)[6b] in 80 ml. of nitrobenzene was heated until gas evolution commenced and for 12 min. thereafter. The nitrobenzene was then concentrated at the water pump, the resulting solution was evaporated nearly dry in an air stream, and ether was added. The solid was collected and washed with ether, 0.5 g. (65%), m.p. 163–168°. The analytical sample was recrystallized several times from toluene, m.p. 162–163° with softening at 158° (reported[8] 158–159°).

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.21; N, 5.57. Mol. Wt., 251. Found: C, 76.54; H, 5.35; N, 5.45. Mol. Wt., 268, 271 (f.p. in camphor).

This compound had an infrared spectrum with absorption bands at 1700 and 1760 cm.$^{-1}$ which were identical with the strong bands of the product obtained by procedure (a). It was further characterized by means of its derivatives: the anil (V), m.p. 223–225° dec. (heated at 5°/min.) (reported[13] 227–228° dec.), mixture m.p. undepressed by authentic V, and infrared spectrum identical with that of V; the oxime (IVa), m.p. 238–239° dec. (heated at 16°/min.), no depression of m.p. by authentic IVa, which had an identical infrared spectrum; and the ethylene ketal, m.p. 145–147° from ethanol (see next experiment).

1,5-Diphenyl-3-ethylenedioxy-2-pyrrolidinone (XIII). A suspension of 1.0 g. (0.0030 mole of 1,5-diphenyl-3-anilino-2(5*H*)-pyrrolone (V) in 10 ml. of ethylene glycol containing 0.3 ml. of methanesulfonic acid was heated on the steam bath for 4 hr., at which time all solid had dissolved. The solution was poured into three times its volume of water and extracted with benzene. After drying with magnesium sulfate, the solvent was evaporated, leaving 0.8 g. (90%) of the ethylene ketal, m.p. 144–146°. After three recrystallizations from ethanol the material was analytically pure, white needles, m.p. 145–146°.

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.21; H, 5.80; N, 4.74. Found: C, 73.36; H, 5.85; N, 4.75.

The melting point of this sample was undepressed on admixture with the ketal prepared from either sample of XI, and the infrared spectra of the samples were identical.

ANN ARBOR, MICH.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

1,5-Diaryl-2,3-pyrrolidinediones. IX. Reassignment of Structure[1]

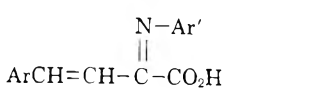
WALTER L. MEYER[2] AND WYMAN R. VAUGHAN

Received April 26, 1957

The compound previously described as 1,5-di(*p*-anisyl)-2,3-pyrrolidinedione has been shown to be 5-(*p*-anisyl)-3-(*p*-anisylamino)-2(5*H*)furanone through synthesis of its dihydro reduction product, α-(*p*-anisylamino)-γ-(*p*-anisyl)-γ-butyrolactone. This enamino lactone structure applies to all previously reported 1,5-diaryl-2,3-pyrrolidinediones having no other substitution in the heterocyclic ring.

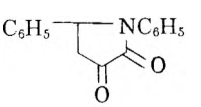
The tautomerism between the enamino lactones (formerly the pyrrolidinediones) and α-arylimino-β-benzylidenepropionic acids is pointed out to be an example of lacto-enoic tautomerism, facilitated by the participation of the free electron pair on the amino nitrogen atom.

The observations that supposed 1,5-diaryl-2,3-pyrrolidinediones (I) underwent thermal decarboxylation to cinnamylideneanilines and were tautomeric with α-arylimino-β-benzylidenepropionic acids (II)[3] were unprecedented and thus may give rise to doubts concerning the validity of the structure assignment of I. When 1,5-diphenyl-2,3-pyrrolidinedione (III) was synthesized and found to be different from the substance (Ia) previously assigned this structure,[4] it was of interest to determine the correct structure of I unequivocally.



IIa: Ar = Ar′ = C_6H_5

IIb: Ar = Ar′ = *p*-$CH_3OC_6H_4$



III

Examination of the literature indicates that little concrete structural information is available for I. The diphenyl compound (Ia) was originally formulated as the 2,3-pyrrolidinedione by Schiff and Gigli[5] on the basis of an assumed analogy between the reactions of pyruvic acid and ethyl oxaloacetate with benzylideneaniline, ethyl oxaloacetate affording 1,5-diphenyl-4-carbethoxy-2,3-pyrrolidinedione (IV) under these conditions,[6] while pyruvic acid led to Ia. The compound IV behaved as was expected for its structure, and although at

(1) Preliminary communication, W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 98 (1957).

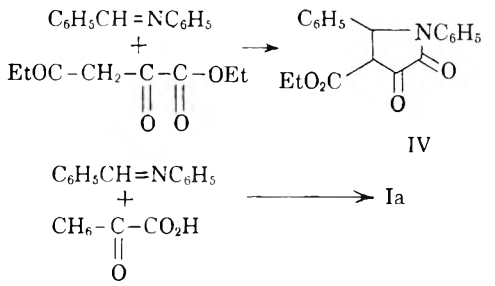
(2) National Science Foundation Predoctoral Fellow, 1954–57. Abstracted from a portion of the Ph.D. dissertation of W. L. Meyer, University of Michigan, 1957.

(3) (a) W. R. Vaughan and L. R. Peters, *J. Org. Chem.*, **18**, 382 (1953); (b) W. R. Vaughan and L. R. Peters, *J. Org. Chem.*, **18**, 393 (1953); (c) W. R. Vaughan and L. R. Peters, *J. Org. Chem.*, **18**, 405 (1953); (d) W. R. Vaughan and D. I. McCane, *J. Org. Chem.*, **20**, 143 (1955).

(4) W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 1554 (1957).

(5) R. Schiff and L. Gigli, *Ber.*, **31**, 1306 (1898).

(6) (a) R. Schiff and C. Bertini, *Ber.*, **30**, 601 (1897); (b) L. J. Simon and A. Conduché, *Ann. chim. et phys.*, [8] **12**, 5 (1907).

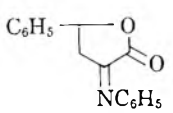


IV

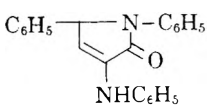
that time no unequivocal proof of its structure existed, recent alternate syntheses have confirmed the original formulation of IV.[3d,7]

In spite of unusual behavior which is not analogous to that of IV, the structure of Ia has been accepted in the literature with but one exception. Garzarolli-Thurnlackh[8] suggested that it was the isomeric imino lactone (V) (with no experimental evidence), but even he abandoned his formulation in a later publication.[9,10,10a]: Other early information which would support this structure, or any other, is indeed sparse. Attempted hydrolytic degradation of Ia afforded no well characterized materials.[11] Although Bücherer and Russischwili[11] isolated a substance which they believed was α-keto-γ-phenyl-γ-anilinobutyric acid from acid hydrolysis, this material was poorly characterized, and the acid was not reconvertible to Ia.

Attempts to prepare ketone derivatives from Ia have failed repeatedly. The anil (VI) is readily prepared,[12] and indeed is found to result even from



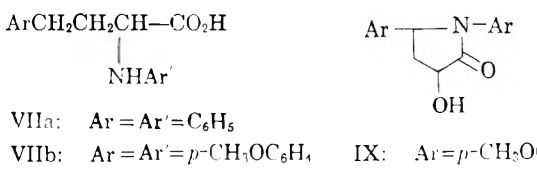
V



VI

heating the substance in ethanol or acetic acid,[12,13] which treatment presumably causes partial decomposition with liberation of aniline. However, no oxime can be obtained on reaction with hydroxylamine,[3d,11,12,14,15] and with phenylhydrazine, although a multiplicity of products is obtained, none of these appears to be a simple phenylhydrazone.[3d,11,12,14] Thus the only evidence for a ketonic carbonyl in Ia is the formation of an anil, which cannot be hydrolyzed to the parent "ketone".[11,16] A reported[3a] alternate synthesis by hydrolysis and decarboxylation of 1,5-diphenyl-4-carbomethoxy-2,3-pyrrolidinedione might appear to give good foundation to the pyrrolidinedione formulation of Ia. However, this reaction has been found incapable of repetition, by the original investigator and others in this laboratory, and thus doubts may be raised as to the value of conclusions based on this work.

The only remaining item of structural information which has been offered is the reduction of α-(*p*-anisylimino)-β-(*p*-anisylidene)propionic acid (IIb) to two products,[3c] the expected saturated amino acid VIIb and a dihydro saturated (and therefore cyclic) compound. The latter product (VIIIb) arose from reduction of the rearranged form of IIb, the supposed pyrrolidinedione Ib, and was assigned the structure 1,5-di(*p*-anisyl)-3-hydroxy-2-pyrrolidinone (IX). Aside from the preparation of a benzoyl derivative and microanalyses of the product and its derivative, no evidence was offered for this structure. This rather tenuous data constituted the only "real" evidence for the pyrrolidinedione structure.



VIIa: Ar = Ar′ = C_6H_5

VIIb: Ar = Ar′ = *p*-$CH_3OC_6H_4$

IX: Ar = *p*-$CH_3OC_6H_4$

When the pyrrolidinedione structure was definitely disproved for Ia,[4] reevaluation of several points of the above behavior suggested a possible isomeric formulation for I. The infrared spectra of Ia and the anil VI bear striking similarities to one another. Thus in the spectrum of Ia (Nujol) are found bands at 3310, 1736, and 1656 cm.$^{-1}$, whereas VI absorbs at 3300, 1674, and 1648 cm.$^{-1}$ The structure of VI being known,[4,17] these spectral data would suggest that Ia and VI have an NH function (3300 cm.$^{-1}$) and a C=C (1650 cm.$^{-1}$) in common; the difference in the third absorption (approximately 62 cm.$^{-1}$) suggested a lactam-lactone isosterism. The expected difference in the frequency of carbonyl absorptions of lactones and lactams is reported to be 60–80 cm.$^{-1}$ [18] with which the

(7) (a) P. L. Southwick and L. I. Seivard, *J. Am. Chem. Soc.*, **71**, 2532 (1949); (b) P. L. Southwick and R. T. Crouch, *J. Am. Chem. Soc.*, **75**, 3413 (1953).

(8) K. Garzarolli-Thurnlackh, *Monatsh.*, **20**, 480 (1899).

(9) K. Garzarolli-Thurnlackh, *Ber.*, **32**, 2274 (1899).

(10) An enamino lactone structure similar to that of Garzarolli-Thurnlackh[8] and subsequently found to be correct[1] was suggested to one of us (W.R.V.) by Dr. J. A. King in a private communication subsequent to the publication of the papers of Vaughan and Peters.[3a,b,c] The suggestion was accompanied by appropriate reassignment of infrared bands with which we now concur (*vide infra*).

(10a) Subsequent to our preliminary communication of this work,[1] Wasserman and Koch presented a reformulation of Ia in concurrence with ours. See H. H. Wasserman and R. C. Koch, *Chemistry & Industry*, 428 (1957).

(11) H. Bücherer and R. Russischwili, *J. prakt. Chem.*, **128**, 89 (1930).

(12) S. Bodforss, *Ann.*, **455**, 290 (1927).

(13) R. Ciusa and L. Musajo, *Gazz. chim. ital.*, **59**, 796 (1929).

(14) W. R. Vaughan, *J. Org. Chem.*, **20**, 1619 (1955).

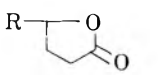
(15) J. L. Spencer in this laboratory has found that Ia yields the oxime of benzylidenepyruvic acid when treated with hydroxylamine hydrochloride.

(16) O. Doebner and M. Gieseke, *Ann.*, **242**, 290 (1887).

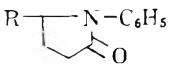
(17) W. R. Vaughan, *J. Org. Chem.*, **20**, 1613 (1955).

(18) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, 1954, pp. 153, 176.

difference between the saturated lactones and lactams X and XI[4] agrees. Thus it appeared that Ia might be 5-phenyl-3-anilino-2(5*H*)-furanone, and this structure was taken as a working hypothesis for the remainder of the work.[10]

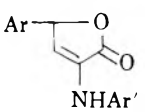


X: R=H or C_6H_5



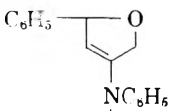
XI: R=H or C_6H_5

This proposed structure for Ia demands an NH group in the compound of similar character to that in the anil VI. Since the anil affords an N-nitroso derivative from this function,[4] Ia was subjected to the nitrosation conditions which produced such a change in VI, and a mononitroso derivative which was transparent in the NH region of the infrared was indeed obtained. In all other respects this derivative was analogous to the N-nitroso derivative of VI,[4] and hence is formulated as 5-phenyl-3-(phenylnitrosamino)-2(5H)-furanone (XII). This supports the proposed structure of Ia by confirm-



Ia: Ar = Ar′ = C_6H_5

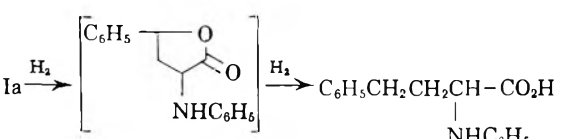
Ib: Ar = Ar′ = *p*-$CH_3OC_6H_4$



XII

ing that the high frequency absorption of the spectrum is due to NH and not OH, and increases the analogy with VI.

Consideration of the proposed structure for I requires that the cyclic dihydro reduction product of Ib obtained by Vaughan and Peters,[3c] rather than having the structure assigned by these investigators, should be α-(*p*-anisylamino)-γ-(*p*-anisyl)-γ-butyrolactone (VIIIb). Hence it was decided to reduce Ia to the analogous α-anilino-γ-phenyl-γ-butyrolactone (VIIIa) and to synthesize this substance in an unequivocal manner for comparison.

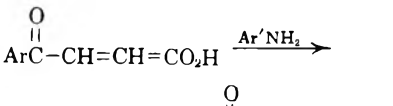


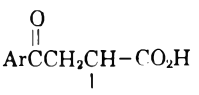
VIIIa

VIIa

All attempts to reduce Ia to a dihydro product failed. The only material isolated from attempted reduction of this substance under any conditions was α-anilino-γ-phenylbutyric acid (VIIa). This amino acid may have arisen from reduction of the tautomeric form of Ia (IIa), due to unfavorable rates of isomerization and reduction of the two tautomeric forms Ia and IIa. However, in view of the proposed structure of Ia, it could as well have arisen from rapid hydrogenolysis of the VIIIa which was the initial reduction product of Ia. Neither occurrence may be argued *a priori* from our experimental evidence; however, that the latter is a possibility is shown by the reduction of VIIIa (*vide infra*) to the amino acid under the same experimental conditions used for the reduction of Ia.

The amino lactone VIIIa was synthesized with the intention of applying the synthesis to the di-(*p*-anisyl) analog (VIIIb) for comparison with the reduction product of Vaughan and Peters.[3c] The

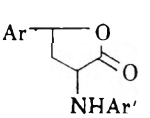


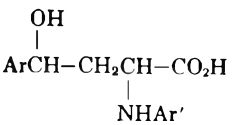


XIIIa: Ar = Ar′ = C_6H_5

XIIIb: Ar = Ar′ = *p*-$CH_3OC_6H_4$

XIIIc: Ar = C_6H_5; Ar′ = *p*-$CH_3OC_6H_4$





VIIIa: Ar = Ar′ = C_6H_5 XIV: Ar = Ar′ = *p*-$CH_3OC_6H_4$

VIIIb: Ar = Ar′ = *p*-$CH_3OC_6H_4$

VIIIc: Ar = C_6H_5; Ar′ = *p*-$CH_3OC_6H_4$

addition of aniline to β-benzoylacrylic acid has been described by Bougault,[19] although it was not shown conclusively whether the α-amino acid or the β-amino acid was the product. One would expect the α-amino acid to result from such a reaction, as addition to the ketone-vinyl system should be favored over addition to the acid-vinyl system.[20,21] On repetition of Bougault's reaction, the product described by him as α-anilino-β-benzoylpropionic acid (XIIIa) was obtained. On treatment with sodium borohydride, the ketone was reduced, and after acidification and warming for a short time, an amino lactone (VIIIa) was obtained. That this lactone had the α-anilino function was shown by its hydrogenolysis to α-anilino-γ-phenylbutyric acid (VIIa) which was compared with a sample prepared from the α-bromo acid. Thus the addition of aniline to benzoylacrylic acid takes place in the presumed manner.

The synthetic VIIIa has an infrared spectrum very similar to that of Vaughan and Peters'[3c] reduction product, VIIIa absorbing at 3350 (NH) and 1742 cm.$^{-1}$ (C=O), and the reduction product VIIIb absorbing at 3320 (NH) and 1758 (C=O). For further evidence along these lines, *p*-anisidine

(19) J. Bougault, *Ann. chim. et phys.*, [8] **15**, 491 (1908). See also P. Chabrier *et al.*, *Compt. rend.*, **230**, 212 (1950); **226**, 1378 (1948); **237**, 1420 (1953).

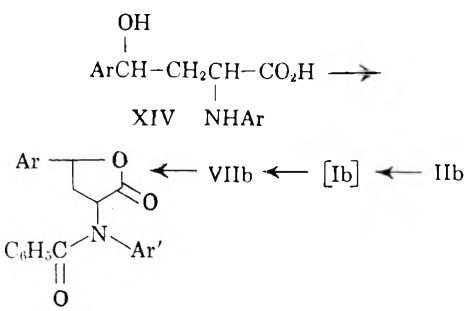
(20) M. M. Fraser and R. A. Raphael, *J. Chem. Soc.*, 2245 (1950).

(21) N. H. Cromwell, P. L. Creger, and K. E. Cook, *J. Am. Chem. Soc.*, **78**, 4412 (1956).

was added to β-benzoylacrylic acid, and the resulting amino keto acid (XIIIc) was reduced and lactonized to α-(*p*-anisylamino)-γ-phenyl-γ-butyrolactone (VIIIc). This amino lactone had an infrared spectrum even more similar to VIIIb, absorbing at 3320 and 1759 cm.$^{-1}$

With the evidence at hand suggesting that our hypothesis was correct, *p*-anisidine was added to β-(*p*-methoxybenzoyl)acrylic acid to yield α-(*p*-anisylamino)-β-(*p*-methoxybenzoyl)propionic acid (XIIIb). This amino keto acid, on treatment with sodium borohydride, was smoothly reduced to an amino hydroxy acid (XIV), but the latter resisted lactonization under conditions which had been successful for the other analogs. Such behavior might suggest that a different type of product was obtained in this case, but the infrared spectrum did not support such a conclusion. The spectrum of the amino keto acid XIIIb was almost indistinguishable from the spectra of the amino keto acids XIIIa and XIIIc, and the spectrum of the amino hydroxy acid XIV was identical with the spectrum of α-(*p*-anisylamino)-γ-(*p*-anisyl)butyric acid (VIIb)[3c] with the exception of two bands assignable to OH and C=O vibrations. Thus it appears that the non-lactonization of XIV is a property peculiar to this hydroxy acid, possibly due to its insolubility in the reaction medium.

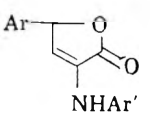
When the amino hydroxy acid XIV was treated with benzoyl chloride in pyridine, lactonization and benzoylation occurred smoothly, and the benzoyl derivative (XV) of the amino lactone VIIIb was isolated. This material was identical in all re-



XIV XV

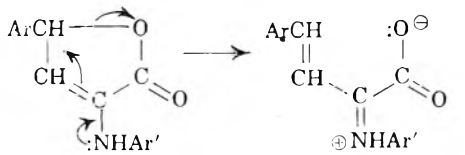
spects (infrared spectrum and mixture melting point) with the benzoyl derivative of Vaughan and Peters' reduction product,[3c] and confirms formulation of this reduction product as α-(*p*-anisylamino)-γ-(*p*-anisyl)-γ-butyrolactone (VIIIb).

Thus the structure of Ib must be that of an α-amino-γ-lactone containing one double bond. The infrared spectrum and the preparation of an *N*-nitroso derivative from the analogous diphenyl compound Ia require the presence of an NH group in the molecule, and hence the double bond must be endocyclic. The carbonyl groups of the reduced materials VIIIa and VIIIb absorb at higher frequencies in the infrared than do the dehydro compounds Ia and Ib. Thus the double bond must be conjugated with the carbonyl in I, for a β,γ double bond would lead to an enol lactone structure, which would absorb at a higher frequency in the infrared than would the corresponding saturated lactone.[22] The foregoing arguments indicate that the only acceptable formulation for Ia and Ib is as 5-aryl-3-arylamino-2(5H)-furanones (I). The similarities in the methods of preparation,[3a] chemical properties,[3] and infrared spectra[3a] of all known and otherwise unsubsti-



I

tuted "1,5-diaryl-2,3-pyrrolidinediones"[23] requires that all have analogous structures, and hence must be formulated as I.[cf. 8,10] Thus the 1,5-diphenyl-2,3-pyrrolidinedione reported in our previous paper[4] is the only known compound of this class. This, of course, does not at all apply to 2,3-pyrrolidinediones having other types of substitution.[3d,7,24] The determination of the enamino lactone structure for I immediately clarifies the tautomeric behavior[3b,c,d] of I and II.[25] This is now seen to be simply an unusually facile case of the reversible lactonization of a β,γ-unsaturated acid, "lacto-enoic tautomerism."[26] The extreme ease of interconversion of the "tautomers" in the present system may well be due to the availability of the free electron pair on nitrogen for participation in the electron shift which produces the isomerism:



I II

In this manner, a concerted electron recession from nitrogen to oxygen produces the zwitterionic form of the imino acid II. From consideration of the infrared spectrum of II and its electrical conductivity[3c] it appears that the imino acid II normally exists as the zwitterion, and hence the system is ideally situ-

(22) Ref. 18, p. 160; F. Ramirez and M. B. Rubin, *J. Am. Chem. Soc.*, **77**, 3768 (1955), and references cited therein.

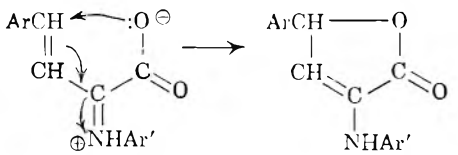
(23) With the exception of the 1,5-diphenyl-2,3-pyrrolidinedione (III) reported in our previous paper,[4] which was shown to have this structure.

(24) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).

(25) There is no doubt concerning the structure of II. Vaughan and Peters[3c] confirmed the structure of IIb through reduction to VIIb, which was prepared in an alternate fashion. Vaughan[17] has reduced IIa to the saturated amino acid VIIa, and this has been shown identical with the authentic sample prepared from the bromo acid in the usual manner.

(26) R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 580 (1933).

ated for the reversal (cyclization) of the isomerism through initial attack of the carboxylate anion at the γ-carbon atom:



II I

This example of tautomeric behavior is unique in that no proton shift is needed to complete the isomerization.

It has been suggested[3b,c] that the decarboxylation of I proceeds through an initial rapid isomerization to II, which is the actual decarboxylating species and loses carbon dioxide in the rate determining step of the reaction. This is certainly a possible, and even probable mechanism for the decarboxylation, but the inverse mechanism cannot be excluded; *i.e.*, the cyclic form may lose carbon dioxide in the slow step, the imino acid cyclizing to this in a preliminary rapid isomerization. Such a possibility is supported by the rapid formation of the ring form (I) from the chain form (II) on warming for recrystallization, suggesting that I is the more stable tautomer at increased temperatures. Also, consideration of the rate and equilibrium data of Vaughan and Peters[3c] for the lone measurable example of the tautomerism, with exactly the same assumptions as were made by these authors, indicates the cyclization, as well as the ring-opening, reaction to be many times more rapid than the decarboxylation. Thus the same kinetic order for decarboxylation would be anticipated for either mechanism. Both mechanisms fit all the known facts, and with the evidence at hand, it is not possible to determine which is correct.

EXPERIMENTAL

All melting and boiling points are uncorrected. Infrared spectra were obtained from Nujol mulls, unless otherwise noted, by means of a Perkin-Elmer Model 21 infrared spectrophotometer. Microanalyses are by Spang Microanalytical Laboratory, Ann Arbor, Mich.

5-Phenyl-3-anilino-2(5H)-furanone (Ia). (*a*) Aniline was condensed with benzylidenepyruvic acid[3d] according to the method of Vaughan and Peters.[3a]

(*b*) By utilizing acetic acid as a solvent, it was found unnecessary to isolate pure benzylidenepyruvic acid from its salt. Sodium benzylidenepyruvate[3d] was dissolved in the minimum amount of glacial acetic acid, and with stirring there was added at room temperature one equivalent of aniline in acetic acid. Precipitation was complete in 30 min. The solid was filtered off and washed with ethanol. By addition of an equal volume of ethanol to the filtrate, a second crop was obtained. The yield was 70%, m.p. 160.5–161.0° dec. (reported[3a] 160.0–160.5° dec.).

Reduction of 5-phenyl-3-anilino-2(5H)-furanone (Ia). To a suspension of 270 mg. (1.07 mmoles) of Ia in 40 ml. of absolute alcohol was added a spatula tipful of 5% palladium-on-carbon catalyst (Baker and Co., Inc.), and the mixture was stirred under one atmosphere of hydrogen at 25°. After 1 hr., absorption of hydrogen had ceased, 64 ml. (114% of 2 equivalents) being taken up. The catalyst was filtered off, washed well with ethanol, and the ethanol evaporated to leave 213 mg. (79%) of white solid which after one recrystallization from ethanol melted at 181–185° dec. (heated at 5°/min.) and showed no depression of m.p. on admixture with the authentic sample (*vide infra*) of α-anilino-γ-phenylbutyric acid (VIIa). The infrared spectrum of this material was indistinguishable from that of the authentic sample.

A methyl ester hydrochloride was prepared by treatment with methanolic hydrogen chloride; after one recrystallization it melted at 157–159°: mixture m.p. with the authentic sample 157–160°.

α-Anilino-γ-phenylbutyric acid (VIIa). In 10 ml. of ethanol was dissolved 1.5 g. (0.0061 mole) of α-bromo-γ-phenylbutyric acid[27] and approximately 2 g. of aniline. The solution was refluxed for 2 days. On cooling, white crystals of the anilino acid VIIa precipitated and were filtered. After one recrystallization from ethanol there was collected 1.1 g. (71%) of the product, m.p. 184–186° dec. One further recrystallization from ethanol and one from ethanol–acetic acid produced the analytical sample, m.p. 186–188° dec. (reported[17] 192–194° dec.).

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.41; H, 6.52; N, 5.45.

A benzene-soluble methyl ester hydrochloride was prepared by refluxing in methanolic hydrogen chloride. Recrystallization was effected by dissolving in a small amount of benzene, passing in dry hydrogen chloride, adding petroleum ether (b.p. 60–75°) to the warmed solution to saturation, and cooling. After several recrystallizations by this procedure, the analytical sample melted at 157–159°.

Anal. Calcd. for $C_{17}H_{20}ClNO_2$: C, 66.77; H, 6.59; Cl, 11.60; N, 4.57. Found: C, 66.84; H, 6.69; Cl, 11.71; N, 4.60.

The anilino acid VIIa and its methyl ester hydrochloride were shown to be identical with the anilino acid of Vaughan[17] obtained by reduction of α-phenylimino-β-benzylidenepropionic acid (IIa) and the methyl ester hydrochloride prepared from it. The melting points and infrared spectra of the samples were identical, and mixture melting points were undepressed.

5-Phenyl-3-(phenylnitrosamino)-2(5H)-furanone (XII). To a solution of 300 mg. (1.2 mmoles) of 5-phenyl-3-anilino-2(5*H*)-furanone (Ia) in 7 ml. of hot glacial acetic acid there was added dropwise a solution of 100 mg. of sodium nitrite in 2 ml. of water. The mixture became bright orange colored. Water was added to the hot solution to incipient precipitation and the solution was cooled. The tan solid which precipitated was filtered off and the mother liquors were allowed to stand for several days to collect a second crop. The total yield was 150 mg. (45%), m.p. 216.0–216.5° dec., after several recrystallizations from acetic acid (fine lemon-yellow needles). The infrared spectrum of the sample was transparent in the high frequency region.

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 10.00. Found: C, 68.71; H, 4.17; N, 10.14.

α-Anilino-γ-phenyl-γ-butyrolactone (VIIIa). To a solution of 647 mg. (2.40 mmoles) of α-anilino-β-benzoylpropionic acid (XIIIa)[19, 28] in 20 ml. of 5% sodium bicarbonate was added a solution of 200 mg. of sodium borohydride in 5 ml. of water. This was allowed to stand at room temperature for 12 hr., and then was acidified with hydrochloric acid. The suspension was warmed on the steam bath for 3 hr. and allowed to stand overnight at room temperature. Excess 5% sodium bicarbonate was added and the solid was filtered off, washed with 5% sodium bicarbonate and water, and dried. This yielded 395 mg. (65%) of the anilino lactone VIIIa, m.p. 118–124°. Several recrystallizations

(27) E. Fischer and W. Schmitz, *Ber.*, 39, 2208 (1906).

(28) The authors are indebted to Prof. P. A. S. Smith for a sample of β-benzoylacrylic acid used in this work.

from ethanol produced small white platelets of analytical purity, m.p. 128–129°.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.84; H, 6.02: N, 5.59.

Reduction of α-anilino-γ-phenyl-γ-butyrolactone (VIIIa). α-Anilino-γ-phenyl-γ-butyrolactone (VIIIa) (258 mg., 1.02 mmoles) was reduced exactly as was 5-phenyl-3-anilino-2(5*H*)-furanone (Ia) above. There was absorbed 112% of one equivalent of hydrogen in 1 hr., and 200 mg. (77%) of α-anilino-γ-phenylbutyric acid (VIIa) was obtained, m.p. 183–186° dec. (heated at 5°/min.) after one recrystallization from ethanol. On comparison with authentic material, infrared spectra were superimposable and the mixture m.p. was 184–188° dec.

α-(p-Anisylamino)-β-benzoylpropionic acid (XIIIc). In a solution of 1.0 g. of sodium carbonate in 10 ml. of water was dissolved 1.0 g. (5.7 mmoles) of β-benzoylacrylic acid and 1.0 g. (8.1 mmoles) of *p*-anisidine. After standing for 16 hr. at room temperature, the solution was acidified with acetic acid, precipitating an oil which soon solidified. This was filtered and washed well with ether, yielding 1.3 g. (77%) of XIIIc. Several recrystallizations from benzene produced the analytical sample, m.p. 134–135° dec.

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.19; H, 5.72; N, 4.68. Found: C, 67.79; H, 5.66; N, 4.53.

α-(p-Anisylamino)-γ-phenyl-γ-butyrolactone (VIIIc). The sodium borohydride reduction of XIIIc was carried out by a procedure identical with that used for the preparation of VIIIa above. The product was recrystallized from ethanol, m.p. 147–148° (21% yield).

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.01; H, 6.02; N, 4.93.

α-(p-Anisylamino)-β-(p-methoxybenzoyl)propionic acid (XIIIb). The addition of *p*-anisidine to β-(*p*-methoxybenzoyl)acrylic acid[19] [prepared from β-(*p*-methoxybenzoyl)-propionic acid[29]] was carried out as was the preparation of XIIIc above. The product was obtained in quantitative yield; m.p. 144.5–145.0° dec. after several recrystallizations from benzene.

Anal. Calcd. for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.69; H, 5.79; N, 4.25.

α-(N-Benzoyl-p-anisylamino)-γ-(p-anisyl)-γ-butyrolactone (XV). To a solution of 1.0 g. (0.0030 mole) of XIIIb and 0.5 g. of sodium carbonate in 20 ml. of water was added 0.5 g. (0.013 mole) of sodium borohydride. After standing at room temperature for 12 hr. acidification with acetic acid precipitated the amino hydroxy acid XIV, which could not be induced to lactonize. This hydroxy acid was dissolved in warm pyridine and treated with benzoyl chloride. After warming for a few minutes, the solution was poured into excess 3% sodium carbonate solution. The XV came down as an oil which soon crystallized and was recrystallized from ethanol, m.p. 157–161°. Several further recrystallizations produced small white needles of analytical purity, m.p. 164.5–165.5° (reported[30] 169.5–170.0°).

Anal. Calcd. for $C_{25}H_{23}NO_5$: C, 71.95; H, 5.55; N, 3.36. Found: C, 71.82; H, 5.53: N, 3.37.

When compared with the material erroneously described by Vaughan and Peters[30] as the benzoate of 1,5-di-(*p*-anisyl)-3-hydroxy-2-pyrrolidinone, this compound was found identical in all respects, and the mixture melting point was undepressed.

ANN ARBOR, MICH.

(29) L. F. Fieser and E. Hershberg, *J. Am. Chem. Soc.*, **58**, 2314 (1936).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

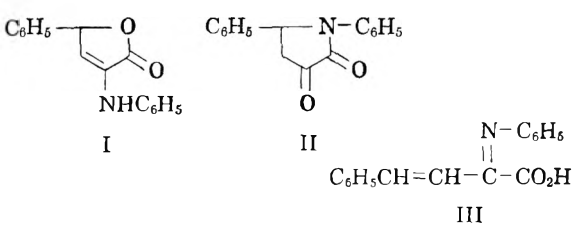
1,5-Diaryl-2,3-pyrrolidinediones. X. Phenylhydrazine Derivatives

WALTER L. MEYER[1] AND WYMAN R. VAUGHAN

Received May 17, 1957

Structures of two of the three products of the reaction of 5-phenyl-3-anilino-2(5*H*)-furanone (I) with phenylhydrazine have been reassigned. One of these, 1,5-diphenyl-2,3-pyrrolidinedione-3-phenylhydrazone (XI) was found to be tautomeric with benzylidenepyruvanilide phenylhydrazone (IX), a new type of tautomerism for which the term "lactam-enamide" is proposed.

5-Phenyl-3-anilino-2(5*H*)-furanone (I), the compound formerly described as 1,5-diphenyl-2,3-pyrrolidinedione (II), affords three distinct products on treatment with phenylhydrazine.[2–5] These compounds, A, B, and C, have been variously formulated in the literature, but inasmuch as they have been considered derived from and analogous to II (which was an incorrect structure), the reformulation of II as I,[5] which may isomerize reversibly to III, has made a re-evaluation of these derivatives desirable.



The simplest of the reaction products of I with phenylhydrazine is A, first obtained by Bücherer and Russischwili[3] and later examined by Vaughan and McCane.[4] This substance, A, has the molecular formula $C_{16}H_{14}N_2O_2$, and arises by substitution of aniline by phenylhydrazine.[4] By analogy with the

(1) National Science Foundation Predoctoral Fellow, 1954–1957. Abstracted from a portion of the Ph.D. dissertation of Walter L. Meyer, University of Michigan, 1957.

(2) S. Bodforss, *Ann.*, **455**, 41 (1927).

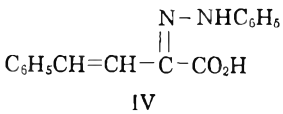
(3) H. Bücherer and R. Russischwili, *J. prakt. Chem.*, **128**, 89 (1930).

(4) W. R. Vaughan and D. I. McCane, *J. Org. Chem.*, **20**, 143 (1955).

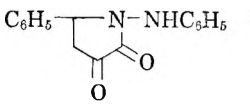
(5) W. R. Vaughan, *J. Org. Chem.*, **20**, 1619 (1955).

(6) (a) W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 98 (1957). (b) W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 1560 (1957).

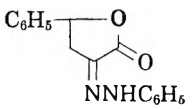
isomeric structures I and III,[6] the readily reversible isomerism[4] of A should now have its members represented by IV and VI rather than IV and V.



IV



V

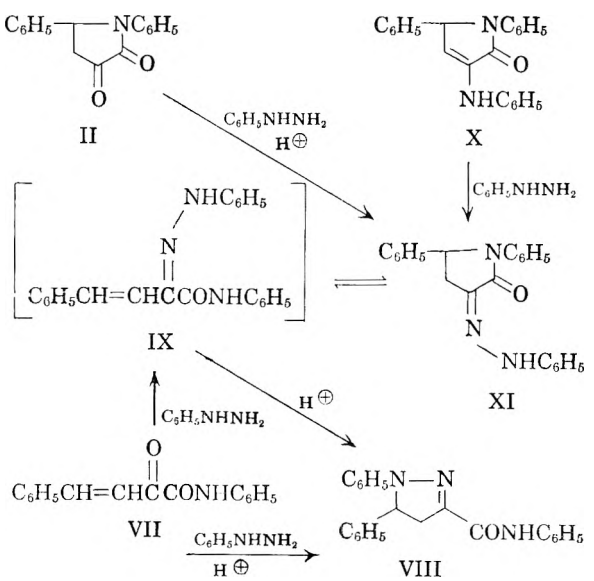


VI

The second product from the interaction of I with phenylhydrazine, B,[2-5] is not so readily formulated. When unsolvated it is found to have the formula $C_{22}H_{19}N_3O$,[5] and has been assigned several structures in the past which are of little consequence in the light of recent knowledge of the structure of I. Thus a complete re-examination of the properties of B is necessary for its accurate formulation (Chart I).

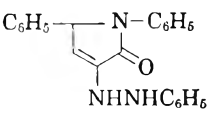
CHART I

STRUCTURE PROOF OF XI



The material (B) is also obtained from benzylidenepyruvanilide (VII) and phenylhydrazine[5] and may be isomerized to 1,5-diphenyl-Δ^2-pyrazoline-3-carboxanilide (VIII). This suggested at least potential existence as benzylidenepyruvanilide phenylhydrazone (IX). However, B is obtained from the pyrrolidinedione anil (X) and phenylhydrazine,[2,3,5] suggesting replacement of anil by phenylhydrazone[7] to give 1,5-diphenyl-2,3-pyrrolidinedione-3-phenylhydrazone (XI). B is also formed from the true 1,5-diphenyl-2,3-pyrrolidinedione (II)[8] under conditions normally used for phenylhydrazone formation, which also supports its formulation as XI. Consequently for B a choice between the structures IX and XI becomes possible on consideration of the following observations (Chart I).

When unsolvated, B contains only one absorption band in the NH region of the infrared. This is consistent with XI, but not IX or the enamine form of XI (XII), either of which should have two such bands. This is not conclusive, of course, as the



XII

two absorptions of IX or XII might fall at the same frequency.

The phenylhydrazone B is formed from II and phenylhydrazine in warm ethanol containing a few drops of acetic acid. Under *identical* conditions, benzylidenepyruvanilide (VII) and phenylhydrazine afford only the pyrazoline VIII, whereas without acetic acid, B is the sole product from VII and phenylhydrazine. That B is obtained from II but not VII in the presence of acid indicates that the pyrazoline is much more readily formed from the primary reaction product of VII and phenylhydrazine than it is from B itself. Therefore, B is *not* the initial reaction product from VII and phenylhydrazine. In consideration of the compounds from which it is formed and the extreme ease of isomerization of this initial product to the pyrazoline, it is reasonable to formulate it as benzylidenepyruvanilide phenylhydrazone (IX); this can account for all these observations.

It having been argued that IX is the initial product of reaction of VII with phenylhydrazine, there remains no objection to the formulation of B as XI. Indeed, it would be highly unlikely that XI would isomerize to the pyrazoline more readily than does IX, which formulation of B as IX would require. That XI is isomerized to the pyrazoline VIII under more vigorous conditions implies its intermediate conversion to IX, and since in the absence of acid, benzylidenepyruvanilide and phenylhydrazine produce XI, from the initial product (IX) it is suggested that IX cyclizes to XI. This implies a reversible isomerism between XI and IX, XI being the normally stable form of the pair, but IX being able to react irreversibly (pyrazoline formation) and force the reaction to proceed in its favor.

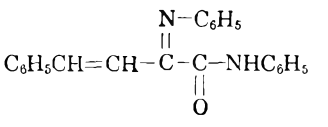
The reversible isomerism between XI and IX appears to be an unique example of the type. It is similar to that of I $\rightleftarrows$ III and of VI $\rightleftarrows$ IV, but involves the corresponding nitrogen functions (lactam and anilide). There is no reason to believe this cannot occur, since as with known types of ring-

(7) Such a substitution is known to occur on X with hydroxylamine, although under somewhat different conditions.[8] Likewise, other aromatic amines have been used to substitute for the anil aniline of X,[2] although the characterization of these products was not complete.

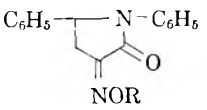
(8) W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, 22, 1554 (1957).

chain tautomerism, the analogous intermolecular reactions are well known. In this case the Michael addition and its reverse of weak acids to a conjugated double bond[9] represents the intermolecular reactions. That this reversible cyclization is much less facile than that of I with III, also found in this series, is to be expected, since the ring-opening reaction here produces a much stronger base (the anilide anion), and thus constitutes an energetically more difficult process.

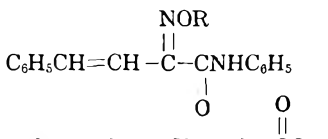
Such apparently tautomeric behavior, suggests the reason the elusive anil of benzylidenepyruvanilide has not been observed. All attempts to obtain this substance (XIII) have resulted in isolation of the pyrrolidinedione anil X.[10] In the anil XIII, no alternate cyclization reaction such as IX undergoes to the pyrazoline, is available and thus its existence has not been demonstrated.



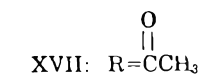
XIII



XV: R=H



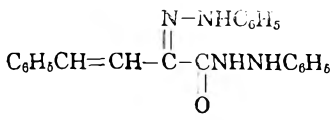
XIV: R=H XVI: R=CCH_3



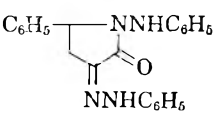
XVII: R=CCH_3

This lactam-enamide tautomerism is not a general behavior of the compounds in this series, however. Thus benzylidenepyruvanilide (VII) and 1,5-diphenyl-2,3-pyrrolidinedione (II) are distinct compounds, as are the corresponding oximes (XIV and XV) and oxime acetates (XVI and XVII). Although extensive attempts have not yet been made to interconvert these forms, it was definitely observed that the cyclization reactions were not spontaneous as seems to be the case for the anil and phenylhydrazone. Further research on the factors governing this reversible cyclization is in progress.

The third product from the reaction of I with phenylhydrazine contains two phenylhydrazine residues and has been formulated as XVIII or XIX.[2,5] At present, as pointed out by Vaughan,[5] no choice between these formulations exists.



XVIII



XIX

(9) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, New York, 1953, pp. 690–6.

(10) L. R. Peters, Ph.D. dissertation, University of Michigan, 1952.

EXPERIMENTAL

All melting points are uncorrected. Microanalyses are by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra were recorded from Nujol mulls, unless otherwise noted, by means of a Perkin-Elmer Model 21 Infrared Spectrophotometer.

1,5-Diphenyl-2,3-pyrrolidinedione-3-phenylhydrazone (XI). (*a*) *From 1,5-diphenyl-3-anilino-2(5H)-pyrrolone* (X). The anil X and phenylhydrazine were heated together according to the directions of Bodforss[2] to produce XI, m.p. 128–131° dec. after several recrystallizations from ethanol (monoethanolate, reported[5] 131–132° dec.). A sample of this material was de-ethanolated by heating in xylene according to the directions of Vaughan.[5] The unsolvated material had but one band, at 3220 $cm.^{-1}$, in the high frequency region of the infrared spectrum. On recrystallization from ethanol it was reconverted to the ethanolate.

(*b*) *From 1,5-diphenyl-2,3-pyrrolidinedione* (II). To 50 mg. (0.20 mmole) of II in 4 ml. of ethanol containing 3 drops of acetic acid was added 5 drops of phenylhydrazine and the solution was warmed for 30 sec. on the steam bath. The product, which precipitated after 6 hr. at room temperature, was recrystallized from absolute ethanol to m.p. 128–131° dec., which was undepressed on admixture with the material obtained by procedure *a* above. The infrared spectra of the samples from the two procedures were identical. This compound gives a blue color on application of the Knorr pyrazoline test, which fades after several hours, as described by Vaughan.[5]

1,5-Diphenyl-Δ^2-pyrazoline-3-carboxanilide (VIII). A solution of 50 mg. (0.20 mmole) of benzylidenepyruvanilide (VII)[11] in 4 ml. of ethanol was treated with acetic acid and phenylhydrazine precisely as was II in procedure *b* above. After standing for 6 hr., no crystallization had occurred. Addition of water threw down an oil which was crystallized from ethanol. The pale yellow solid melted at 189–194°. Several more recrystallizations raised the m.p. to 197–198° (reported 203–204°).[5] The infrared spectrum of this sample was identical with that of the authentic material,[5] and a mixture melting point was undepressed. This substance gives a bright emerald green color on application of the Knorr test as described by Vaughan.[5]

Benzylidenepyruvanilide oxime (XIV). To a solution of 181.8 mg. (0.725 mmole) of benzylidenepyruvanilide (VII) in 20 ml. of absolute ethanol was added 77.0 mg. (1.12 mmoles) of hydroxylamine hydrochloride, and the solution was refluxed overnight. Following the cooling of the solution to room temperature, an equal volume of water was added, throwing down a white precipitate. This was filtered and amounted to 134 mg. (70%) of XIV, m.p. 201–207° dec. Several recrystallizations from ethanol produced the analytical sample, m.p. 203.5–204.5° dec. (highly dependent on rate of heating).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.10; H, 5.37; N, 10.42.

The oxime acetate was prepared by the use of acetic anhydride in acetic acid, m.p. 144.0–144.5° after recrystallization from ethanol.

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.23. Found: C, 70.36; H, 5.43.

Both the oxime and its acetate are definitely different from the corresponding 1,5-diphenyl-2,3-pyrrolidinedione derivatives (XV, m.p. 229–230° dec. and XVII, m.p. 190–192° dec.).[10]

ANN ARBOR, MICH.

(11) W. R. Vaughan and L. R. Peters, *J. Org. Chem.*, 18, 393 (1953).

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, UNIVERSITY COLLEGE, CORK AND UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Studies in the Pyrazole Series. VIII.[1] Aminolyses of Some 3,5-Dimethyl-1-acylguanylpyrazoles

F. L. SCOTT[2]

Received February 18, 1957

The aminolytic deguanylations of four types of 1-acylguanylpyrazole, wherein the acyl group varies from *N*-*p*-toluenesulfonyl to *N*-benzoyl to *N*-phenylthiocarbamyl to *N*-α-naphthylcarbamyl, has been examined. The comparative unreactivity of the first three of these types toward bases in ethanol is consistent with a BAc2 mechanism of deguanylation. The fourth type of acyl derivative behaved anomalously. Use of the displacing amines as both solvents and reactants did effect ready deguanylation, mono- and di-substitutions being detected therein. Evidence was obtained from the scissions of some substituted *S*-methylpyrazolyl thioureides that the pyrazolide leaving group can have a greater mobility than the labile thiomethoxide ion. The detection of this difference depended upon the aminolysis temperature; above a certain temperature level both pyrazolide and thiomethoxide were eliminated to form trisubstituted biguanides. Reaction conditions were devised, *viz.*, with dialkyl cyanamides in chloroform, wherein some substituted 1-guanylpyrazole free bases underwent eliminations to yield dicyandiamide. This elimination process was not encountered with comparable acyclic systems.

In some previous papers in this series,[1,3] we have examined the reactions of certain substituted 1-acylpyrazoles (*e.g.* Ia, Ib and Ic) with nucleophiles, the over-all reaction observed therein being a fragmentation of the substituted (I) substrate with the liberation of 3,5-dimethylpyrazole (Id) and the formation of the nucleophilic adduct of the articulated acyl group (X). The possible mechanisms of these deacylations have also received some consideration. One of these mechanisms, the equivalent of a carbonyl addition-elimination process, a so-called BAc2 reaction,[4] has been established by kinetic methods[5] as the operative mode of decarbamylation of a variety of 1-carbamylpyrazoles in neutral ethanolic solution, and as the sole mode of deacylation of 3,5-dimethyl-1-(*N*,*N*-diphenylcarbamyl)pyrazole (Ie), even in basic media, because of the structural prohibition this substance offers toward other types of heterolytic cleavage.[3a] The other available heterolytic mechanisms for the general 1-pyrazolyl deacylations involve an intermediate anion and may consist of either a simple elimination process[6] or a base-catalyzed modification of the $B_{Ac}2$ reaction.[7] The present work, amidst its consideration of a diversity of pyrazolyl aminolyses, has some further pertinence with regard to the possibility of the intrusion of such an anionic intermediate.

Thus if such an intermediate were involved in the base-induced deacylations then an increase in the acidity of the 1-carbamyl- or 1-guanyl-pyrazolyl substituents should greatly increase the population of intermediate anion and thereby result in an overall facilitation of the deguanylation process.[8] Such (small) acidity increases were incorporated into the 1-guanylpyrazole system with four types of acyl substitution therein. With three of the resulting compounds, *viz.* 3,5-dimethyl-1-[*N*-*p*-toluenesulfonyl (If)-, *N*-benzoyl (Ig)-, and *N*-(*N'*-phenyl)-thiocarbamyl (Ih)]guanylpyrazoles, the relative reactivities towards aminolytic deacylations were greatly below that of the parent 1-guanylpyrazole (Ij).[9,10] That is, refluxing If, Ig or Ih in ethanolic solution for 3- to 6-hour periods in the presence of equimolar quantities, or an excess, of such nucleophiles as aniline, *n*-butylamine, cyclohexylamine, morpholine, phenylhydrazine or piperidine resulted in the substituted pyrazoles being recovered in *ca.* 80–95% yields. With the fourth pyrazole derivative used, *viz.* 3,5-dimethyl-1-(*N*-α-naphthylcarbamyl)guanylpyrazole (Ik) the aminolytic reactions detected under these conditions were anomalous–a facile scission occurring at the naphthyl-proximate carbonyl group therein, perhaps *via* the anion (II).[8] Thus, when refluxed with phenylhydrazine or cyclohexylamine for 1 hour in ethanolic solution, Ik afforded 4-α-naphthyl-1-phenyl-

(1) Part VII, F. L. Scott, D. G. O'Donovan, M. R. Kennedy, and J. Reilly, *J. Org. Chem.*, **22**, 820 (1957).

(2) Present address, Pennsalt Chemical Corp., Whitemarsh Research Labs., Box 4388, Phila. 18, Pa.

(3) (a) Part IX, This Series, F. L. Scott, A. Ahearne, and J. Reilly, to be submitted for publication; (b) F. L. Scott, M. T. Kennedy, and J. Reilly, *J. Am. Chem. Soc.*, **75**, 1294 (1953).

(4) Compare C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, pp. 752 *et seq.*, in which the symbolism BAc2 is used to represent a base-induced bimolecular hydrolysis of an ester with acyl scission.

(5) F. L. Scott, *Chimia* (*Switz.*), **11**, 163 (1957).

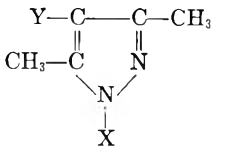
(6) See p. 420 *et seq.* of Ingold, *op. cit.*

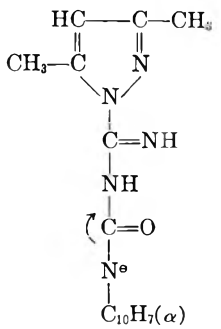
(7) *Cf.* D. G. Crosby and C. Niemann, *J. Am. Chem. Soc.*, **76**, 4458 (1954).

(8) For some related kinetic data see F. L. Scott, R. E. Glick, and S. Winstein, *Experientia*, **13**, 183 (1957).

(9) Compare the data in (a) F. L. Scott and J. Reilly, *J. Am. Chem. Soc.*, **74**, 4562 (1952), and (b) F. L. Scott, D. G. O'Donovan, and J. Reilly, *J. Am. Chem. Soc.*, **75**, 4053 (1953).

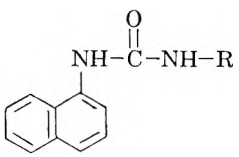
(10) Strictly speaking, one should compare the reactivities of If, Ig and Ih *versus* the 3,5-dimethyl-1-guanylpyrazole free base (Ip) rather than Ij. This does not change the reactivity sequence as Ip is even more prone to solvolytic deguanylation than Ij.



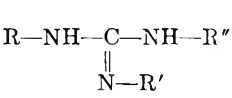


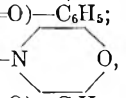
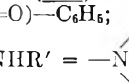
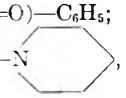
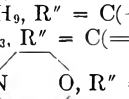
II

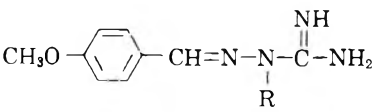
I, a*, X = $CONH_2$;
b*, X = $CSNH_2$;
c*, X = $C(=NH)NHNO_2$;
d*, X = H;
e*, X = $CON(C_6H_5)_2$;
f*, X = $C(=NH)NHSO_2C_6H_4CH_3(p)$;
g*, X = $C(=NH)NHCOC_6H_5$;
h*, X = $C(=NH)NHCSNHC_6H_5$;
j*, X = $C(=NH)NH_2 \cdot HNO_3$;
k*, X = $C(=NH)NHCONHC_{10}H_7(\alpha)$;
l*, X = $C(=NH)NHC(SCH_3)=N-C_6H_5$
m Y = Cl, X as in l;
n, Y = Br, X as in l;
p*, X = $C(=NH)NH_2$;
q, Y = Cl, X as in p;
r, Y = Br, X as in p;
Those symbols starred (*) have Y = h.



III, a, R = $-NH-C_6H_5$;
b, R = C_6H_{13};
c, R = $C(=O)-NH_2$



IV, a*, R″ = $SO_2-C_6H_4-CH_3(p)$;
b*, R = n-C_4H_9,
R″ = $C(=O)-C_6H_5$;
c*, R = C_6H_{13},
R″ = $C(=O)-C_6H_5$;
d, R = R′ = C_6H_{13},
R″ = $C(=O)-C_6H_5$;
e*, RNH =  ,
R″ = $C(=O)-C_6H_5$;
f, RNH = NHR′ =  ,
R″ = $C(=O)-C_6H_5$;
g*, RNH =  , R″ = $C(=O)-C_6H_5$;
h*, R = C_6H_5,
R″ = $-C(-SCH_3)=N-C_6H_5 \cdot HI$;
j*, R = n-C_4H_9, R″ = $C(-SCH_3)=N-C_6H_5$;
k*, R = C_6H_{13}, R″ = $C(=N-C_6H_5)-NHC_6H_{13}$;
l*, RNH =  , R″ = $C(=N-C_6H_5)-$;
Those symbols starred (*) have R′ = h.



V, A, R = H;
b, R = $C(=NH)N(CH_3)_2$;

semicarbazide (IIIa) or 1-cyclohexyl-3α-naphthylurea (IIIb) in 85 or 90% yields respectively. In that connection, it is interesting to note that under acidic conditions, *i.e.* on refluxing Ik for 90 minutes with an excess of 10% hydrochloric acid solution, its cleavage resembles that normally detected with the 1-guanylpyrazoles,[9] the product of the acidolysis being an 80% yield of 1-α-naphthyl biuret (IIIc).

The experiments conducted with If, Ig and Ih, clearly indicating that their rates of aminolytic deacylation were much slower than that obtaining for the parent 1-guanyl compound (Lj),[10] strongly suggest that the base-induced deacylations of at least the substituted 1-guanylpyrazoles do not involve an intermediate anion. This in turn would again point to the $B_{AC}2$ mechanism. Now the detailed formulation of such a $B_{AC}2$ process reveals it has 2 stages: (1) addition of the displacing nucleophile to the carbonyl site, with some retrogression of the adduct, and (2) elimination of the (anionic) leaving group from the resulting adduct.[11] Acyl substitution in Ip should increase the electrophilicity of its guanyl moiety and thereby favor step (1) in its ($B_{AC}2$) mode of deguanylation. Such electrophilicity increase should also inhibit the dissociation step (2) therein. The present results suggest therefore that with the compounds examined, step (2) is more important in formulating the transition state of the over-all $B_{AC}2$ displacement than is step (1). This point[5] is elaborated on in a subsequent report on the kinetics of such 1-pyrazolyl deacylations.[12-14]

In an effort to overcome the lack of reactivity of the pyrazoles If, Ig, and Ih their reaction conditions were modified, *i.e.*, to the use of the displacing amine in large excess as both reactant and solvent. Under these conditions the aminolyzing pyrazolyl substrate was enveloped in a medium of displacing nucleophile, the nuances of mechanism discussed earlier were essentially obscured, and the over-all reaction was reduced to that of a pseudo first order solvolysis. The modified conditions did, however,

(11) *Cf.* C. A. Bunton, T. A. Lewis, and D. R. Llewellyn, *Chemistry & Industry*, 1154 (1954).

(12) F. L. Scott and R. Rubin, forthcoming paper in this series.

(13) For some earlier discussion on the varying importances of bond-formation *versus* bond rupture in the transition states of related acyl halide solvolyses, see the interesting paper of E. W. Crunden and R. F. Hudson, *J. Chem. Soc.*, 501 (1956).

(14) For a more complete discussion of the solvolysis mechanisms at a reactive carbonyl function, and the solvent-dependency of such mechanisms, see S. Winstein and A. H. Fainberg, forthcoming publication.

lead to 1-deguanylations. Thus, If, when refluxed without further solvent other than an excess of the amines aniline, *n*-butylamine, cyclohexylamine, morpholine, or piperidine, for 30-minute periods, formed the appropriate 1-*p*-toluenesulfonyl-3-substituted guanidines (IVa) in 70–100% yields. While aniline reacted anomalously when similarly refluxed with Ig, *n*-butylamine cleaved this substituted pyrazole to form 3-benzoyl-1-*n*-butylguanidine (IVb) in 98% yield. Dual substitution reactions were encountered between Ig and both cyclohexylamine, which afforded not only 1-benzoyl-3-cyclohexylguanidine (IVc) but also 1-benzoyl-2,3-dicyclohexylguanidine (IVd), and morpholine, which similarly resulted in 4-(*N*-benzoyl)guanylmorpholine (IVe) and *N*-benzoyl-(4,4′-dimorpholino)keto-imine (IVf). With piperidine as base the sole product isolated under these forcing conditions with Ig was 1-(*N*-benzoyl)guanylpiperidine (IVg). With Ik, even under these conditions, the anomalous scission pattern encountered in the earlier ethanolic reactions of this material was duplicated. For example, *n*-butylamine and cyclohexylamine when refluxed with Ik in the absence of further solvent resulted in the formation of the appropriate 3-substituted-1-α-naphthylureas (III). With an excess of morpholine and piperidine, in addition to the formation of compounds of type (III), Ik also yielded both 1-guanylmorpholine and -piperidine, respectively, in small yields. Finally, with aniline Ik appeared to afford a double displacement, the final product isolated being 1,3-diphenylurea in high yield. In all of the above experiments, accompanying the main products cited, 3,5-dimethylpyrazole was formed in good yield.

Thioureide systems are prone to base-induced eliminations and desulfurizations[15] and hence an effort was made to avoid these complications with Ih, and related molecules, in the aminolyses attempted with these substances. This attempt consisted of replacing the acidic thiol function of Ih by an *S*-ether grouping; in the case of Ih, the *S*-methyl derivative (Il) being so prepared. Despite this the aminolysis reactions of Il were generally complex and have not as yet been completely clarified. However, some data have been obtained. Thus, when Il, as its hydriodide, was refluxed for 1 hour with one equivalent of either cyclohexylamine, morpholine, or piperidine in ethanolic solution, the free base Il was the only solid recovered, and that in only 40–60% yield. The 4-chloro (Im)- and 4-bromo (In)-analogs of Il behaved similarly. However, with aniline, Il did yield a displacement reaction, 40% Id being isolated as well as a 30% yield of 1-(phenylamidino)-2-methyl-3-phenylthiouronium hydriodide (IVh). This result suggested that even under these mild conditions the pyrazolide leaving group has at least comparable lability with the labile thiomethoxide ion.[16] When some reactions were attempted between Il, Im, and In in the displacing amines as solvent, this lability comparison was further supported. Thus, when either Il, Im, or In was refluxed in 10 equivalents of *n*-butylamine for 30 minutes, the same compound, *viz.* 1-(*n*-butylamidino)-2-methyl-3-phenylthiourea (IVj), was formed in *ca.* 95% yield in all 3 experiments, together with the respective derivatives of Id. These results would imply that, in the given competitive situation at least, the pyrazolide ion has a *greater* affinity for separation than the thiomethoxide group. Incidentally, if one combines this observation with other data,[17] the following lability sequence might be predicted: azide $\geq$ pyrazolide > thioalkoxide > nitramide. Finally, when these thioureidopyrazoles were treated with both cyclohexylamine and morpholine, again at reflux temperatures in the amines as solvent, the higher reaction temperatures involved (134° and 126° as compared to 78° with *n*-butylamine) obscured the discrimination in leaving tendency just commented on and the main products isolated were 1,4-dicyclohexyl-5-phenylbiguanide (IVk) and 1,4-di(tetramethyleneoxy)-5-phenylbiguanide (IVl), respectively, corresponding to a replacement of both pyrazolide and thiomethoxide groups by base. In addition to describing more fully the reactions just discussed the Experimental Section has some further data on the synthesis of thioureido substituted pyrazoles similar to Ih and Il.

The above deguanylations, as already mentioned, occur by the $B_{AC}2$ mechanism. However, in some cognate experiments, a set of deguanylation conditions were realized in which the operative mechanism appeared to be unequivocally of the elimination type.[6] Thus, when 4-unsubstituted (Ip)-, 4-chloro (Iq)-, and 4-bromo (Ir)- 3,5-dimethyl-1-guanylpyrazole free bases were refluxed in anhydrous chloroform solution with either dimethyl or diethyl cyanamides as potential (but weak) nucleophiles, no incorporation of the dialkyl cyanamide molecule within the guanylpyrazole system resulted. Instead, deguanylation to yield dicyandiamide in good yield was the sole process detected. Under these conditions no form of solvolytic displacement was possible, no products were isolated to suggest the operation of any $B_{AC}2$ displacements, and hence the observed reaction would appear to correspond to an initial (E_2)[6] elimination of cyanamide from Ip, Iq, and Ir, followed by dimerization of the cyana-

(15) Compare (a) F. L. Scott, D. G. O'Donovan, M. Paye, and J. Reilly, to be submitted for publication; (b) F. L. Scott, *Chemistry & Industry*, 1350 (1956); (c) W. H. R. Shaw and D. G. Walker, *J. Am. Chem. Soc.*, **78**, 5769 (1956) and references therein; (d) F. L. Scott, *Experientia*, **13**, 275 (1957).

(16) Compare for example F. L. Scott, D. A. O'Sullivan, and J. Reilly, *J. Appl. Chem.*, **2**, 184 (1952) and references therein.

(17) *Cf.* F. L. Scott, A. J. Kocjarski, and J. Reilly, to be submitted for publication; L. Fishbein and G. A. Gallaghan, *J. Am. Chem. Soc.*, **76**, 1877 (1954).

mide to dicyandiamide.[18] No formation of this latter material occurred when these reactions were attempted in ethanolic solution, ethanolysis evidently being far superior to the elimination mechanism as a deguanylating process. Again no elimination, or displacement, was detected when Ij, *i.e.* Ip-nitrate, was refluxed for 2 hours without further solvent other than an excess of diethyl cyanamide. To emphasize the labilizing effect of the readily displayed pyrazolide ion[1] on such guanyl systems as Ip, *et al.*, some cognate reactions with acyclic systems were investigated. Some of the results obtained were as follows. When aminoguanidine nitrate was refluxed in an excess of dimethyl cyanamide for 3 hours, or with diethyl cyanamide in aqueous ethanolic solution for 6 hours, it was recovered in 90% yield. A similar unreactivity was demonstrated under comparable conditions by triaminoguanidine nitrate. An anomalous reaction was detected when aminoguanidine free base was refluxed for 3 hours in aqueous solution with an equimolar proportion of diethyl cyanamide. Finally, although *p*-methoxybenzylidene aminoguanidine (Va) when refluxed with dimethyl cyanamide for 3 hours in either ethanolic or chloroform solution was recovered in 97% yield, when this reaction was conducted in the dialkyl cyanamide itself as solvent only 30% Va was isolated, together with a 17% yield of *p*-methoxybenzylidene 1-amino-4,4-dimethyl-2-guanyl-guanidine (Vb).[19] In all of the above reactions no evidence of dicyandiamide was detected; hence, within the material balances indicated, the pyrazolyl elimination mechanism was not reproduced by comparable acyclic systems.

EXPERIMENTAL[20]

The substituted 3,5-dimethyl-1-acylguanylpyrazoles, If to Ik, and Ip, Iq, and Ir, were prepared by the methods of Scott and Reilly.[9a] The melting points of these compounds found in the present work agreed with those reported previously.

Aminolysis experiments with If, Ig, and Ih. (1) *In ethanolic solution.* The following is typical of the runs attempted. To 1.0 g. of Ig dissolved in 20 ml. of ethanol was added 0.3 ml. of cyclohexylamine and the whole was refluxed for 2 hr. On allowing the solution to cool some Ig separated. After addition of an excess of water to the ethanolic filtrate a further quantity was obtained. These crops, added to the trace of Ig obtained on ethereal extraction (5 × 50 ml.) of the aqueous ethanolic mother-liquor, corresponded to a 98% recovery of starting material. A similar result was obtained when Ig was refluxed, again in ethanol, with even a 10-molar excess of aniline for a 6-hr. period. Variation of the base employed had but little effect on the comparative aminolytic unreactivity of Ig, under these conditions. The results were similar with If, it being recovered in 95–98% yields after 6 hr. refluxing with either aniline or morpholine in ethanol.

As mentioned earlier, Ik did react under these conditions though not in the expected manner. Thus, when 0.5 g. of Ik dissolved in 20 ml. of ethanol was refluxed with 0.17 ml. of phenylhydrazine, after 10 min., a heavy separation of solid was detectable. Refluxing was continued for a further 35 min. and the solution was then allowed to cool overnight. The solid which had deposited (0.22 g., 48% yield), had a m.p. of 215–218°, and after the substance had been recrystallized from aqueous ethanol, it melted at 224°. It corresponded to 4-α-naphthyl-1-phenylsemicarbazide (IIIa).

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.6; H, 5.4; N, 15.2. Found: C, 73.5; H, 5.7; N, 15.2.

From the original ethanolic filtrate was isolated, on further work-up, 0.23 g. (48% yield) of unchanged Ik. Cyclohexylamine when treated with Ik under analogous conditions yielded 37% starting material and 56% of 1-cyclohexyl-3-α-naphthylurea (IIIb),[21] m.p. 237–239°.

Anal. Calcd. for $C_{17}H_{20}N_2O$: C, 76.1; H, 7.5; N, 10.4 Found: C, 76.1; H, 7.4; N, 10.0.

The following experiment is an acidolysis cognate to the above. To 0.5 g. of Ik was added 30 ml. of 10% hydrochloric acid solution and the resulting mixture was then refluxed for 90 min. The residual solid, 300 mg., 80% yield, with m.p. 214° (it re-solidified and then sublimed after melting), was recrystallized from aqueous ethanol as a white paperlike amorphous solid, m.p. 217–218° (again with re-solidification and sublimation). This was 1-α-naphthylbiuret (IIIc), reported[22] m.p. 217.3–217.6°.

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.9; H, 4.8: N, 18.3. Found: C, 63.2; H, 4.8; N, 18.1.

(2) *In various amines as solvents.* The following is typical of this series of experiments. To 1.21 g. of Ig was added 4.5 ml. of morpholine. The resulting solution was then refluxed for 30 min., during which time the reaction liquor adopted a mauve tint and a faint odor of ammonia developed. The liquor was allowed to stand for 24 hr. and was then poured into 100 ml. of water. A white solid, 0.40 g., m.p. 145–148°, was immediately precipitated and on standing a further 0.30 g. of this same substance also separated. This crystallized from 95% ethanol as a gelatinous solid which dried to a white amorphous powder, m.p. 148°. It proved to be 4-(*N*-benzoyl)guanylmorpholine (IVe).

Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.8; H, 6.4; N, 18.0. Found: C, 61.6; H, 6.0; N, 18.3.

Ethereal extraction of the original filtrate afforded a further 0.25 g. of the above substance, the total yield obtained was 81%, as well as 0.29 g. (60% yield) of 3,5-dimethylpyrazole (Id).[23] The residual aqueous mother liquor was concentrated to small bulk. To it was then added an excess of aqueous picric acid solution, and the oily material which separated was filtered off and washed with a little ethanol and water. After recrystallization from ethanol, the picrate (0.22 g., 8% yield) was obtained as small rhombic crystals, m.p. 165°, and it corresponded to the salt of *N*-benzoyl-(4,4′-dimorpholino)keto-imine (IVf).

(18) An alternative to a direct elimination process is an initial $B_{AC}2$ displacement *e.g.* of the type: 2 Py—C(=NH)—NH_2 → PyH + Py—C(=NH)—NH—C(=NH)—NH_2 (A), where Py represents a substituted pyrazolyl group. However, (A) still has to undergo elimination to yield dicyandiamide. The possibility of a homolytic reaction rather than a heterolytic process cannot still be discounted.

(19) Compare the observations of A. D. Ainley, F. H. S. Curd, and F. L. Rose, *J. Chem. Soc.*, 98 (1949) and previous papers in that series.

(20) All melting points are uncorrected and all microanalyses are by Drs. Wieler and Strauss, Oxford, England.

(21) This compound was formed in 93% yield when Ik was refluxed in an excess of cyclohexylamine, without further solvent, for 30 min.

(22) T. L. Davis and K. C. Blanchard, *J. Am. Chem. Soc.*, 51, 1801 (1929).

(23) In all of the aminolysis experiments conducted in an excess of the amine as sole solvent, Id was isolated in from 60–70% yields. It was identified in each case not only by mixture m.p. with an authentic sample but also by mixture m.p. of its picrate with an authentic sample.

Anal. Calcd for $C_{22}H_{24}N_6O_{10}$: C, 49.6; H, 4.5; N, 15.8. Found: C, 49.8; H, 4.1; N, 16.0.

Most of the remaining aminolyses effected with this trio of 1-acylguanylpyrazoles are summarized in Table I.

Aminolyses of Ih and related compounds. (1) *In ethanol.* The following represents a typical experiment. To 1.37 g. of Ih dissolved in 20 ml. of ethanol was added 0.45 ml. of aniline. The resulting solution was then refluxed for 1 hr. and allowed to cool overnight. On the addition of an excess of water 0.97 g. of Ih were precipitated and a further 0.30 g. of this substance was recovered on work-up of the aqueous mother liquor. The total recovery of Ih was 95%. Analogous results were obtained when the base employed was either cyclohexylamine or morpholine. For reasons discussed earlier, Ih, and the analogous 4-chloro- and 4-bromo-3,5-dimethyl-1-(*N*-phenylthiocarbamyl)guanylpyrazoles, were then methylated. The following illustrates how this was effected. A solution of 1.0 g. of Ih in 25 ml. of methyl iodide was refluxed for 30 min. The pale yellow liquor was then poured into a large excess, *ca.* 300 ml., of anhydrous ether. A white oil was immediately precipitated but this solidified on scratching. This substance, 1.50 g., 99% yield, m.p. 84–85°, was recrystallized from a mixture of ethanol and ether as a fine white powder which turned yellow on prolonged exposure to light, m.p. 87–88°. It proved to be 3,5-dimethyl-1-(*N*-phenyl-*S*-methyl-thiocarbamyl)guanylpyrazole (Il) hydriodide.

Anal. Calcd. for $C_{14}H_{18}N_5SI \cdot H_2O$: C, 38.8; H, 4.6; N, 16.2; S, 7.4. Found: C, 38.4; H, 4.6; N, 15.7; S, 7.7.

The other methiodides, and their free bases Il, Im, and In, together with a number of related aryl- and alkylthiocarbamylguanylpyrazoles have their properties summarized in Table II.

When the pyrazolyl substrate aminolyzed was either Il, Im or In hydriodide, and the reaction conditions consisted of 1 hr.'s refluxing in ethanolic solution with either cyclohexylamine, morpholine, or piperidine, in each reaction some methyl mercaptan was evolved but the only solids isolated were the respective free bases Il, Im or In, in *ca.* 40–60% yields. There was only one exception to this pattern and that was as follows. To 4.16 g. of Il, as its hydriodide, dissolved in 50 ml. of ethanol, was added 1.86 ml. of aniline. The mixture was refluxed for 1 hr. during which time a little methyl mercaptan was evolved. The solution was then allowed to cool and was evaporated in a stream of air. On work-up of the resulting oil, both 3,5-dimethylpyrazole, 0.38 g., 40% yield[23] and crystals of m.p. 145–150° (1.20 g., 30% yield) were obtained. This latter substance after further crystallization from aqueous ethanol proved to be 1-(*N*-phenylamidino)-2-methyl-3-phenylthiourenium hydriodide (IVh), m.p. 158°.

Anal. Calcd. for $C_{15}H_{17}N_4SI$: C, 43.7; H, 4.1; N, 13.6; S, 7.8; I, 30.8 Found: C, 44.1; H, 3.9; N, 13.6; S, 7.8; I, 31.1.

(2) *In various amines as solvents.* These reactions were generally quite complex but some definite products have been identified therefrom. The following illustrates a comparatively clean-cut aminolysis within this group. To 1.0 g. of Il was added 3 ml. of *n*-butylamine and the resulting solution was then refluxed for 30 min. During this time, a slight evolution of methyl mercaptan was detected from the liquor. After it had been allowed to cool the solution was poured into 50 ml. of distilled water. An oil separated immediately but after a short while, with vigorous scratching, this crystallized. The white powder thus obtained, 0.90 g., 98% yield, had a m.p. of 70–75°. After recrystallization from 50% aqueous ethanol it proved to be 1-(*n*-butylamidino)-2-methyl-3-phenylthiourea (IVj), m.p. 78–80°.

Anal. Calcd. for $C_{13}H_{20}N_4S$: C, 59.1; H, 7.6; N, 21.2; S, 12.1. Found: C, 58.8, 59.5; H, 7.4, 7.7; N, 21.6, 21.6; S, 11.5, 11.8.

This same compound was also obtained, and in good yield, from the similar aminolyses of Im and In. In each case 3,5-dimethylpyrazole, or the appropriate 4-chloro- or 4-bromo-derivative thereof,[24] was isolated in *ca.* 60–70% yields from the aqueous mother liquors.

While all three pyrazoles Il, Im, and In, under the above conditions, afforded unworkable oils with both aniline and benzylamine, with cyclohexylamine they afforded the same compound in *ca.* 70% yields, together with some methyl mercaptan evolution. This common product, m.p. 135° after 3 recrystallizations from aqueous ethanol, proved to be 1,4-dicyclohexyl-5-phenylbiguanide (IVk).

Anal. Calcd. for $C_{26}H_{31}N_5$: C, 70.4; H, 9.1; N, 20.5. Found: C, 70.3; H, 9.0; N, 20.4.

With morpholine as the basic medium, Il afforded a strong evolution of methyl mercaptan and a white solid, insoluble in ether and very soluble in ethanol, with m.p. 105°, which is still unidentified.

Anal. Calcd. for $C_{10}H_{16}N_3O_2$: C, 57.1; H, 7.6; N, 20.0. Found: C, 57.2; H, 7.4; N, 20.4.

Also isolated from this reaction was a picrate in 70% yield, m.p. 204° (Il-picrate melts at 123–125°), which proved to be the salt of 1,4-di(tetramethyleneoxy)-5-phenylbiguanide (IVe).

Anal. Calcd. for $C_{22}H_{26}N_8O_9$: C, 48.4; H, 4.8; N, 20.5. Found: C, 48.0; H, 5.0; N, 19.9.

This same picrate was isolated from the analogous experiments with Im and In, and morpholine, again in *ca.* 75% yield. However, in neither of these last two experiments was the white solid, m.p. 105°, re-encountered.

Some dialkyl cyanamide reactions. (1) *With Ij.* Equimolar quantities of 3,5-dimethyl-1-guanylpyrazole nitrate (Ij) and dimethyl cyanamide were refluxed in ethanolic solution for 5 hr. On allowing the solution to cool unchanged Ij separated in 64% yield. The filtrate was then evaporated to dryness in a stream of air and the residual solid washed with ether. Unexpectedly, the ethereal washings afforded not only a 5% yield of Id[24] but a 14% yield of the free base Ip. This latter substance, after careful crystallization from benzene, melted at 70°, reported[9a] m.p. 70–71°.

Anal. Calcd. for $C_6H_{10}N_4$: C, 52.7; H, 7.2; N, 40.6. Found: C, 52.6; H, 7.4; N, 40.5.

The ether-insoluble solid was a further quantity (16%) of unchanged Ij. When the substituted cyanamide employed in this experiment was the diethyl compound, with a 6-hr. reflux period, 38% Id and 60% Ij were isolated, and no formation of Ip was detected. Finally, when Ij was dissolved in a 10-molar proportion of diethyl cyanamide and refluxed under anhydrous conditions for 2 hr., it crystallized out in 41% yield on standing. After the removal of the major portion of the dialkyl cyanamide "solvent" by distillation *in vacuo*, the residual viscous liquor was taken up in aqueous ethanol, and excess saturated aqueous picric acid solution was added to it. A 30% yield of Ij-picrate, m.p. 207–209°, reported[9a] 207–208.5°, separated.

Anal. Calcd. for $C_{12}H_{13}N_7O_7$: C, 39.2; H, 3.5; N, 26.7. Found: C, 39.1; H, 3.5; N, 27.0.

(2) *With the substituted 1-guanylpyrazole free bases, Ip, Iq, and Ir.* (a) When Ip was refluxed in ethanolic solution for 6 hr. with an equimolar proportion of diethyl cyanamide it yielded Id in 48% yield and Ip was recovered to the extent of 46%. No dicyandiamide was detected With dimethyl cyanamide under identical conditions the deguanylation effect was less, 59% Ip being isolated and 38% Id. (b). When Iq was refluxed in chloroform solution with an equimolar proportion of either dimethyl or diethyl cyanamides for 3 hr. it was recovered in 42 and 40% yields, and also formed in 20 and 57% yields, respectively, dicyandiamide, m.p. 208°, which did not depress a mixture m.p. with an authentic sample, reported[25] m.p. 207–209°.

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(24) These were identified by mixture m.p. with authentic samples, which in turn were prepared by the methods of G. T. Morgan and I. Ackermann, *J. Chem. Soc.*, 1308 (1923).

(25) I. Heilbron and H. M. Bunbury, *Dictionary of Organic Compounds*, 4th edition, Eyre and Spottiswoode, London, 1953, p. 177.

TABLE I

AMINOLYSES OF SOME SUBSTITUTED 1-ACYLGUANYLPYRAZOLES

Amine	Product	Molecular Formula	M.P., °C.	Yield, %	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Aniline[a,b]	1-Phenyl-3-*p*-toluenesulfonylguanidine[c]	$C_{14}H_{15}N_3SO_2$	185–186	70	58.1	57.8	5.2	5.0	14.5	14.4[d]
n-Butylamine[a]	1-*n*-Butyl-3-*p*-toluenesulfonylguanidine	$C_{12}H_{19}N_3SO_2$	118–120	99	53.5	53.8	7.1	6.6	15.6	15.4[e]
Cyclohexylamine[a]	1-Cyclohexyl-3-*p*-toluenesulfonylguanidine	$C_{14}H_{21}N_3SO_2$	170	72	57.0	57.1	7.1	6.8	14.2	14.0[f]
Morpholine[a]	4-(N-*p*-Toluenesulfonyl) guanylmorpholine	$C_{12}H_{17}N_3SO_3$	163–164	84	50.9	51.4	6.0	5.8	14.8	15.4[g]
Piperidine[a]	1-(N-*p*-Toluenesulfonyl) guanylpiperidine	$C_{13}H_{19}N_3SO_2$	148	91	55.5	55.8	6.8	6.4	14.9	14.9[h]
Aniline[i,b]	Unidentified[j,k]	$(C_8H_7N_2)_x$	208–210[l]	36[m]	73.3	73.7	5.3	5.2	21.3	20.8
n-Butylamine[i]	1-Benzoyl-3-*n*-butylguanidine + 1-Benzoyl-3-*n*-butylguanidine picrate	$C_{12}H_{17}N_3O$	114	98	65.8	66.4	7.8	7.8	—	—
		$C_{18}H_{20}N_6O_8$	126[n]	–	48.2	48.5	4.5	4.2	18.8	19.3
Cyclohexylamine[i]	1-Benzoyl-3-cyclohexylguanidine + 1-Benzoyl-2,3-dicyclohexylguanidine	$C_{14}H_{19}N_3O$	131–132	63	68.6	69.1	7.8	7.7	17.1	16.7
		$C_{20}H_{29}N_3O$	155–156	15	73.4	73.3	8.9	8.7	12.8	12.2
Piperidine[i]	1-(N-Benzoyl)guanylpiperidine	$C_{13}H_{17}N_3O$	142–143	95	67.5	67.8	7.4	6.9	—	—
Aniline[o,b]	1,3-Diphenylurea	$C_{13}H_{12}N_2O$	236[p]	84	73.6	73.7	5.7	5.6	13.2	12.8
n-Butylamine[o]	1-*n*-Butyl-3-α-naphthylurea	$C_{15}H_{18}N_2O$	146–147	98	74.4	74.3	7.4	7.2	11.6	11.2
Morpholine[o]	1-(N-α-Naphthyl) carbamylmorpholine + 1-Guanylmorpholine[r]	$C_{15}H_{16}N_2O_2$	195[q]	95	70.3	70.4	6.3	6.1	10.9	10.9
		$C_{11}H_{14}N_6O_3$	229–230[s]	*ca.* 4	36.9	37.5	3.9	3.8	23.5	23.9
Piperidine[o]	1-(N-α-Naphthyl) carbamylpiperidine + 1-Guanylpiperidine[r]	$C_{16}H_{18}N_2O$	159[t]	98	75.6	75.3	7.1	6.9	11.0	10.4
		$C_{12}H_{16}N_6O_7$	244[u]	*ca.* 6	40.4	41.0	4.4	4.3	23.6	23.3

[a] These represent reactions with If. [b] General reaction conditions consist of 30 min. refluxing of the substituted 1-acylguanylpyrazole in a nine-fold excess of amine. [c] This was accompanied by some evolution of ammonia. [d] Calcd.: S, 11.1. Found: S, 11.4. [e] Calcd.: S, 11.9. Found: S, 12.1. [f] Calcd.: S, 10.8. Found: S, 10.2. [g] Calcd.: S, 11.3. Found: S, 11.0. [h] Calcd.: S, 11.4. Found: S, 11.5. [i] These represent reactions with Ig. [j] This substance was accompanied by another of m.p. 91–92° in 30% yield. *Anal.* Calcd. for $C_{13}H_6N_2O$: C, 75.7; H, 2.9; N, 13.6. Found: C, 76.0; H, 2.4: N, 13.1. [k] During this reaction a copious evolution of ammonia was detected. [l] The m.p. of 3-benzoyl-1-phenylguanidine has been reported as 199° by F. Arndt and B. Rosenau, *Ber.*, **50**, 1248 (1917). [m] This was calculated on the basis of a molecular formula of $C_{16}H_{14}N_4$. [n] The m.p. of 1-*n*-butylguanidine picrate is 154.5°, as reported by T. L. Davis and R. C. Elderfield, *J. Am. Chem. Soc.*, **54**, 1499 (1932). [o] These correspond to reactions with Ik. [p] Reported m.p. 238°, R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 287. [q] Reported m.p. 197–198°, by R. A. Henry and W. M. Dehn, *J. Am. Chem. Soc.*, **71**, 2297 (1949). [r] The data reported are for the picrate salt. [s] Reported m.p. 230°, Scott, O'Donovan, and Reilly, *loc. cit.* [t] Reported m.p. 160.5–161.5°, Henry and Dehn, *loc. cit.* [u] Reported m.p. 245°, by Davis and Elderfield, *loc. cit.* and as 244°, by Scott, O'Donovan and Reilly, *loc. cit.*

TABLE II

SOME DERIVATIVES OF TYPE R—C(=NH)—NH—C(=X)=N—R′

R	X	R′	Molecular Formula	M.P., °C.	Analyses							
					Carbon		Hydrogen		Nitrogen		Sulfur	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Py[a]	SCH_3	C_6H_5[b]	$C_{14}H_{17}N_5S$	94	58.5	58.4	5.9	5.7	24.4	24.8	11.1	11.5
Py′[c]	SCH_3	C_6H_5	$C_{14}H_{16}N_5SCl$	113–114	52.3	52.3	5.0	4.8	21.8	21.2	—	—
Py″[d]	SCH_3	C_6H_5	$C_{14}H_{16}N_5SBr$	123	45.9	46.4	4.4	4.5	19.1	19.7	8.7	8.4
Py[a]	SH	CH_2=CH—CH_2—	$C_{10}H_{15}N_5S$[e]	83–84	50.6	50.7	6.3	6.5	29.5	29.0	13.5	13.3
Py[a]	SCH_3	CH_2=CH—CH_2—	$C_{11}H_{18}N_5SI$[f]	118	34.8	35.1	4.7	5.1	18.5	18.0	8.4	7.9
Py[a]	SH	n-C_3H_7	$C_{10}H_{17}N_5S$[e]	79–80	50.2	50.4	7.1	7.0	29.3	29.0	13.4	13.2
Py[a]	SCH_3	n-C_3H_7	$C_{11}H_{20}N_5SI$[f]	114.5–115	34.6	34.8	5.2	5.4	18.4	18.5	8.4	8.5[g]
Py[a]	SH	n-C_4H_9	$C_{11}H_{19}N_5S$[e]	78–79	52.2	51.8	7.5	7.3	27.7	28.1	12.6	13.0
Py[a]	SCH_3	n-C_4H_9	$C_{12}H_{22}N_5SI$[f]	119–120	36.5	36.5	5.6	5.4	17.7	17.9	8.1	8.0[h]
Py[a]	SH	1-$C_{10}H_7$	$C_{17}H_{17}N_5S$[e]	130–131	63.2	62.7	5.3	5.1	21.7	21.2	9.9	10.0
Py[a]	SCH_3	1-$C_{10}H_7$	$C_{18}H_{20}N_5SI$[f]	143–145	46.5	46.4	4.3	4.6	15.1	14.9	6.9	6.7[i]

[a] Py represents 3,5-dimethyl-1-pyrazolyl. [b] This is II. It and the other free bases Im and In were prepared from the corresponding hydriodides by first dissolving the salts in ethanol and then adding an excess of cold 20% sodium hydroxide solution to the ice-cold salt solution. The free bases were thus quantitatively precipitated They were appreciably less soluble in ethanol than the corresponding hydriodide salts. They crystallized well and did not exhibit any tendency towards phototropism. [c] Py′ represents 4-chloro-3,5-dimethyl-1-pyrazolyl. [d] Py″ corresponds to 4-bromo-3,5-dimethyl-1-pyrazolyl [e] These thiocarbamylguanylpyrazoles were prepared by the method of Scott and Reilly, *loc. cit.*, *viz.* by warming gently a solution of the appropriately substituted 1-guanylpyrazole free base in ethanol with the respective aryl or alkyl isothiocyanate. The addition products separated in from 80–90% yields [f] The data recorded are for the hydriodide salt of an S-methyl ether This was prepared by the general technique described in the text and was usually isolated in quantitative yield. [g] Calcd.: I, 33.3. Found: I, 33.2, 33.4. [h] Calcd.: I, 32.2. Found: I, 31.8, 32.2. [i] Calcd.: I, 27.3 Found: I, 26.9.

Anal. Calcd. for $C_2H_4N_4$: C, 28.9; H, 4.8; N, 66.0. Found: C, 28.6; H, 4.8; N, 66.5.

(c) When Ir was analogously refluxed with either of the above 2 cyanamides in chloroform it was recovered in 92 and 70% yields, respectively, and formed dicyandiamide in 25% yield in the latter experiment. (d) Finally, when Id was refluxed with either dialkyl cyanamide in ethanolic solution for 6 hr. it was recovered in 70–80% yields.

(3) *With substituted aminoguanidines.* (*a*) When aminoguanidine nitrate was refluxed, without further solvent, in either a small or large excess of dimethyl cyanamide for 3 hr. it was recovered in 90% yield. However, when aminoguanidine, as its free base, was refluxed with an equimolar proportion of diethyl cyanamide for 3 hr., fumes of ammonia were readily detectable from the reaction liquor and a white solid, m.p. 88°, was isolated, total yield 50% (on the basis of a provisional molecular weight of 140). This has not been identified as yet.

Anal. Calcd. for $C_6H_{12}N_4$: C, 51.4; H, 8.6; N, 40.0. Found: C, 51.5; H, 8.3; N, 39.7.

The aminoguanidine free base incidentally was used in the form of its aqueous solution and this was obtained by titration of aminoguanidine sulfate in water with a barium solution. (*b*) When triaminoguanidine nitrate was refluxed with an excess of dimethyl cyanamide in ethanol or without further solvent, for 3-hr. periods, it was recovered in 95 and 92% yields, respectively. (*c*) When *p*-methoxybenzylidene aminoguanidine (Va) was refluxed with dimethyl cyanamide either in ethanol or in chloroform solution for 3 hr. it was recovered in 95 and 92% yields, respectively. However, when Va was refluxed in dimethyl cyanamide, without further solvent and under anhydrous conditions, again for 3 hr., it yielded 30% unchanged Va and *ca.* 17% of a cream-colored substance, m.p. 248–250°, which proved to be *p*-methoxybenzylidene 1-amino-4,4-dimethyl-2-guanylguanidine (Vb).

Anal. Calcd. for $C_{12}H_{18}N_6O$: C, 55.0; H, 6.9; N, 32.1. Found: C, 54.7; H, 7.0; N, 32.2.

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Contributions to the Study of Marine Products. XLIII. The Nucleosides of Sponges. V. The Synthesis of Spongosine[1]

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Spongosine has been synthesized by two different methods and shown to be 9-β-D-ribofuranosyl-2-methoxyadenine.

Spongosine, one of the unusual nucleosides obtainable from the Caribbean sponge, *Cryptotethia crypta*, has recently been shown[2] to be the ribofuranoside of 2-methoxy-6-aminopurine.[3] The present communication deals with two syntheses of spongosine which establish beyond doubt the point and configuration of the junction between the purine and ribose moieties. In the first synthesis 2-methoxyadenine, prepared by a modification of the method previously reported,[2] was converted to its chloromercuri salt[4] which was treated with 2,3,5-tri-*O*-acyl-D-ribosyl chloride. In this reaction the triacetyl derivative[5] afforded a mixture of products difficult to separate. The tribenzoate, however, which has recently been used with conspicuous success by Kissman, Pidacks, and Baker,[6] reacted smoothly to give a product which after *O*-debenzoylation with catalytic amounts of sodium methoxide afforded the glycoside in a 30% yield. The identity of the reaction product with spongosine was shown by a comparison of the melting points, rotations, and the chromatographic, electrophoretic,

(1) This investigation was supported by a research grant (G-3789) from the National Institutes of Health, Public Health Service.

(2) W. Bergmann and D. C. Burke, *J. Org. Chem.*, **21**, 226 (1956).

(3) It was pointed out in the previous publication[2] that spongosine not only appears to be the first methoxypurine to be found in nature, but also one of the first *O*-methyl compounds to be isolated from animal tissues. It should be mentioned in this connection that prior to this observation the occurrence of some phenolic methylethers had been noted in animals, such as methanethol in the sponge, *Spheciospongia vesparia* [W. Bergmann and W. J. McAleer, *J. Am. Chem. Soc.*, **73**, 4969 (1951)], and of quinol monomethylether, chavicol, *p*-methoxyacetophenone, and 5-methoxysalicylic acid in the scent gland of the beaver [E. Lederer, *J. Chem. Soc.*, 2120 (1949)]. Ferulic acid, *m*-methoxybenzoic acid, and vanillic acid have been isolated from the urine of horses [E. Lederer and J. Polonski, *Biochim. et Biophys. Acta*, **2**, 431 (1948)] and men [M. D. Armstrong, K. N. F. Shaw, and P. E. Wall, *J. Biol. Chem.*, **218**, 293 (1956)]. These compounds may well have been derived from methyl ethers in dietary plant material. More recent observations, however, show that *O*-methylations may occur within the animal, *cf.* N. F. MacClagan and J. H. Wilkinson, *Biochem. J.*, **56**, 2111 (1954); J. M. Price and L. W. Dodge, *J. Biol. Chem.*, **223**, 699 (1956); S. Kraychy and T. F. Gallagher, *J. Am. Chem. Soc.*, **79**, 754 (1957); and F. DeEds, A. N. Booth, and F. T. Jones, *J. Biol. Chem.*, **225**, 615 (1957).

(4) J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.*, **73**, 1650 (1951).

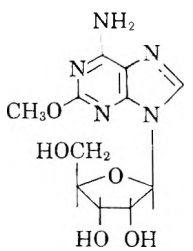
(5) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 967 (1948).

(6) H. M. Kissman, C. Pidacks, and B. R. Baker, *J. Am. Chem. Soc.*, **77**, 18 (1955).

and spectrophotometric behavior of the synthetic and natural material.

While this synthesis strongly indicates that the configuration of the glucosidic link in spongosine is 9-β as in I, it cannot be accepted as the final proof. It is true that in the great majority of the naturally occurring purine nucleosides the carbohydrate moiety is attached to the 9-position of the purine ring and in a β-glycosidic linkage. It is also known that the 2,3,5-tri-*O*-benzoyl-D-ribosyl chloride used in the present synthesis has so far always afforded the β-ribosides under similar conditions.[6] Since none of these methods, however, has previously been applied to *O*-methylpurines, there remained some doubt concerning the validity of such analogies.

The second synthesis was based on the assumption that spongosine is the 2-*O*-methylderivative of crotonoside, a compound of known configuration,[7] and that it might be obtainable from it by selective methylation. Although such methylations are not too well known, some promise of success was indicated by the fact that the silver salt of 2-anilino-6-oxypyrimidine reacts with methyl iodide to give 2-anilino-6-methoxypyrimidine.[8] Treatment of the silver salt of crotonoside with methyl iodide under similar conditions gave a mixture of products which was separated by chromatography on paper into four fractions. Of these, the major product proved to be unreacted crotonoside. One of the other fractions was found to be chromatographically indistinguishable from spongosine in three different solvent systems. Its ultraviolet spectra in both acidic and aqueous solutions were of the same uniqueness as those of spongosine.[2] The occurrence of spongosine among the methylation products of crotonoside therefore furnishes additional evidence that its structure is that of a 9-β-D-ribofuranosyl-2-methoxyadenine (I).



I

EXPERIMENTAL

2-Methoxyadenine.[2] A mixture of 3 g. of 2-chloroadenine, a solution of 6 g. of sodium in 120 ml. of absolute methanol, and an additional 80 ml. of absolute methanol was heated in a stainless steel bomb at 150° for 5 hr. After this time, chromatography of a small amount of the reaction mixture dissolved in water, showed the presence of 2-chloroadenine, adenine, and 2-methoxyadenine. Attempts to separate this mixture by the ion-exchange chromatography recommended by Bergmann and Burke[2] failed because the purine mixture began to crystallize on the resin as the *p*H of the eluent dropped to 9.5. The material was recovered by extracting the mixture of resin and purines with 3 portions of 1 l. each of hot, 10% formic acid. Cooling of the combined extracts afforded a solid, shown chromatographically to consist of 2-chloro and 2-methoxyadenine. When this mixture was dissolved in 300 ml. of aqueous methanol (1:1) only 2-methoxyadenine separated upon cooling to room temperature. The pure product was obtained in a 50% yield.

Spongosine. Chloromercuri-2-methoxyadenine. To a suspension of 1.0 g. of 2-methoxyadenine in 2 ml. of water was added 6.5 ml. of *N* sodium hydroxide, and the solution warmed gently with shaking to dissolve the purine. To this solution, 1.7 g. of mercuric chloride dissolved in 20 ml. of warm ethanol was added. A heavy, white precipitate formed which was collected by filtration. The precipitate was washed with water and dried *in vacuo* at room temperature over sodium hydroxide. *2,3,5-Tri-O-benzoyl-D-ribofuranosyl-chloride.*[6] One-half g. of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose of m.p. 128–129°, prepared according to the directions of Kissman *et al*,[6] was dried *in vacuo* for 5 hr. at 69° and dissolved in a saturated solution (0°) of anhydrous hydrogen chloride in 50 ml. of anhydrous ether. The solution was kept for 4 days at −14° in a flask covered with a polyethylene seal. After this time, the ether and excess hydrogen chloride were removed at reduced pressure, and the residue, a yellowish sirup, dissolved in 20 ml. of anhydrous benzene. The benzene was removed at reduced pressure, and the process repeated twice to insure complete removal of hydrogen chloride. The crude 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride was used without further purification.

The chloromercuric salt of 2-methoxyadenine (0.8 g.) was suspended in 55 ml. of xylene, and about 5 ml. of the solvent was distilled to insure removal of traces of water. To the remaining suspension was added the ribosyl chloride dissolved in a small amount of xylene. The mixture was refluxed with continuous stirring for 4 hr., after which the xylene was removed at reduced pressure and the residue extracted with hot chloroform.

The chloroform extracts were washed twice with 35 ml. portions of 30% potassium iodide solution, twice with water, decolorized with Norit and dried over anhydrous sodium sulfate. The solvent was then removed at reduced pressure, and the residue, a dark brown oil (1.49 g.), dissolved in 50 ml. of anhydrous methanol. One ml. of a *N* solution of sodium methoxide in methanol was added and the mixture refluxed for 30 min. A second 1 ml. of sodium methoxide solution was added, and the reflux continued until the *p*H of the solution was greater than 8, indicative of complete debenzoylation (20 min.). The solution was taken down to dryness *in vacuo*, and the semi-solid residue triturated with ether to remove methylbenzoate. The remaining crude spongosine (0.6 g.) was dissolved in hot water, the solution made slightly basic with sodium hydroxide, and decanted from a brown, oily residue. The extract was then made acidic with hydrochloric acid, and all the liquid was removed by freeze-drying. The residual, brown solid was extracted with chloroform, and the extract evaporated to dryness. The white residue of 50 mg. (31% yield) consisted of spongosine, which was recrystallized from hot water; needles of m.p. 191–191.5°; $[\alpha]_D$ −43.5° (9.2 mg. in 2 ml. of 8% sodium hydroxide); reported[9]: m.p. 192–193°; $[\alpha]_D$ −42.5°. A mixed melting point with authentic spongosine showed no depression. Infrared spectra of both synthetic and natural spongosine in a potassium bromide disk showed the same bands.

Anal. Calcd. for $C_{11}H_{15}N_5O_5$: C, 44.4; H, 5.08; N, 23.56; OCH_3, 10.44. Found: C, 44.5; H, 5.14; N, 23.31; OCH_3, 10.36.

A 2.9 mg. sample of synthetic spongosine was dissolved

(7) J. Davoll, *J. Am. Chem. Soc.*, **73**, 3174 (1951).

(8) T. B. Johnson and F. W. Heyl, *Am. Chem. J.*, **38**, 241 (1907).

(9) W. Bergmann and R. J. Feeney, *J. Org. Chem.*, **16**, 981 (1951).

in 0.1*N* sodium hydroxide solution and made up to 50 ml. with each of the following solutions: 0.1*N* hydrochloric acid, *p*H 7.2 phosphate buffer, and 0.1*N* sodium hydroxide. The ultraviolet spectra and *p*H values of these solutions are shown in Table I.

TABLE I

ULTRAVIOLET SPECTRA OF SYNTHETIC SPONGOSINE

*p*H	1.35	7.2	12.2
Max. (mμ)	251, 275 (252, 275)[10]	268 (268)	268 (268)
Min. (mμ)	257, 228 (258, 229)	232 (233)	233 (232)

Spongosine from Crotonoside. A 50-mg. sample of crystalline crotonoside prepared from croton seed[11] was suspended in 1 ml. of water and 1.8 ml. of 0.1*N* sodium hydroxide solution. The mixture was warmed until the crotonoside had dissolved, and an excess of silver nitrate solution was added with stirring. The precipitate was collected by centrifugation, washed three times with water and twice with methanol, and finally dried *in vacuo* over anhydrous potassium hydroxide. It was then ground to a fine powder and suspended in 5 ml. of absolute methanol; 2 ml. of methyl iodide was added and the mixture stirred at room temperature for 2 hr. The precipitate of silver iodide was separated by centrifugation, and the liquid taken to dryness at reduced pressure. The residue was dissolved in a few drops of hot water and chromatographed on paper in three solvent systems; see Table II.

TABLE II

PAPER CHROMATOGRAPHY OF METHYLATED CROTONOSIDE

Solvent System	BuOH-NH_3-H_2O[12]		BuOH-EtOH-H_2O[13]		BuOH-H_2O[14]	
Solvent front	36.0 cm.	R_F	37.9 cm.	R_F	39.6 cm.	R_F
Spongosine	13.0 cm.	0.36	12.5 cm.	0.33	12.9 cm.	0.33
Crotonoside	0.9 cm.	0.025				
Reaction mixture	0.7 cm.	0.019			0.4 cm.	0.010
	2.4 cm.	0.067	2.2 cm.	0.057	2.3 cm.	0.058
	4.4 cm.	0.122	4.2 cm.	0.111	4.4 cm.	0.111
	13.3 cm.	0.37	12.7 cm.	0.34	13.9 cm.	0.35

TABLE III

ULTRAVIOLET SPECTRA OF METHYLATED CROTONOSIDE (SPONGOSINE)

0.1*N* NaOH	0.1*N* HCl
Max. 267 mμ (268)[10]	Max. 274, 248 mμ (275, 251)[10]
Min. 232 mμ (233)	Min. 257, 228 mμ (257, 228)
280/260 0.645 (0.65)	280/260 1.45 (1.41)
250/260 0.77 (0.85)	250/260 1.02 (1.0)

Two chromatograms were run in the BuOH-NH_3-H_2O solvent system and the spots with R_F values corresponding to spongosine were eluted with 0.1*N* hydrochloric acid and 0.1*N* sodium hydroxide solution. The principal features of the ultraviolet absorption spectra of these solutions are shown in Table III.

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(10) The bracketed figures are those reported for natural spongosine.[2]

(11) E. Cherbuliez and K. Bernhard, *Helv. Chim. Acta*, 15, 464 (1932).

(12) W. S. Macnutt, *Biochem. J.*, 50, 384 (1952).

(13) E. Chargaff, E. Vischer, R. Doniger, R. Green, and F. Misani, *J. Biol. Chem.*, 177, 405 (1949).

(14) 1-Butanol saturated with water at 23°.

[CONTRIBUTION FROM THE WARNER-CHILCOTT LABORATORIES]

Thyroxine Analogs

ROBERT I. MELTZER, DAVID M. LUSTGARTEN, AND ALEX FISCHMAN

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3,5-Diiodo-4-(4′-hydroxyphenoxy)benzoic, 3,5-diiodo-4-(4′-hydroxyphenoxy)phenylacetic, and β-[3,5-diiodo-4-(4′-hydroxyphenoxy)phenyl]propionic acids were prepared by improved procedures.

Reports on the activity of 3,5-diiodo-4-(4′-hydroxy-3′-iodophenoxy)phenyl acetic acid as a thyroxine-like material in rats[1] *in vitro*[2] and clinically[3] resulted in these laboratories in a renewed and enlarged interest in this type of compound. For the preparation of such compounds we required 3,5-diiodo-4-(4′-hydroxyphenoxy)benzoic acid (Va), 3,5-diiodo-4-(4′-hydroxyphenoxy)phenylacetic acid (Vb), and β-[3,5-diiodo-4-(4′-hydroxyphenoxy)phenyl] propionic acid (Vc).

Of these compounds, the benzoic[4] (Va) and phenylacetic[5] (Vb) acid analogs had been previously prepared *via* a comparatively cumbersome proce-

(1) R. Pitt-Rivers, *Lancet*, II, 234 (1953).

(2) O. Thibault and R. Pitt-Rivers, *Lancet*, I, 285 (1955).

(3) J. Lerman and R. Pitt-Rivers, *J. Clin. Endocrinol.*, 15, 653 (1955).

(4) C. R. Harington and G. Barger, *Biochem. J.*, 21, 169 (1927).

(5) C. R. Harington and R. Pitt-Rivers, *Biochem. J.*, 50, 438 (1952).

dure. The β-[3,5-diiodo-4-(4′-hydroxyphenoxy)-phenyl]propionic acid (Vc) had been prepared by Clayton *et al.*[6] by an elegant sequence of reactions which we planned to adopt for the preparation of all three of the required compounds. After we had finished our own laboratory work, a report appeared by Wilkinson[7] recording the preparation of the acetic analog by a series of reactions also based on the work of Clayton. Recent publication of the details[8] indicated, however, that our differences in procedure are worth noting.

Demethylation of the commercially[9] available *p*-methoxyphenylacetic acid, gave *p*-hydroxyphenylacetic acid which was esterified and nitrated. The resulting ethyl 3,5-dinitro-4-hydroxyphenylacetate (Ib) was allowed in turn to react in pyridine with methanesulfonyl chloride and then with *p*-methoxyphenol to yield ethyl 3,5-dinitro-4-(4′-methoxyphenylacetate (IIb). Clayton *et al.*[6] and Wilkinson[8] used p-toluenesulfonyl chloride in place of methanesulfonyl chloride. Their reactions required an elevated temperature for a period of at least an hour. In our hands, the yields were not consistent. We considered that part of the difficulty might result from the reaction of the pyridine with the product under the very conditions used in the preparation. The reaction of pyridine with dinitrophenyl ethers of this type had been reported.[10] We had further noticed the instability of this compound even when left wet with pyridine at room temperature for two days. We therefore changed reagents with the thought that the methanesulfonyl chloride might permit a faster reaction under milder conditions which would spare the resultant ether. The result was an improved yield of a cleaner product in a shorter period of time.

Like Wilkinson[8] we found that the ethyl 3,5-dinitro-4-(4′-methoxyphenoxy)phenylacetate (IIb) required considerable purification to induce crystallization. Instead of resorting to chromatographic procedures, however, we hydrolyzed our crude reaction mixture to yield the corresponding acid, IIc, which crystallized readily. When this product was catalytically reduced to the diamine, IIIb, and then tetrazotized and treated with sodium iodide according to procedures similar to those reported by Clayton for related compounds, there was obtained 3,5-diiodo-4-(4′-methoxyphenoxy)phenylacetic acid (IVb). Demethylation gave the required 3,5-diiodo-4-(4′-hydroxyphenoxy)phenylacetic acid (Vb).

For the preparation of 3,5-diiodo-4-(4′-hydroxyphenoxy)benzoic acid (Va), methyl 3,5-dinitro-4-hydroxybenzoate was etherified to form methyl 3,5-dinitro-4-(4′-methoxyphenoxy)benzoate (IIa). Catalytic reduction to IIIa, followed by tetrazotization and treatment with sodium iodide gave methyl 3,5-diiodo-4-(4′-methoxyphenoxy)benzoate (IVa). Reaction with hydriodic acid cleaved both methyl ether and methyl ester to give the required compound, Va.

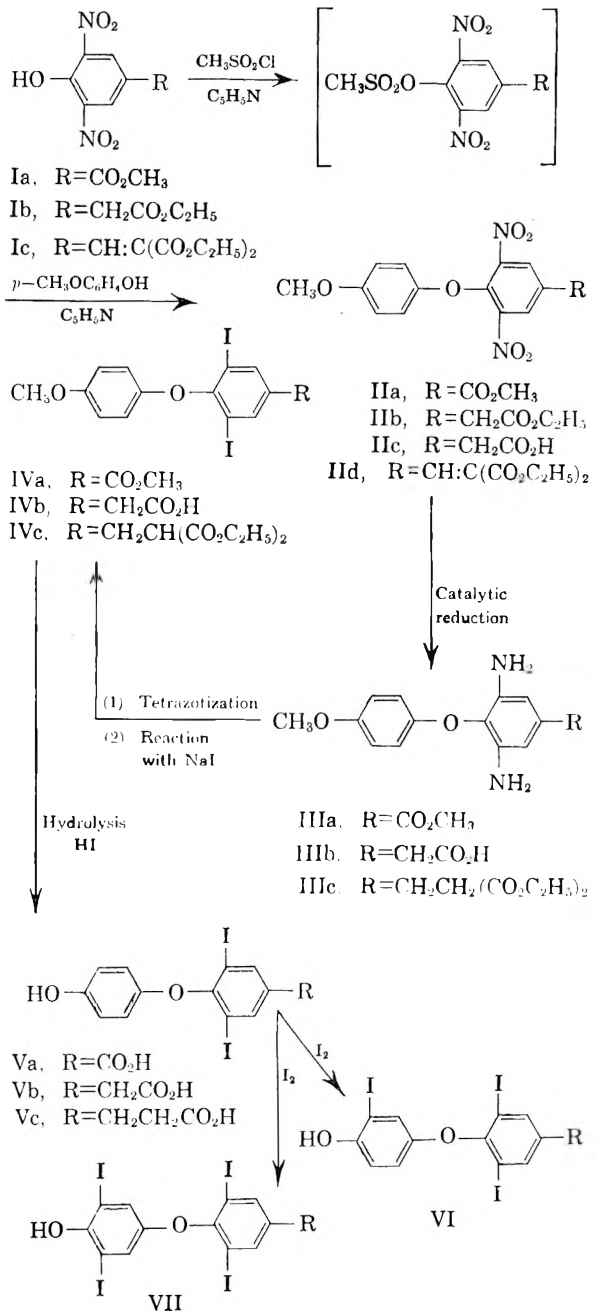
Reduction of methyl 3,5-diiodo-4-(4′-methoxyphenoxy)benzoate (IVa) by excess lithium aluminum hydride in ether was attempted in the expectation of attaining the corresponding benzyl alcohol. The product obtained, however, was iodine-free and analyzed satisfactorily for 4-(4′-methoxyphenoxy)benzyl alcohol. Even at −30°, considerable amounts of iodine were liberated.

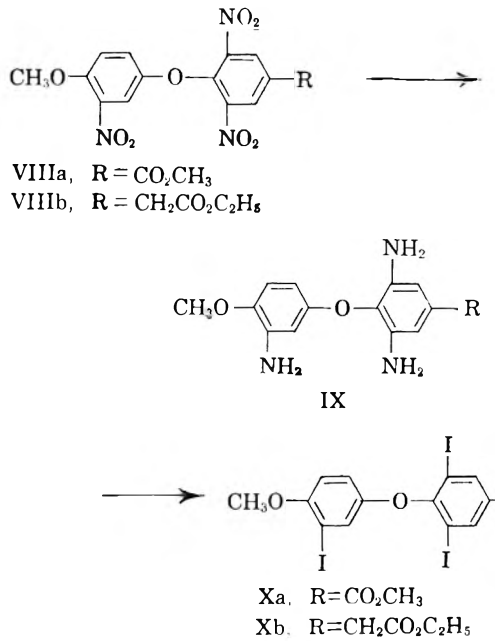
The greater ease of etherification of the methyl 4-hydroxy-3,5-dinitrobenzoate over the ethyl 4-hydroxy-3,5-dinitrophenylacetate, be it with *p*-toluenesulfonyl chloride or with methanesulfonyl chloride, suggested that the carbomethoxy group exerted an activating effect. Further, Barnes *et al.*[10] found that although they could replace the chloro group of methyl 4-chloro-3,5-dinitrobenzoate by *p*-methoxyphenoxyl they could not so replace the chloro group of 4-chloro-3,5-dinitrotoluene. For the preparation of our phenylpropionic acid series we therefore did not use as starting material β-(4-hydroxyphenyl)propionic acid as had previously been used (Clayton *et al.*[6] and subsequently Tomita *et al.*[11]). Rather we chose the more easily attainable diethyl 4-hydroxybenzalmalonate in which the activating effects of the carbethoxy groups might be transmitted to the ring through the ethylene linkage. Etherification of the nitrated product, Ic, occurred almost as rapidly as the reagents were added to one another in the proper sequence. Reduction of the resulting diethyl 3,5-dinitro-4-(4′-methoxyphenoxy)benzalmalonate (IId) gave the diamine, IIIc. Tetrazotization was used to introduce two iodine atoms. Hydrolysis of the methyl ether and the ethyl esters was accompanied by decarboxylation to give the previously described β-[3,5-diiodo-4-(4′-hydroxyphenoxy)phenyl]propionic acid[6] (Vc).

Iodination of the diiodo compounds (V) according to procedures in the literature,[5,6] gave the corresponding triiodo (VI) and tetraiodo (VII) compounds. Because all the triiodo compounds showed some contamination with the tetraiodo compounds, it was thought to prepare the pure materials using 4-methoxy-3-nitrophenol in place of *p*-methoxyphenol. Hexazotization at that point in a series where tetrazotization had been carried out, should then give triiodo compound free of tetraiodo compound. Accordingly, the reactions were carried out in both the benzoic and phenylacetic acid series. In the phenylacetic acid series, pure ethyl 3,5-dinitro-4-(4′-methoxy-3′-nitrophenoxy)phenylacetate (VIIIb) was obtained, but it could not be con-

(6) J. C. Clayton, G. F. H. Green, and B. A. Hems, *J. Chem. Soc.*, 2467 (1951).
(7) J. H. Wilkinson, *Chemistry & Industry*, 1352 (1955).
(8) J. H. Wilkinson, *Biochem. J.*, **63**, 601 (1956).
(9) Kay-Fries Chemicals, Inc., New York, N. Y.
(10) J. H. Barnes, E. T. Borrows, J. Elks, B. A. Hems, and A. G. Long, *J. Chem. Soc.*, 2824 (1950).
(11) K. Tomita and H. A. Lardy, *J. Biol. Chem.*, **219**, 595 (1956).

verted to pure ethyl 3,5-diiodo-4-(3′-iodo-4′-methoxyphenoxy)phenylacetate (Xb). We did not have this difficulty in the benzoic acid series and obtained both methyl 3,5-dinitro-4-(4′-methoxy-3′-nitrophenoxy)benzoate (VIIIa) and methyl 3,5-diiodo-4-(3′-iodo-4′-methoxyphenoxy)benzoate (Xa) in a pure state. Demethylation of the latter material without simultaneously removing some or all of the 3′-iodo group was not feasible. This was true whether we used hydrobromic or hydriodic acids with or without red phosphorus. Gemmill *et al.*[12] subsequently reported a similar experience in attempts to demethylate α-benzamido-3-iodo-4-(3′-iodo-4′-methoxyphenoxy)cinnamic acid.





EXPERIMENTAL[13]

Diethyl p-hydroxybenzalmalonate. A mixture of 160 g. (1 mole) of diethyl malonate, 122 g. (1 mole) of *p*-hydroxybenzaldehyde, 20 ml. of acetic acid, 6 ml. of piperidine, and 250 ml. of dry benzene was stirred at reflux under a water separator until no further collection of water occurred. The reaction mixture was cooled and filtered. The precipitate was washed with cold benzene. The product, which was suitable for nitration, weighed 170 g. (65%) and melted at 89–91°. After recrystallization from benzene the product melted at 91–93° (reported[14] 93°).

Ethyl p-hydroxyphenylacetate. A mixture of 200 g. (1.2 moles) of 4-methoxyphenylacetic acid, 10 g. of red phosphorus, 1 l. of acetic acid and 500 ml. of 57% (d 1.7) hydriodic acid was maintained at reflux for 1.5 hr. The filtered reaction mixture was concentrated to dryness and the residue was esterified with ethanol in the presence of hydrogen chloride.[15] The product, 136 g., (63%) distilled at 155–157° (1.5 mm.) and had n_D^{25} 1.5213.

Diethyl 3,5-dinitro-4-hydroxybenzalmalonate (Ic). To 2 l. of concentrated sulfuric acid at −10° to −5°, there was added portionwise with stirring 100 g. (0.38 mole) of powdered diethyl *p*-hydroxybenzalmalonate. After 10 min. the stirred mixture was cooled to −15° and 125 ml. of concentrated nitric acid was added dropwise. Stirring was continued while the temperature of the mixture was allowed to rise to 2–5° at which point the mixture was poured onto ice and filtered. The precipitate was washed with water and with petroleum ether (b.p. 60–71°). Recrystallization from acetonitrile gave 98 g. (73%) of product, m.p. 142–144°.

Anal. Calcd. for $C_{14}H_{14}N_2O_9$: C, 47.46; H, 3.98. Found: C, 47.06; H, 4.11.

Ethyl 3,5-dinitro-4-hydroxyphenylacetate (Ib). The nitration was carried out in a manner similar to that used for the preparation of Ic. The crude product was purified by solution in cold benzene, by filtration, and by precipitation by the addition of petroleum ether (b.p. 60–71°). When this was done the product in 82% yield melted at 72° (reported 71°).

Anal. Calcd. for $C_{10}H_{10}N_2O_7$: C, 44.45; H, 3.73. Found: C, 44.23; H, 3.84.

(12) C. L. Gemmill, J. J. Anderson, and A. Burger, *J. Am. Chem. Soc.*, **78**, 2434 (1956).

(13) Temperatures are not corrected. Melting points were taken on a Fisher-Johns melting point block.

(14) A. Chrzaszczewska, *Roczniki Chem.*, **5**, 72; *Chem. Zentr.*, **II**, 2905 (1926).

(15) H. Salkowski, *Ber.*, **22**, 2137 (1889).

Diethyl 3,5-dinitro-4-(4'-methoxyphenoxy)benzalmalonate (IId). To a solution of 35.4 g. (100 mmoles) of diethyl 3,5-dinitro-4-hydroxybenzalmalonate in 90 ml. of dry pyridine at about 80° was added dropwise with stirring 15.2 ml. (22.8 g.; 200 mmoles) of methanesulfonyl chloride. Gentle cooling was required during the addition. There was then added 43.5 g. (350 mmoles) of *p*-methoxyphenol. Stirring was continued for 10 min. before the reaction was poured into 1.5 l. of cold water. The resulting solid was taken up in benzene and washed well with 4*N* hydrochloric acid and then with water. The benzene solution was concentrated to dryness and the residue was recrystallized from 95% ethanol to give 42 g. (90%) of product, m.p. 115.5–116.5°.

Anal. Calcd. for $C_{21}H_{20}N_2O_{10}$: C, 54.78; H, 4.38; N, 6.09. Found: C, 55.03; H, 4.15; N, 6.10.

3,5-Dinitro-4-(4'-methoxyphenoxy)phenylacetic acid (IIc). To 2.3 g. (8.5 mmoles) of ethyl 3,5-dinitro-4-hydroxyphenylacetate dissolved in 12 ml. of dry pyridine, was added 0.75 ml. (1.1 g., 9.6 mmoles) of methanesulfonyl chloride. The mixture was heated to reflux and maintained at reflux for 2 min. There was then added 3.1 g. (25 mmoles) of 4-methoxyphenol and the reaction mixture was maintained at reflux for an additional 5 min. At the end of this time the reaction mixture was poured into water. This aqueous mixture was extracted with benzene. The benzene was washed with 4*N* hydrochloric acid and then with water. The benzene solution was dried over magnesium sulfate and the solvent was removed by evaporation. The residue was dissolved in 75 ml. of glacial acetic acid and 35 ml. of 6*N* hydrochloric acid and heated at reflux for 40 min. The reaction mixture was then evaporated to dryness. The residue from this hydrolysis was taken up in 20 ml. of cold 5% sodium hydroxide solution. The solution was filtered and the filtrate was acidified to precipitate the product. This product after recrystallization from aqueous acetic acid, melted at 187–189° and weighed 2.1 g. (73%).

Anal. Calcd. for $C_{16}H_{12}N_2O_8$: C, 51.72; H, 3.47; N, 8.05. Found: C, 51.55; H, 3.75; N, 7.81.

Ethyl 3,5-dinitro-4-(4'-methoxy-3'-nitrophenoxy)phenylacetate (VIIIb). This was prepared similarly to the manner in which the analogous dinitro compound was prepared. 3-Nitro-4-methoxyphenol was used in place of *p*-methoxyphenol and the period of reflux after the addition of the phenol was increased to 10 min. Extraction of the decomposed reaction mixture with chloroform gave, after washing, a chloroform residue which crystallized on heating with 50% methanol. Recrystallization from *n*-propanol gave 60% yield of product m.p. 149.5–150.5°. The free acid melted at 172.5–173°.

Anal. Calcd. for $C_{17}H_{15}O_{10}N_3$: C, 48.46; H, 3.59; N, 9.97. Found: C, 48.73; H, 3.52; N, 9.93.

Methyl 3,5-dinitro-4-(4'-methoxyphenoxy)benzoate (IIa). Etherification of methyl 3,5-dinitro-4-hydroxybenzoate[16] (Ia) in a manner similar to that used in the preparation of diethyl 3,5-dinitro-4-(4'-methoxyphenoxy)benzalmalonate, gave similar or higher yields of product, IIa. Recrystallization from alcohol resulted in a product m.p. 131–132° (reported[17] 129°).

Methyl 3,5-dinitro-4-(4'-methoxy-3'-nitrophenoxy)benzoate (VIIIa). This preparation was similar to the preparation of methyl 3,5-dinitro-4-(4'-methoxyphenoxy)benzoate except that 3-nitro-4-methoxyphenol was used in place of *p*-methoxyphenol. The product, obtained in 82% yield, melted at 175–178° after recrystallization from aqueous acetic acid.

Anal. Calcd. for $C_{15}H_{11}O_{10}N_3$: C, 45.81: H, 2.82. Found: C, 45.23; H, 2.79.

Diethyl 3,5-diamino-4-(4'-methoxyphenoxy)benzylmalonate (IIIc). Reduction of 18.4 g. (40 mmoles) of diethyl 3,5-dinitro-4-(4'-methoxyphenoxy)benzalmalonate in 150 ml. of acetic acid in the presence of 1 g. of 10% palladium-on-charcoal in a Parr shaker required about 1 hr. for reduction of both nitro groups and the double bond. Concentration of the filtered acetic acid solution left an oily residue which crystallized from absolute ethanol solution to give 12 g. (75%) of product which melted at 71.5–72.5°.

Anal. Calcd. for $C_{21}H_{26}N_2O_6$: C, 62.67; H, 6.51. Found: C, 62.75; H, 6.43.

It is not essential that this product be isolated. The over-all yield may be substantially increased by carrying out the tetrazotization on the filtered reaction mixture.

3,5-Diamino-4-(4'-methoxyphenoxy)phenylacetic acid (IIIb). The reduction was similar to that used for the preparation of the analogous benzylmalonate, IIIc. The product, obtained in 63% yield on recrystallization from acetic acid, melted at 177.5–178°.

Anal. Calcd. for $C_{15}H_{13}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.22; H, 5.53; N, 9.46.

Methyl 3,5-diamino-4-(4'-methoxyphenoxy)benzoate (IIIa). The reduction was similar to that used for the preparation of the analogous benzylmalonate, IIIc. The product, recrystallized from aqueous acetone, melted at 171–173° (reported[17] 166°).

Methyl 3,5-diamino-4-(3'-amino-4'-methoxyphenoxy)benzoate (IX, R = CO_2CH_3). The preparation was similar to that of the analogous diamino compound, IIIa. Recrystallization from acetonitrile gave 57% yield of product m.p. 185–6°.

Anal. Calcd. for $C_{16}H_{17}N_3O_4$: C, 59.39; H, 5.65. Found: C, 59.03; H, 5.01.

Diethyl 3,5-diiodo-4-(4'-methoxyphenoxy)benzylmalonate (IVc). To a solution of 11.2 g. (28 mmoles) of diethyl 3,5-diamino-4-(4'-methoxyphenoxy)benzylmalonate in 23 ml. of acetic acid, was added with cooling 17.5 ml. of sulfuric acid. The resulting solution was immediately added at −10° to a solution of 5.1 g. (74 mmoles) of powdered sodium nitrite in 38 ml. of cold sulfuric acid and 75 ml. of acetic acid while being kept cold. The reaction mixture was stirred in an ice bath for 1 hr. and then rapidly added to a stirred mixture of 30 g. (200 mmoles) of sodium iodide, 21 g. (83 mmoles) of iodine, 3.2 g. (53 mmoles) of urea, 400 ml. of water, and 230 ml. of chloroform at room temperature. The resultant mixture was stirred at room temperature for 1 hr. and then warmed to 40°. The layers were separated and the aqueous layer was further extracted with chloroform. The combined chloroform layers were washed twice with water, with aqueous sodium metabisulfite, and finally again with water. The chloroform solution was dried over magnesium sulfate; the solvent was evaporated; and the residue was recrystallized from absolute ethanol to give 11 g. (63%) of product which melted at 88.5–89.5°.

Anal. Calcd. for $C_{21}H_{22}I_2O_6$: C, 40.40; H, 3.55. Found: C, 40.18; H, 3.69.

3,5-Diiodo-4-(4'-methoxyphenoxy)phenylacetic acid (IVb). The preparation was similar to that of diethyl 3,5-diiodo-4-(4'-methoxyphenoxy)benzylmalonate (IVc). The yield, starting with isolated amine, was 70% of product melting at 163–165°. Wilkinson[8] found 161–162°.

Methyl 3,5-diiodo-4-(4'-methoxyphenoxy)benzoate (IVa), was similarly prepared from pure amine in 45% yield, m.p. 152.5–154° (reported[17] 153–154°).

β-[3,5-Diiodo-4-(4'-hydroxyphenoxy)phenyl]propionic acid (Vc). A solution of 11.2 g. (18 mmoles) of diethyl 3,5-diiodo-4-(4'-methoxyphenoxy)benzylmalonate in 100 ml. of 57% hydriodic acid and 200 ml. of acetic acid was maintained at reflux for 2 hr., during which time there was a vigorous evolution of methyl iodide and carbon dioxide. The reaction mixture was concentrated to about 125 ml. and then cooled. The product which crystallized weighed 6.9 g. (75% yield) and melted at 247–249° on a block or at 238–238.5° in a capillary (reported[6] melting point, 250°).

3,5-Diiodo-4-(4'-hydroxyphenoxy)phenylacetic acid (Vb). The procedure for the preparation from IVb was similar

(16) F. Reverdin, *Bull. soc. chim. France*, [4] **3**, 592 (1908).

(17) E. T. Borrows, J. C. Clayton, and B. A. Hems, *J. Chem. Soc.*, S185 (1949).

to that for the preparation of the analogous propionic acid from IVc. Recrystallization from aqueous acetic acid gave 90% of product m.p. 218–219.5°. Further recrystallization could raise the melting point to 223.5–225° (reported[8] 219°).

3,5-Diiodo-4-(4'-hydroxyphenoxy)benzoic acid (Va). The procedure for the preparation from IVa was similar to that for the preparation of the analogous propionic acid from IVc. The product, in 80% yield, melted at 264.5–265.5° (reported[6] 260°).

Methyl 3,5-diiodo-4-(3'-iodo-4'-methoxyphenoxy)benzoate (Xa). To nitrosyl sulfate prepared from 7.8 g. (113 mmoles) sodium nitrate and 120 ml. of sulfuric acid, was added at −10° to 0° a solution of 2.7 g. (9 mmoles) of methyl 3,5-diamino-4-(3'-amino-4'-methoxyphenoxy)benzoate in 60 ml. of acetic acid. After stirring the reaction mixture in an ice bath for 0.5 hr., 45 ml. of phosphoric acid was added and stirring was continued for an additional 0.5 hr. in an ice bath. Replacement of the diazonium groups by iodine was carried out as in the preparation of IVc. The product weighed 1.9 g. (10%) and melted at 180–181°. Repeated recrystallization from acetonitrile raised the melting point to 192–193°.

Anal. Calcd. for $C_{15}H_{11}O_4I_3$: C, 28.33; H, 1.74; I, 59.87. Found: C, 28.99, 28.73; H, 1.79, 1.69; I, 59.84, 59.61.

4-(4'-Methoxyphenoxy)benzyl alcohol. In a Soxhlet Thimble was placed 5 g. of methyl 3,5-diiodo-4-(4'-methoxyphenoxy)-benzoate. This material was extracted by refluxing ether into a solution of 1.5 g. of lithium aluminum hydride in 200 ml. of dry ether. When practically all of the ester had been extracted into the reaction mixture, 120 ml. of 10% sulfuric acid was added. The separated aqueous layer was washed with ether and the combined ether solutions were washed with water and dried over magnesium sulfate. Evaporation of the ether gave a solid melting at about 93°. Recrystallization of the ether from aqueous ethanol raised the melting point to 100–100.5°. Analysis was in agreement for 4-(4'-methoxyphenoxy)benzyl alcohol.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.55; H, 6.02.

MORRIS PLAINS, N. J.

[CONTRIBUTION FROM THE L. G. RYAN RESEARCH LABORATORIES OF MONSANTO CANADA LIMITED]

Nitration of 1-Substituted-2-iminoimidazolidines

A. F. McKAY AND M.-E. KRELING

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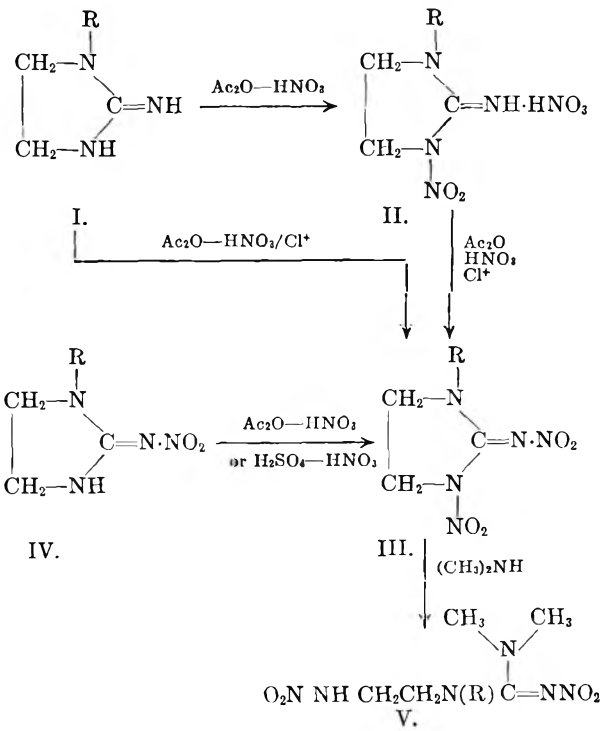
Nitration of 1-substituted-2-iminoimidazolidines in acetic anhydride–nitric acid medium in the absence of chlorine gives 1-substituted-2-imino-3-nitroimidazolidine nitrates. The same nitration medium containing chloride ion converts both 1-substituted-2-iminoimidazolidines and 1-substituted-2-imino-3-nitroimidazolidine nitrates into the corresponding 1-substituted-2-nitrimino-3-nitroimidazolidines. Thus electropositive chlorine catalyzes the nitration of an imino group to a nitrimino group in this series of compounds. 1-Methyl-2-nitrimino-3-nitroimidazolidine adds dimethylamine to give *N*-(β-nitraminoethyl)-*N*-methyl-*N'*,*N'*-dimethyl-*N''*-nitroguanidine, which is a tetrasubstituted nitroguanidine derivative.

Recently[1] it was found that 1-(β-hydroxyethyl)-2-iminoimidazolidine hydrochloride (I, HCl, R = $HOCH_2CH_2$) could be nitrated in acetic anhydride-nitric acid medium to 1-(β-nitroxyethyl)-2-nitrimino-3-nitroimidazolidine (III, R = $NO_3CH_2CH_2$). A further study of this reaction showed that nitration of the imino group in 1-substituted-2-iminoimidazolidines (I) is catalyzed by chlorine. The catalysis of amine nitration by electropositive chlorine and the mechanism of this reaction have been described fully by Wright.[2] The same mechanism will explain the results obtained in the nitration of the 1-substituted-2-iminoimidazolidines.

1-(β-Hydroxyethyl)- and 1-methyl-2-iminoimidazolidines (I, R = CH_3) as their free bases or their nitrate salts are converted respectively into 1-(β-nitroxyethyl)-2-imino-3-nitroimidazolidine nitrate (II, R = $NO_3CH_2CH_2$—) and 1-methyl-2-imino-3-nitroimidazolidine nitrate (II, R = CH_3) on nitration in acetic anhydride-nitric acid medium in the absence of chloride ion. If these nitrate salts are nitrated further in acetic anhydride-nitric acid solution containing ammonium chloride, they are converted into 1-(β-nitroxyethyl)-2-nitrimino-3-nitroimidazolidine (III, R = $NO_3CH_2CH_2$—) and 1-



(1) A. F. McKay, G. Y. Paris, and M.-E. Kreling, *J. Am. Chem. Soc.*, 79, 5276 (1957).

(2) H. Gilman, *Organic Chemistry*, John Wiley and Sons Inc., New York, 1953, Vol. IV, p. 988.

methyl-2-nitrimino-3-nitroimidazolidine (III, R = CH_3) respectively.

1-Methyl-2-imino-3-nitroimidazolidine nitrate (II, R = CH_3) on treatment with concentrated sulfuric acid or mixed acid gave only 1-methyl-2-imino-3-nitroimidazolidine hydrogen sulfate. There was no indication of the formation of 1-methyl-2-nitrimino-3-nitroimidazolidine (III, R = CH_3). On the other hand it was previously[3] shown that 1-methyl-2-nitriminoimidazolidine (IV, R = CH_3) could be converted into 1-methyl-2-nitrimino-3-nitroimidazolidine (III, R = CH_3) by nitration with either mixed acid or acetic anhydride-nitric acid in the absence of chloride ion. 1-(β-Hydroxyethyl)-2-nitriminoimidazolidine behaves in the same way as the methyl derivative (IV, R = CH_3).

The yields of 1-methyl-2-nitrimino-3-nitroimidazolidine (III, R = CH_3) from 1-methyl-2-imino-3-nitroimidazolidine nitrate (II, R = CH_3) on treatment with acetic anhydride-nitric acid at 32° in the absence of chloride ion for twenty-five minutes and two hours were 0 and 18% respectively. In the presence of chloride ion after nitration periods at 32° of twenty-five minutes, one hour, and two hours, the yields were respectively 23, 45, and 56%. These results clearly show the catalytic effect of addition of chloride ion on the nitration of the imino group in 1-substituted-2-imino-3-nitroimidazolidines.

It has been demonstrated[4] that 1-nitro-2-nitriminoimidazolidines add amines to give substituted nitroguanidines. This reaction also occurs with 1-methyl-2-nitrimino-3-nitroimidazolidine. Dimethylamine combined with this compound (III, R = CH_3) to give the tetrasubstituted nitroguanidine derivative, N-(β-nitraminoethyl)-N-methyl-N′,N′-dimethyl-N″-nitroguanidine (V, R = CH_3). This tetrasubstituted nitroguanidine gives an ultraviolet absorption maximum at 265 mμ with a ϵ_m of 12,400. This absorption maximum is unexpected for a tetrasubstituted nitroguanidine on the basis of previous observations[5] and it will be discussed more fully in a forthcoming publication. The infrared absorption spectrum possessed an N—H stretching band at 3180 cm.$^{-1}$ There were no bands in the unsaturated region before 1586 cm.$^{-1}$ The band at 1586 cm.$^{-1}$ is present in the absorption spectra of propylenedinitramine and it is considered to be associated with the nitro group. Another band occurs at 1520 cm.$^{-1}$

1-Methyl-2-iminoimidazolidine, which was used in the above described nitration studies, was prepared in good yield by the ammonolysis of 1-methyl-2-methylmercapto-2-imidazolinium iodide.

(3) A. F. McKay, J. R. G. Bryce, and D. E. Rivington, *Can. J. Chem.*, 29, 382 (1951).

(4) A. F. McKay and W. G. Hatton, *J. Am. Chem. Soc.*, **75**, 963 (1953); A. F. McKay, W. G. Hatton, and W. G. Taylor, *J. Am. Chem. Soc.*, **75**, 1120 (1953); and A. F. McKay, *J. Am. Chem. Soc.*, **77**, 1057 (1955).

(5) A. F. McKay, J. P. Picard, and P. E. Brunet, *Can. J. Chem.*, 29, 746 (1951).

EXPERIMENTAL[6]

1-Methyl-2-imidazolidinethione. A vigorously stirred solution of *N*-methylethylenediamine (65.8 g., 0.89 mole) in absolute ethanol (125 cc.) was cooled to 5° and a solution of carbon disulfide (67.6 g., 0.89 mole) in absolute ethanol (80 cc.) was added dropwise over a period of 30 min. The stirring was continued for 15 min. after which the crystalline precipitate (m.p. 129–132° with dec.) of the inner salt of β-methylaminoethyldithiocarbamate was recovered by filtration, yield 122.5 g. (92%).

A portion (110 g.) of the inner salt was placed in a wide-mouth Erlenmeyer flask and heated in an oil bath at 135–140° for 0.5 hr. The crude product (m.p. 130–132°) was obtained in 80% yield (68.1 g.). Crystallization from ethanol raised the melting point to 131.5–132°.

Anal. Calcd. for $C_4H_8N_2S$: C, 41.34; H, 6.94; N, 24.13; S, 27.60. Found: C, 41.39; H, 6.90; N, 24.40; S, 27.41.

1-Methyl-2-methylmercapto-2-imidazolinium iodide. Methyl iodide (67.4 g., 0.47 mole) was added dropwise over a period of 15 min. to a boiling suspension of 1-methyl-2-imidazolidinethione (55.2 g., 0.47 mole) in absolute methanol (150 cc.) and the refluxing was continued for 30 min. After the solution had cooled, ether (150 cc.) was added and the solution was cooled further in freezing mixture. A crystalline product (m.p. 97–98°) was obtained in 91% (111.3 g.) yield. This melting point was not increased by recrystallization.

Anal. Calcd. for $C_5H_{11}IN_2S$: C, 23.26; H, 4.29; I, 49.17; N, 10.86; S, 12.42. Found: C, 23.79; H, 4.49; I, 48.77; N, 10.89; S, 12.27.

A picrate formed in the usual manner from absolute ethanol melted at 119–119.5°, yield 59%.

Anal. Calcd. for $C_{11}H_{13}N_5O_7S$: C, 36.76; H, 3.65; N, 19.50; S, 8.92. Found: C, 36.64; H, 3.79; N, 19.84; S, 8.68.

1-Methyl-2-iminoimidazolidine. 1-Methyl-2-methylmercapto-2-imidazolinium iodide (30 g., 0.16 mole) in concentrated aqueous ammonia solution (36.5 cc.) was refluxed in a fume hood for 3 hr. After the solution cooled to room temperature, it was diluted to a volume of 530 cc. with methanol. This methanolic solution was passed through a column of IRA-400 resin (400 cc. of resin in the hydroxyl form) at a rate of 20 cc. per minute. The column was washed with methanol (750 cc.) and the combined eluate and washings were taken to dryness *in vacuo* under nitrogen. The free base, 1-methyl-2-iminoimidazolidine, was obtained as an oil in quantitative yield. The oil solidified after standing several days in a vacuum desiccator. Attempts to purify the free base by crystallization gave mixtures of the free base and its carbonate.

The picrate (m.p. 194.5–195°) was prepared in 88% yield in the usual manner from alcohol. The melting point reported[7] in the literature is 194–195°.

Anal. Calcd. for $C_{10}H_{12}N_6O_7$: C, 36.58; H, 3.69; N, 25.60. Found: C, 36.54; H, 3.84; N, 25.67.

1-(β-Nitroxyethyl)-2-imino-3-nitroimidazolidine nitrate. A sample of 1-(β-hydroxyethyl)-2-iminoimidazolidine hydrochloride[1] (15.3 g., 0.092 mole) was dissolved in water (300 cc.) and the solution was passed through a column of IRA-400 resin (300 cc. of resin in the hydroxyl form) at a rate of 18 cc. per minute. The column was washed with water (500 cc.) and the combined eluate and washings were evaporated to dryness *in vacuo* under nitrogen. A pale yellow oil was obtained in 95% yield, which crystallized partially after standing a few days in a desiccator.

The free base (1.11 g., 0.0086 mole) was dissolved in water

(6) All melting points are uncorrected. Microanalyses by Micro-Tech Laboratories, Skokie, Ill.

(7) H. Schotte, H. Priewe, and H. Roeschesen, *Z. physiol. Chem.*, **174**, 119 (1928).

(1.5 cc.) and the solution was acidified with concentrated nitric acid. Removal of the solvent *in vacuo* gave a yellow oil which crystallized from ethanol-ether (1:2 solution). The crystals (m.p. 64–73°) were dried and used for nitration, yield 1.57 g. (95%).

The dry 1-(β-hydroxyethyl)-2-iminoimidazolidine nitrate (0.96 g., 0.005 mole) was added to a nitration solution of absolute nitric acid (0.05 mole) in acetic anhydride (0.05 mole) at 0° over a period of 10 min. This solution was allowed to warm up to 32° and the stirring was continued for a further 30 min. The resulting solution was poured into cold ether (50 cc.) and the precipitated crystals (m.p. 126–133° with dec.) were removed by filtration, yield 1.23 g. (87%). Crystallization from absolute methanol raised the melting point to a constant value of 146–147° with dec.

Anal. Calcd. for $C_5H_{10}N_6O_8$: C, 21.28; H, 3.57; N, 29.78. Found: C, 21.09; H, 3.69; N, 29.47.

Its picrate (m.p. 135.5–136.5° with dec.) was prepared in 85% yield in the usual manner from water.

Anal. Calcd. for $C_{11}H_{12}N_8O_{12}$: C, 29.47; H, 2.70; N, 24.99. Found: C, 29.73; H, 3.02; N, 24.92.

The crystals melting at 146–147° gave a positive test with Nitron for the nitrate ion.[8]

Nitration of 1-(β-nitroxyethyl)-2-imino-3-nitroimidazolidine nitrate in the presence of chloride ion. 1-(β-Nitroxyethyl)-2-imino-3-nitroimidazolidine nitrate (0.56 g., 0.002 mole) was added to nitrating medium consisting of absolute nitric acid (0.02 mole), acetic anhydride (0.02 mole) and ammonium chloride (0.26 g., 0.005 mole) at 0°. The temperature was raised to 32° and held at this level for 30 min. The reaction mixture was poured onto ice (5 g.) and the crystalline precipitate (m.p. 112–114° with dec.) was recovered by filtration and dried, yield 0.362 g. (69%). One crystallization from absolute methanol raised the melting point to 114–115.5° with dec. These crystals on admixture with an authentic sample of 1-(β-nitroxyethyl)-2-nitrimino-3-nitroimidazolidine[3] (m.p. 116° with dec.) gave no melting point depression.

1-Methyl-2-imino-3-nitroimidazolidine nitrate. A nitration medium of absolute nitric acid (1.16 moles) in acetic anhydride (1.16 moles) was prepared at 0°. A solution of 1-methyl-2-iminoimidazolidine (11.5 g., 0.116 mole) in glacial acetic acid (45 cc.) was added dropwise to this nitrating solution at 0° over a period of 40 min. The temperature of the stirred solution was raised to 32° and held at this level for 25 min. This solution was poured into cold absolute ether (300 cc.) and the crystals (m.p. 139–143° with dec.) were removed by filtration and washed with ether, yield 17.7 g. (71%). One crystallization from absolute ethanol gave colorless crystals melting at 144.5–145° with dec.

Anal. Calcd. for $C_4H_9N_5O_5$: C, 23.19; H, 4.38; N, 33.81. Found: C, 23.32; H, 4.30; N, 34.17.

A picrate (m.p. 164.5–165° with dec.) was prepared in 77% yield in the usual way from water.

Anal. Calcd. for $C_{10}H_{11}N_7O_9$: C, 32.18; H, 2.97; N, 26.27. Found: C, 32.19; H, 3.00; N, 26.43.

The crystals melting at 144.5–145° gave a positive test for the nitrate ion with Nitron.[8]

Nitrations of 1-methyl-2-imino-3-nitroimidazolidine nitrate. Method A. A nitrating medium of absolute nitric acid (0.1 mole) and acetic anhydride (0.1 mole) was prepared as described above and ammonium chloride (1.34 g., 0.025 mole) was added. After 1-methyl-2-imino-3-nitroimidazolidine nitrate (2.07 g., 0.01 mole) was added at 0° over a period of 5 min., the temperature was raised to 32° and maintained at this level for 25 min. The reaction mixture was poured onto ice (15 g.) and the precipitate was recovered and washed with water, yield 0.428 g. (23%). The melting point (168° with dec.) of these crystals was not depressed on admixture with an authentic sample of 1-methyl-2-nitrimino-3-nitroimidazolidine[3] (m.p. 169–170° with dec.).

Similar nitrations were carried out in which the time of reaction at 32° was increased to 1 hr. and to 2 hr. and one reaction was completed using double the quantity of ammonium chloride and a reaction time of 2 hr. at 32°. The yields were respectively 45%, 56%, and 58%.

When 1-methyl-2-imino-3-nitroimidazolidine nitrate was nitrated under the conditions above with 2 hr. reaction time at 32° and in the absence of ammonium chloride, an 18% yield of 1-methyl-2-nitrimino-3-nitroimidazolidine was obtained. If the reaction time at 32° was decreased to 25 min. in the absence of chloride ion, then none of the nitrimino compound was obtained.

Method B. 1-Methyl-2-imino-3-nitroimidazolidine nitrate (5.8 g., 0.028 mole) was added to concentrated sulfuric acid (17 cc.) at −5° over a period of 20 min. The sulfuric acid solution was stirred for a further 20 min. after which it was poured into cold ether (130 cc.). The crystalline product (m.p. 162–169° with dec.) was recovered and washed with ether, yield 4.85 g. (71%). One crystallization from methanol-ether (1:2) solution raised the melting point of the 1-methyl-2-imino-3-nitroimidazolidine hydrogen sulfate to 186.5–187° with dec. The same compound was obtained from the mixed acid nitration of 1-methyl-2-imino-3-nitroimidazolidine nitrate.

Anal. Calcd. for $C_4H_{10}N_4O_6S$: C, 19.83; H, 4.16; N, 23.13; S, 13.24. Found: C, 19.86; H, 4.46; N, 22.86; S, 12.85.

The picrate melted at 164° with dec. and it did not depress the melting point of 1-methyl-2-imino-3-nitroimidazolidine picrate (m.p. 165°) described above.

The reaction of dimethylamine with 1-methyl-2-nitrimino-3-nitroimidazolidine. 1-Methyl-2-nitrimino-3-nitroimidazolidine (0.378 g., 0.002 mole) in aqueous dimethylamine solution (2 cc. of 40% solution) was allowed to stand at room temperature for 36 hr. After the aqueous solution was allowed to evaporate at room temperature over a period of 3 days, the remaining yellow oil was dissolved in water (1 cc.) and acidified to a pH of 4 with dilute hydrochloric acid solution. A crystalline product separated immediately, yield 0.173 g. (37%). The melting point was raised from 149–150° with dec. to 151.5–152° with dec. by two crystallizations from methanol-ether (1:1) solution.

Anal. Calcd. for $C_5H_{14}N_6O_4$: C, 30.77; H, 6.02; N, 35.88. Found: C, 30.59; H, 5.94; N, 36.05.

The crystals gave a pale green color, which faded rapidly in the Franchimont[9] test using dimethylaniline.

Acknowledgment. The ultraviolet and infrared absorption spectra were determined by Dr. C. Sandorfy of the University of Montreal, Montreal, Quebec.

VILLE LASALLE
QUEBEC, CANADA

(8) J. E. Heck, H. Hunt, and M. G. Mellon, *Analyst*, 59, 18 (1934).

(9) A. P. N. Franchimont, *Rec. trav. chim.*, 16, 213 (1897).

[Contribution from the Organic Chemistry Department, Indian Institute of Science]

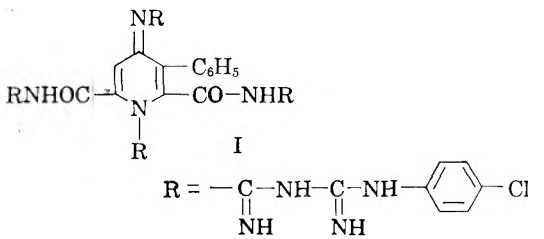
Biguanide Derivatives of γ-Pyridones

L. NEELAKANTAN

Received March 25, 1957

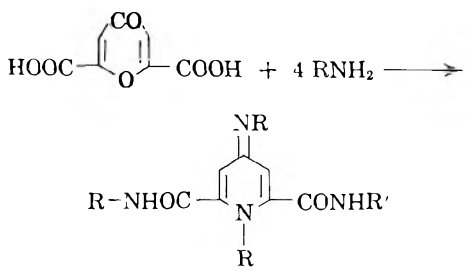
In a search for compounds with antimalarial activity, chelidonic acid, γ-pyrone, and 2,6-diphenyl-γ-pyrone were allowed to react with various aryl biguanides. The synthesis and properties of twenty-three new compounds are given.

Examination of some 3-phenyl chelidamic acids and related compounds showed that biguanide derivatives (I) were active against *P. gallinaceum* in chicks.[1]



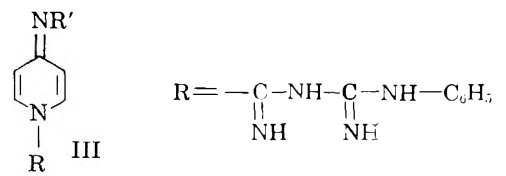
I

It was therefore decided to prepare the phenyl-free analogs to study their antimalarial activity. These compounds were made by reacting the appropriate γ-pyrone with four molecular proportions of the different aryl biguanides by refluxing in alcohol for six to eight hours. Products of type II were obtained.



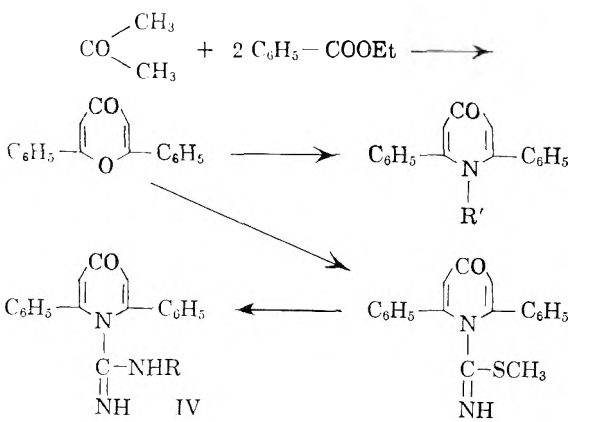
II

A natural development was the preparation of pyridine biguanides of Type III without any substitution at the α-positions. The reactivity of γ-pyrone with 1-aryl biguanides was utilized to achieve this. γ-Pyrone was synthesized in a novel way, by condensing acetone with ethyl formate using sodium ethoxide as the catalyst.[2] Two molecular proportions of the biguanides were then reacted with one of pyrone by heating the ingredients in alcohol on the water bath to give the desired products.



III

2,6-Diphenylpyridone derivatives may also be prepared from the corresponding pyrones. 2,6-Diphenyl-γ-pyrone was obtained in excellent yields by condensing ethyl benzoate with acetone in the presence of sodium ethoxide. This pyrone, unlike γ-pyrone, reacted with only one molecule of the aryl biguanide to give the corresponding γ-pyridone. By first reacting the pyrone with *S*-methylisothiourea and subsequent reaction with aliphatic amines it was possible to prepare a few *N*-amidino-γ-pyridones. These compounds have the general structure IV.



IV

EXPERIMENTAL

Chelidonic acid. This compound was made according to the procedure in *Organic Syntheses*.[3]

1-Aryl biguanides. These were all made by following well known procedures.[4]

Reaction of the pyrones with amines. Chelidonic acid (0.5 g.) and 1-phenyl biguanide (2 g.) were heated under reflux for 6 hr. with alcohol (50 ml.) as the solvent. On cooling, a white crystalline mass separated which was collected and crystallized from water twice to give colorless needles of the product. (Using the same molecular proportions of the reactants other 1-aryl biguanides were reacted with chelidonic acid to give the corresponding derivatives.)

γ-Pyrone (0.5 g.) and phenyl biguanide (1.8 g.) were refluxed in alcohol (40 ml.) for 8 hr. on the water bath. On cooling, a white crystalline mass was thrown out; this was collected and recrystallized from aqueous alcohol to give white needles. (Other aryl biguanides were similarly reacted

(1) L. Neelakantan *et al.*, *J. Indian Chem. Soc.*, **29**, 131 (1952).

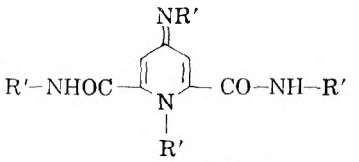
(2) L. Neelakantan, unpublished results.

(3) E. R. Riegel and F. Zwilgmeyer, *Org. Syntheses*, **Coll. Vol. II**, 126 (1944).

(4) F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 729 (1946).

TABLE I

BIGUANIDE DERIVATIVES OF CHELIDONIC ACID



—R′	M.P., °C.	Yield, %	Formula	% N Found	% N Calcd.
—C(=NH)—NH—C(=NH)—NH—C_6H_5	240	70	$C_{39}H_{40}N_{20}O_2$	34.01	34.15
—C(=NH)—NH—C(=NH)—NH—C_6H_4Cl-*p*	248 (dec.)	65	$C_{39}H_{36}N_{20}Cl_4O_2$	28.90	29.17
—C(=NH)—NH—C(=NH)—NH—$C_6H_4CH_3$-*p*	244 (dec.)	60	$C_{43}H_{48}N_{20}O_2$	31.53	31.97
—C(=NH)—NH—C(=NH)—NH—$C_6H_4OCH_3$-*p*	236 (dec.)	55	$C_{43}H_{48}N_{20}O_6$	29.43	29.8
—C(=NH)—NH—C(=NH)—NH—$C_6H_4NO_2$-*p*	230 (dec.)	75	$C_{39}H_{36}N_{24}O_{10}$	33.28	33.6
—C(=NH)—NH—C(=NH)—NHCH$(CH_3)_2$	190 (dec.)	75	$C_{27}H_{48}N_{20}O_2$	40.58	40.94

TABLE II

BIGUANIDE DERIVATIVES OF γ-PYRONE

—R′	M.P., °C.	Yield, %	Formula	% N Found	% N Calcd.
—C(=NH)—NH—C(=NH)—NHC$_6H_5$	128	75	$C_{21}H_{22}N_{10}$	33.71	33.82
Hydrochloride	240				
—C(=NH)—NH—C(=NH)—NHC$_6H_4$Cl-*p*	120	60	$C_{21}H_{20}Cl_2N_{10}$	28.49	28.98
Hydrochloride	230				
—C(=NH)—NH—C(=NH)—NHC$_6H_4CH_3$-*p*	115	60	$C_{23}H_{26}N_{10}$	31.29	31.67
Hydrochloride	234				
—C(=NH)—NH—C(=NH)—NHC$_6H_4OCH_3$-*p*	158	65	$C_{23}H_{26}N_{10}O_2$	29.33	29.53
Hydrochloride	234				
—C(=NH)—NH—C(=NH)—NHC$_6H_4ONO_2$-*p*	124	75	$C_{21}H_{20}N_{12}O_4$	33.12	33.34
Hydrochloride	242				

using two molecular proportions of the biguanide to one of the pyrone.)

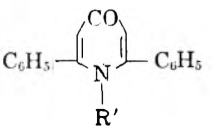
2,6-Diphenyl-γ-pyrone (2.5 g.) was refluxed with phenyl biguanide (1.8 g.) in alcohol (50 ml.) for 8 hr. After cooling and separating the solid it was crystallized from water to give the pure product. (The other *N*-biguanyl pyridones were prepared in the same manner by reacting molecular proportions of the reactants.)

N-(S-Methyl thiocarboximino)-2,6-Diphenyl-γ-pyridone. To a saturated solution of 2,6-diphenylpyrone (12.5 g.) in water was added an aqueous solution of *S*-methylisothiourea. It was then heated on the water bath for 6 hr. and then another 4 hr. using a free flame. On cooling, crystals separated which were collected and crystallized from water twice to give the pure product.

This compound was now reacted with ammonia, benzyl

TABLE III

DERIVATIVES OF 2,6-DIPHENYL-γ-PYRONE



—R′	M.P.[a]	Yield, %	Formula	% N Found	% N Calcd.
—C(=NH)—C(=NH)—NH—C_6H_5	170	70	$C_{23}H_{21}N_5O$	17.2	17.22
—C(=NH)—C(=NH)—NHC$_6$H$_4$Cl-*p*	154	75	$C_{25}H_{20}ClN_5O$	16.02	15.84
—C(=NH)—C(=NH)—NHC$_6$H$_4$CH$_3$-*p*	168	70	$C_{26}H_{23}N_5O$	16.91	16.62
—C(=NH)—C(=NH)—NHC$_6$H$_4$OCH$_3$-*p*	168	75	$C_{26}H_{25}N_5O_2$	16.37	16.02
—C(=NH)—C(=NH)—NHC$_6$H$_4$ONO$_2$-*p*	140	72	$C_{25}H_{20}N_6O_3$	18.90	18.59
—C(=NH)—C(=NH)—NH—	142	75	$C_{22}H_{23}N_5O$	19.01	18.76
—C(=NH)—SCH$_3$	192	95	$C_{19}H_{16}N_2OS$	8.98	8.75
—C(=NH)—NH$_2$	210	80	$C_{18}H_{15}N_3O$	14.61	14.53
—C(=NH)—NH—CH$_2$	130	75	$C_{25}H_{21}N_3O$	11.70	11.34
—C(=NH)—C(=NH)—NH$_2$	184	65	$C_{19}H_{17}N_5O$	21.38	21.16
—C(=NH)—NEt$_2$	182	65	$C_{22}H_{23}N_3O$	12.41	12.2
—C(=NH)—NMe$_2$	240	70	$C_{20}H_{19}N_3O$	13.44	13.24

[a] The compounds were crystallized from hot water as colorless crystals.

amine, diethyl amine, dimethyl amine, and guanidine, respectively, to give the corresponding *N*-amidinopyridones. The reaction was conducted by heating molecular proportions of the ingredients in alcohol in presence of freshly prepared, well-powdered lead hydroxide. The lead mercaptan was filtered off, the filtrate concentrated and the product recrystallized.

Pharmacological evaluation. Many of the compounds prepared were tested for their suppressive activity against *P. gallinaceum* in chicks. None of them, however, showed any appreciable activity in experimental malaria.

Acknowledgment. I wish to express my sincere thanks to Dr. P. C. Guha and Dr. B. H. Iyer for their valuable guidance and help during the course of the work. My thanks are also due to the Director, Indian Institute of Science, for the laboratory facilities, to the Pharmacology section, I. I. Science, for the screening tests and to the Government of Cochin for the award of a research scholarship.

BANGALORE 3, INDIA

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, INDIAN INSTITUTE OF SCIENCE]

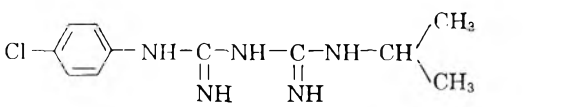
Preparation of Some 1,5-Diaryl Biguanides

L. NEELAKANTAN

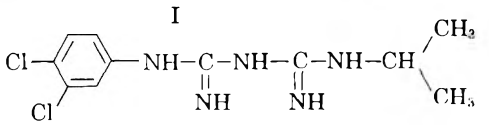
Received March 25, 1957

A series of 1,5-diaryl biguanides were prepared by treating arylcyanoguanidines with various aromatic amines in the presence of hydrochloric acid. Some of the symmetrical diarylbiguanides were made by treating dicyanimide with arylamines. A few of the compounds showed appreciable activity in experimental malaria.

Curd and Rose[1] first postulated that the toxicity of the quinoline and acridine antimalarials was mainly due to the fact that the ring systems involved were foreign to the body. From these and other considerations[2] they finally developed a new class of antimalarials of which paludrine (I) and more recently the dichloro analog (II) showed the greatest promise.[3,4] Compounds with the chlorophenyl group replaced by phenanthryl, quinolyl, etc., were inactive.[5] However, the isopropyl group could be replaced by others like quinolyl, phenylarsonic, sulfonamidophenyl, etc., without loss of activity.[6,7] It was found by Srinivasan[8] that biguanides that are inactive *in vivo* showed considerable activity in inhibiting the respiration of the malarial parasite *in vitro*. Diarylbiguanides with terminal groups which might help in absorption and resist detoxication were made to permit their study in experimental malaria.

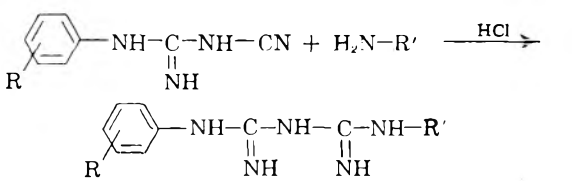


I

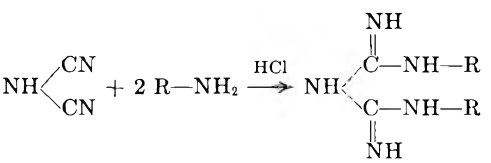


II

A convenient synthesis of such compounds consists in reacting arylcyanoguanidines with arylamines in the presence of hydrochloric acid.[3] *p*-Chloroaniline, 3,4-dichloroaniline, sulfanilic acid, metanilic acid, aniline, and diphenylamine were reacted with *p*-chlorophenylcyanoguanidine and phenylcyanoguanidine respectively to give the desired products as their hydrochlorides.



When dicyanimide is reacted with two moles of arylamines symmetrically substituted diarylbiguanides are obtained. Sulfanilic acid, metanilic acid, and diphenylamine were used to give the corresponding derivatives.



EXPERIMENTAL

Aryl cyanoguanidines were prepared according to well known procedures.[3] *1,5-diphenylbiguanide hydrochloride.* Aniline (2.4 g.), phenylcyanoguanidine (4 g.), concentrated hydrochloric acid (5 ml.), water (10 ml.), and alcohol (50 ml.) were heated on the water bath for 8 hr. On cooling, a crystalline mass separated, which was collected, decolorized, and recrystallized from water twice to give the pure product.

Molecular proportions of arylcyanoguanidines and different arylamines were reacted in this manner to give the various diarylbiguanides listed in the table.

Reaction of dicyanimide with amines. Calcium cyanamide (10 g.) was made to react with cyanogen bromide (10 g. of a 50% solution) in aqueous medium at room temperature for 12 hr. The reaction mixture was then warmed on the water bath and filtered hot. To the filtrate containing the dicyanimide was added sulfanilic acid (8 g.) and concentrated HCl (5 ml.) and the whole was refluxed for 6 hr. The hot solution was decolorized with Norit, filtered, and cooled to deposit crystals which were collected and recrystallized from water to give the pure hydrochloride of the product. Metanilic acid and diphenylamine were also reacted in this manner.

Pharmacological evaluation. Screening tests showed that compounds 3, 5, 8, 12, and 15 have appreciable activity against *P. gallinaceum* in chicks. Compounds 1, 3, and 12 showed 60–65% inhibition of the respiration of the malarial parasite *in vitro*, using the Warburg technique. Srinivasan obtained similar results with various other N^1, N^5-disubstituted biguanides which were inactive *in vivo*.

The formation of a dihydrotriazine like the active metabolite of paludrine or its dichloro analog is unlikely in the case of these diarylbiguanides. It is possible that the biguanide structure in itself has antimalarial activity; groups like arylsulfonic at the end of the biguanide chain probably

(1) F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 343 (1946).
(2) A. R. D. Adams *et al.*, *Ann. Trop. Med. Parasitol.*, **39**, 165 (1945).
(3) F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 729 (1946).
(4) F. L. Rose, *Endeavour*, **18**, 65 (1946).
(5) E. L. May *et al.*, *J. Org. Chem.*, **12**, 437 (1947).
(6) H. L. Bami *et al.*, *J. Indian Inst. Sci.*, **29A**, 15.
(7) H. L. Bami et al., *J. Indian Inst. Sci.*, **29A**, 1.
(8) V. R. Srinivasan, Ph.D. thesis, University of Madras.

TABLE I

1,5-DIARYL BIGUANIDES

R—NH—C(=NH)—NH—C(=NH)—NH—R′ · HCl

No.	—R	—R′	M.P.[a]	Yield, %	Formula	% N Found	% N Calcd.
1	*p*-Chlorophenyl	*p*-Chlorophenyl	254	70	$C_{14}H_{14}Cl_3N_5$	19.62	19.55
2	3,4-Dichlorophenyl	*p*-Chlorophenyl	248	75	$C_{14}H_{13}Cl_4N_5$	17.68	17.82
3	*p*-Benzenesulfonic acid	*p*-Chlorophenyl	>300	75	$C_{14}H_{15}Cl_2N_5O_3S$	17.52	17.33
4	*p*-Benzenesulfonic acid	*p*-Chlorophenyl	>300	70	$C_{14}H_{15}Cl_2N_5O_3S$	17.18	17.33
5	*p*-Biphenyl	*p*-Chlorophenyl	262	65	$C_{20}H_{19}Cl_2N_5$	17.70	17.54
6	Phenyl	*p*-Chlorophenyl	242	65	$C_{14}H_{15}Cl_2N_5$	21.75	21.90
7	*p*-Biphenyl	Phenyl	180	65	$C_{20}H_{20}ClN_5$	19.01	19.17
8	*p*-Benzenesulfonic acid	Phenyl	>300	70	$C_{14}H_{16}ClN_5O_3S$	18.78	18.98
9	*m*-Benzenesulfonic acid	Phenyl	>300	65	$C_{14}H_{16}ClN_5O_3S$	18.87	18.98
10	Phenyl	Phenyl	220	70	$C_{14}H_{16}ClN_5$	24.37	24.22
11	3,4-Dichlorophenyl	Phenyl	213	65	$C_{14}H_{14}Cl_3N_5$	19.62	19.50
12	*p*-Benzenesulfonic acid	*p*-Benzenesulfonic acid	>300	35	$C_{14}H_{16}ClN_5O_6S_2$	15.80	15.50
13	*m*-Benzenesulfonic acid	*p*-Benzenesulfonic acid	>300	30	$C_{14}H_{16}ClN_5O_6S_2$	15.38	15.50
14	*p*-Biphenyl	*p*-Biphenyl	268	35	$C_{26}H_{24}ClN_5$	16.18	16.00
15	*p*-Biphenyl	*p*-Benzenesulfonic acid	>300	65	$C_{20}H_{20}ClN_5O_2S$	15.91	15.70

[a] All the compounds were crystallized from hot water as white crystals.

render it more resistant to detoxication by the host as well as facilitate absorption and penetration of the drug.

Acknowledgment. The author wishes to express his sincere thanks to Dr. P. C. Guha and Dr. B. H. Iyer for their valuable suggestions and help; the Director of the Indian Institute of Science for the laboratory facilities; and to Dr. V. R. Srinivasan for the pharmacological testing of the compounds.

BANGALORE 3, INDIA.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF QUEENS COLLEGE]

Replacement of Halogen by Hydrogen in Nitro Aryl Halides: Some Applications in the Thiophene Series[1]

A. H. BLATT, NORMA GROSS, AND E. W. TRISTRAM[2]

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The use of bromine as a blocking group during nitration of thiophene derivatives is described. The bromine in the bromonitrothiophenes is removed by treatment with hypophosphorous acid or with copper in acid medium.

The blocking groups commonly used to prevent aromatic substitution in a particular position (the sulfonic acid group which is removed by hydrolysis[3] and the nitro group which is removed by reduction to an amino group and replacement of the latter by hydrogen[4]) are *meta* directing. The methods recently described[5] for the replacement of halogen by hydrogen in nitro aryl halides permit the use of the *o,p*-directing halogens for the same purpose. This use of the halogens as removable blocking groups can be employed either for the determination of structure or for the synthesis of hitherto unavailable substituted aromatic compounds. These applications, which offer the most promise with heterocyclic aromatic compounds, are illustrated in the following paragraphs with examples from the thiophene series.

Thiophene on nitration furnishes almost exclusively the 2-nitro derivative which on further nitration yields, contrary to the usual statements,[6] principally 2,4-dinitrothiophene. The difficultly accessible 3-nitrothiophene furnishes on nitration exclusively 2,4-dinitrothiophene. On attempted further nitration, 2,4-dinitrothiophene is either unattacked or, if the conditions are sufficiently drastic, is destroyed. 2,5-Dinitrothiophene is not affected by attempts at further nitration.

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(2) Present address: Merck & Co., Rahway, N. J.

(3) *o*-Chlorophenol: Takagi and Kutani, *J. Pharm. Soc. Japan*, 517, 260 (1925) [*Chem. Abstr.*, 20, 2669 (1926)]. *o*-Bromophenol: R. C. Huston and M. M. Ballard, *Org. Syntheses*, Coll. Vol. II, 97 (1943).

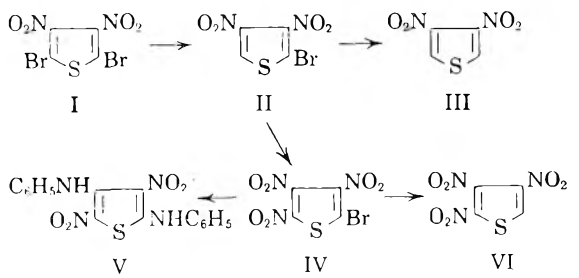
(4) N. Kornblum, *Org. Reactions*, II, 262 (1944).

(5) A. H. Blatt and Norma Gross, *J. Org. Chem.*, 22, 1046 (1957).

(6) A clarification of some inconsistencies in the chemistry of the mononitrothiophenes and the 2,4- and 2,5-dinitrothiophenes is given in the accompanying note, p. 1693.

We undertook to make use of the halogens as temporary blocking groups for the purpose of arriving at more highly nitrated thiophenes. We began with 2,5-dibromothiophene which was nitrated to the known 2,5-dibromo-3,4-dinitrothiophene (I).[7] This completely substituted thiophene undergoes replacement of one bromine by hydrogen on treatment with either hydriodic acid or hypophosphorous acid in acetone at room temperature to furnish 2-bromo-3,4-dinitrothiophene (II) in 88–90% yield. The halogen in the monobromo compound is not removed by hydriodic acid or hypophosphorous acid or by aniline in methanol, but can be removed by heating with copper in an acid medium[8] to furnish 3,4-dinitrothiophene (III).

On treatment with mixed acid the monobromo derivative II is nitrated to 2-bromo-3,4,5-trinitrothiophene (IV) in 90% yield. As would be expected, the halogen in this trinitro derivative is extraordinarily reactive; so reactive that the only solvent suitable for crystallization is concentrated nitric acid. As would also be expected, one nitro group in the trinitro derivative is readily displaced. Most of the reactions of the trinitro derivative lead to intractable products, but the reaction with aniline leads to a dianilino derivative which we formulate as V. The halogen in the trinitrobromothiophene can be replaced by hydrogen to furnish 2,3,4-trinitrothiophene (VI) in 75% yield using hypophosphorous acid as the reagent. This reaction cannot be brought about satisfactorily by hydriodic acid, presumably because the process is complicated by displacement of the central nitro group.



2,3,4-Trinitrothiophene is the first of the two possible trinitrothiophenes to be prepared. One trinitro derivative of thiophene, 2-acetamido-3,4,5-trinitrothiophene, is known.[9] As would be expected of a vicinal trinitro compound, the trinitrothiophene VI contains one very labile nitro group. On treatment with aniline in methanol, potassium acetate in acetic acid, or hydriodic acid in acetone the trinitrothiophene is destroyed. All of these reactions, unfortunately, lead to intractable products. As would also be expected, the trinitrothiophene VI shows the stabilizing and deactivating affects of the nitro groups on the thiophene nucleus. All attempts to nitrate the material failed, and 60% of the starting material could be recovered after heating the compound for four hours at 130° with a mixture of nitric and sulfuric acids containing only 0.1% of water. This resistance to nitration made it impossible to prepare what would have been the first completely nitrated aromatic compound, tetranitrothiophene.

All the dinitro- and trinitro-thiophenes prepared in this work gave the characteristic yellow (dinitro) or red-brown (trinitro) colors with sodium iodide in acetone.[5]

EXPERIMENTAL

Melting points are uncorrected.

Crude 2,5-dibromo-3,4-dinitrothiophene[7] can be crystallized from methanol (30 ml./g.) with a 60% recovery; but it is preferably purified by solution in acetone (2 ml./g.) and treatment with decolorizing carbon, followed by concentration of the filtered solution to half its original volume and dilution with methanol (2 ml./g.).

On treatment with aniline in methanol one bromine atom is displaced by an anilino group to furnish a product which melts at 150.5–151° after crystallization from acetone and water.

Anal. Calcd. for $C_{10}H_6BrN_3O_4$: C, 34.9; H, 1.7. Found: C, 35.1; H, 1.33.

2-Bromo-3,4-dinitrothiophene (II). (a) A solution of 45 g. (0.3 mole) of sodium iodide in 125 ml. of acetone was cooled to 10–15° and added to a similarly cooled solution of 20 g. (0.06 mole) of the dibromodinitrothiophene I in 100 ml. of acetone and 20 ml. of glacial acetic acid. The reaction mixture developed an orange-yellow color and a precipitate (NaBr) formed. After it had been left for one week, the reaction mixture was added to 800 ml. of water containing 10 g. of sodium bisulfite. This removed most of the color and left a gray precipitate of the crude bromodinitrothiophene II that weighed 13.8–14.0 g. (90%) and melted at 87–89°. (b) To a solution of 20 g. (0.06 mole) of the dibromodinitrothiophene I in 200 ml. of acetone that had been cooled to 10–15°, was added 36 ml. (0.3 mole) of 50% hypophosphorous acid. The reaction mixture, which developed an orange-red color, was kept in an ice water bath for 5 min. during which time a mildly exothermic reaction took place, and was then left at room temperature for 2 hr. On pouring the solution into water, 13.5 g. (88%) of the bromodinitrothiophene II, melting at 88–89° was obtained.

2-Bromo-3,4-dinitrothiophene can be crystallized from methanol (2 ml./g.) with an 80% recovery as clusters of stout, almost colorless prisms, or from ether (4 ml./g.) and 30–60° petroleum ether (6 ml./g.). It is soluble in fuming nitric acid at the ordinary temperature and, after remaining in such a solution for 18 hr., can be recovered by dilution with ice and water. Treatment with nitric acid in this way removes impurities and, consequently, the crude material can be used directly for nitration to the bromotrinitrothiophene IV. The analytical sample, which was crystallized from ethanol, melted at 93–94°.

Anal. Calcd. for $C_4HBrN_2C_4S$: C, 18.75; H, 0.5; N, 11.1. Found: C, 19.15; H, 0.88; N, 10.8.

The bromodinitrothiophene II reacts with aniline in ethanol to form a highly colored intractable product. The reaction with potassium acetate in acetic acid also leads to colored, intractable material. The bromine in II is not removed by treatment with either hydriodic acid or hypophosphorous acid. In order to be able to identify the bro-

(7) R. Mozingo, S. A. Harris, D. E. Wolf, C. E. Hoffhine, Jr., N. R. Easton, and K. Folkers, *J. Am. Chem. Soc.*, **67**, 2092 (1945).

(8) W. T. Smith, Jr., *J. Am. Chem. Soc.*, **71**, 2855 (1949); W. T. Smith, Jr., and L. Campanaro, *J. Am. Chem. Soc.*, **75**, 3602 (1953).

(9) H. M. Priestley and C. D. Hurd, *J. Am. Chem. Soc.*, **69**, 1173 (1947).

mine-free product. 3,4-dinitrothiophene (III), if it were formed we prepared a sample of the material by the reaction between the bromodinitrothiophene II and copper in boiling butyric acid.[8] 3,4-Dinitrothiophene, which has already been prepared in similar fashion from the dinitrodibromothiophene I by Dr. Ellis Brown and which will be described in detail by him later, melts at 94–95° and mixtures of the monobromodinitrothiophene II and the dinitrothiophene III melt below 75°.

2-Bromo-3,4,5-trinitrothiophene (IV). Twenty grams (0.08 mole) of the crude bromodinitrothiophene II was added with stirring during 5 min. to a mixture of 100 ml. of concentrated sulfuric acid and 100 ml. of fuming nitric acid (d. 1.59–1.60). The solid dissolved in the nitrating acid, which was at room temperature, without an appreciable evolution of heat. In about 0.5 hr. the trinitro compound began to precipitate. Stirring was continued for 2 hr., after which time the reaction mixture was left overnight before it was poured onto 300 g. of ice. The yield of crude nitration product, melting at 123–125°, was 21.5 g. (90%).

2-Bromo-3,4,5-trinitrothiophene is a pale yellow solid which is soluble in the common solvents, but apparently with solvolysis; the solutions develop much color and the solute crystallizes poorly or not at all. The only satisfactory procedure for purification is to dissolve the trinitrobromothiophene in concentrated nitric acid (10 ml./g.) by heating on the steam bath. On cooling the filtered solution, the product is obtained with an 80% recovery as lemon yellow crystals melting at 130–131°.

Anal. Calcd. for $C_4BrN_3O_6S$: C, 16.10; H, 0.0; Br, 26.8. Found: C, 16.16; H, 0.0; Br, 26.7.

The trinitrobromothiophene furnishes only intractable material on treatment with potassium acetate in acetic acid. With aniline in methanol it yields a dianilino derivative (V), which is obtained as orange needles melting at 196–196.5° after crystallization from acetone-methanol.

Anal. Calcd. for $C_{16}H_{12}N_4O_4S$: C, 53.9; H, 3.39. Found: C, 54.05; H, 3.46.

2,3,4-Trinitrothiophene (VI). A solution of 5.0 g. (0.017 mole) of the crude bromotrinitrothiophene IV in 100 ml. of acetone was cooled to about 10° and 10 ml. (0.85 mole) of 50% hypophosphorous acid was added. An orange-red color developed at once. The solution was kept at room temperature by immersing the flask in cold water from time to time. After 1 hr. the solution was poured into 800 ml. of water and the tan precipitate was filtered; yield, 2.8 g. (76%), m.p. 138–141°. The product was purified by crystallization from ether (30 ml./g.) and an equal volume of 30–60° petroleum ether. The recovery was 70%.

Anal. Calcd. for $C_4HN_3O_6S$: C, 21.90; H, 0.46. Found: C, 21.93; H, 0.60.

2,3,4-Trinitrothiophene is a colorless solid which melts at 143°. When a small sample of the material in a sealed melting point tube is heated in a free flame it explodes vigorously. The material, which analyzes satisfactorily for carbon and hydrogen, gives low values for nitrogen and sulfur. The trinitrothiophene is unaffected by the ordinary nitric acid–sulfuric acid nitrating mixtures at steam bath temperatures. When one gram of the material was heated at 130° for 1.5 hr. with 10 ml. of concentrated sulfuric acid and 2 g. of potassium nitrate or for 4 hr. with 5 ml. of nitrating acid of the composition 82.3% H_2SO_4–17.6% HNO_3–0.1% H_2O, there was no indication that nitration had taken place and 60% of essentially pure starting material was recovered.

FLUSHING 67, N. Y.

[CONTRIBUTION FROM THE RESEARCH STATION, THE BRITISH PETROLEUM COMPANY LIMITED]

Preparation and Physical Properties of Sulfur Compounds Related to Petroleum. VII. 2-, 6- and 8-Thiabicyclo[3.2.1]octane and 2-Thiabicyclo[2.2.2]octane

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2-, 6-, and 8-Thiabicyclo[3.2.1]octane and 2-thiabicyclo[2.2.2]octane have been synthesized and their physical properties have been recorded. Each sulfide has been characterized by the preparation of derivatives.

In an earlier paper[1], Birch *et al.* reported the isolation from an Agha Jari (S. Persia) kerosine of a sulfide which was apparently 8-thiabicyclo[3.2.1]-octane and suggested that other thiabicyclooctanes were also present in this kerosine. It has previously been found possible to identify certain other sulfides as constituents of the kerosine, by comparison of the infrared spectra of the isolated sulfides or sulfide mixtures with those of synthetic compounds which have been prepared in these laboratories.[2] Consequently, the synthesis of 2-, 6- and 8-thiabicyclo[3.2.1]octane (IX, XIII and IV) and 2-thiabicyclo[2.2.2]octane (XVII) was carried out, as reported in the present paper. 3-Thiabicyclo-[3.2.1]octane, the fifth member of the group of thiabicyclooctanes containing only five- and six-membered rings and having an atomic bridge, has already been described.[3] The stereochemistry of the thiabicyclo[3.2.1]- and thiabicyclo[2.2.2]octane systems is such that the *trans*- forms would be extremely strained and, as with the corresponding hydrocarbons, it is probable that only one form having a *cis*- configuration can exist.[4] As recently

(1) S. F. Birch, T. V. Cullum, R. A. Dean, and R. L. Denyer, *Ind. Eng. Chem.*, 47, 240 (1955).

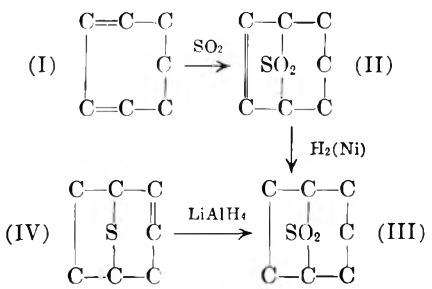
(2) S. F. Birch, R. A. Dean, N. J. Hunter, and E. V. Whitehead, *J. Org. Chem.*, 20, 1178 (1955).

(3) S. F. Birch and R. A. Dean, *Chem. Ber.*, 585, 234 (1954) in which this sulfide is referred to as 6-thiabicyclo-[1.2.3]octane.

(4) H. Gilman, *Organic Chemistry*, 2nd. Ed., John Wiley and Sons, Inc., New York, 1948, Vol. 1, p. 485.

reported,[5] it has been confirmed that all five of the above thiabicyclooctanes are in fact present in the kerosine under investigation.

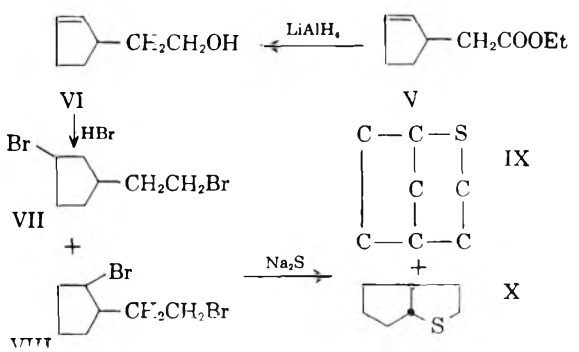
These "atomic-bridge" bicyclic sulfides have not been synthesized previously, although the corresponding hydrocarbons and certain nitrogen and oxygen analogues have been prepared. In common with other bicyclic sulfides which we have synthesized[2,6] they were obtained by two general methods: (*a*) hydrogenation and reduction of the unsaturated sulfones obtained by condensation of sulfur dioxide and the appropriate diene and (*b*) cyclization of the appropriate dibromide or ditosylate[7] with sodium sulfide. The yields obtained by method (*b*) were rather poor but method (*a*), which gives better yields, can be used only for compounds in which the sulfur atom is part of a five-membered ring, and then only when the structure of the intermediate unsaturated sulfone would not violate Bredt's Rule.[8] Accordingly, of the required sulfides, only 8-thiabicyclo[3.2.1]octane (IV) was prepared by method (*a*); the reaction route is shown schematically (I-IV).



1,3-Cycloheptadiene (I) reacted with sulfur dioxide at a lower temperature (20°) and gave a better yield (95%) of the corresponding unsaturated sulfone than did 1-vinylcyclopentene in the analogous preparation of *cis*-2-thiabicyclo[3.3.0]-octane.[2] Reduction of the unsaturated sulfone (II) proceeded smoothly and no poisoning of the catalyst was experienced during this reaction. In common with other saturated bycyclic sulfones[2]; 8-thiabicyclo[3.2.1]octane-8,8-dioxide (III) was incompletely reduced by lithium aluminum hydride (2 moles) and gave only 65% of the expected sulfide together with 30% of unreduced sulfone. No isomerization[2] occurred during this reduction, since the degree of strain required in the *trans*-isomer of the sulfone precludes its formation. The sulfide was purified by crystallization and sublimation.

The other three sulfides were obtained by method (*b*). The replacement of the secondary bromide or tosylate group of the intermediates used in this method, is accompanied by Walden inversion.[9,10] Accordingly, on reaction with sodium sulfide, a *cis*-intermediate should give a *trans*-sulfide, and a *trans*-intermediate a *cis*-sulfide. Since the formation of a *trans*-sulfide is prohibited the *cis*-intermediates actually give entirely polymeric material. Moreover, even with the *trans*-isomers, the formation of the required sulfides is hindered by the tendency for the secondary bromide or tosylate groups to eliminate with a neighboring ring hydrogen atom[11,12] and, possibly, by the difference in the reactivities of the primary and secondary bromide or tosylate groups[9,10] which may favor intermolecular reaction. It is thus not surprising that poor yields were obtained in these preparations.

The dibromides and ditosylates required as intermediates in method (*b*) are, in general, most conveniently obtained from the corresponding diols by hydrobromination and treatment with *p*-toluenesulfonyl chloride respectively. Rearrangements usually occur during hydrobromination of secondary alcohols[13,14] resulting in the formation of mixtures of isomeric dibromides. Consequently, in the dibromide route tedious separation processes may be required at either the dibromide or sulfide stage and/or there may be some uncertainty as to the structure of the pure sulfide finally isolated. On the other hand, tosylation of secondary alcohols takes place without isomerization[15] and with retention of configuration,[9,10] and the structure of a sulfide obtained *via* the ditosylate is thus unambiguous. However, this advantage may be offset if the parent diol of the required ditosylate is not easily prepared while the corresponding dibromide can be obtained from another compound. In addition, better yields are obtained by the dibromide



(5) S. F. Birch, T. V. Cullum, and R. A. Dean. Paper presented before the Division of Petroleum Chemistry, 130th Meeting of the American Chemical Society, Atlantic City, New Jersey, September, 1956.

(6) S. F. Birch, R. A. Dean, and E. V. Whitehead, *J. Org. Chem.*, **19**, 1449 (1954).

(7) Di-*p*-toluenesulfonate.

(8) F. S. Fawcett, *Chem. Revs.*, **47**, 219 (1950).

(9) M. F. Clarke and L. N. Owen, *J. Chem. Soc.*, 2108 (1950).

(10) L. N. Owen and P. A. Robins, *J. Chem. Soc.*, 326 (1949).

(11) L. N. Owen and P. A. Robins, *J. Chem. Soc.*, 320 (1949).

(12) M. F. Clarke and L. N. Owen, *J. Chem. Soc.*, 2103 (1950).

(13) B. Rothstein, *Ann. Chem.*, 14, 461 (1930).

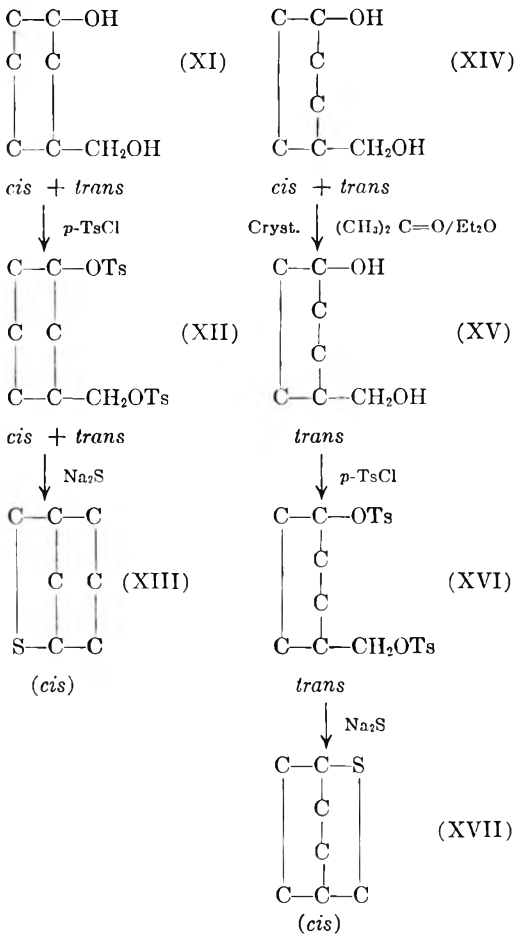
(14) H. Pines, A. Rudin, and V. N. Ipatieff, *J. Am. Chem. Soc.*, **74**, 4063 (1952).

(15) H. Phillips, *J. Chem. Soc.*, 2552 (1925).

route and for these reasons, 2-thiabicyclo[3.2.1]-octane (IX) was prepared by this route, as shown in the reaction scheme (V-X).

The alcohol VI was obtained in good yield when the ester V (prepared by the method of Noller and Adams[16]) was reduced with lithium aluminum hydride. v. Braun *et al.*[17] reported that on hydrobromination of VI they obtained 1-bromo-3-(2-bromoethyl)cyclopentane (VII) and not the corresponding 2-(2-bromoethyl) compound (VIII). However, even if isomerization did not occur under the conditions employed by these workers, it seems unlikely that VII was the only addition product, and certainly their identification of their dibromide as this compound does not appear conclusive. We anticipated that the corresponding 1- and 2-(2-bromoethyl) compounds would accompany 1-bromo-3-(2-bromoethyl)cyclopentane in our preparation, and the decomposition, accompanied by evolution of hydrogen bromide, which occurred on distillation of our hydrobromination product, and the occurrence of 2-thiabicyclo[3.3.0]octane in addition to the required 2-thiabicyclo[3.2.1]octane in the product obtained on treatment of the distilled dibromide with sodium sulfide, confirmed our expectations. Fractional distillation of the mixture of bicyclic sulfides (34% yield) separated from the polymeric portion of the product, followed by fractional crystallization of the mercuric chloride complexes of the liquid and solid fractions so obtained, gave a quantity of the 2-thiabicyclo[3.2.1]-octane complex, and the sulfide regenerated from this was purified by crystallization and sublimation. The sulfide regenerated from the combined residual complexes was shown by spectroscopic examination to contain *cis*-2-thiabicyclo[3.3.0]-octane; no *trans*-2-thiabicyclo[3.3.0]octane[18] could be detected, however, and it seems that the amount of the *cis*-isomer of VIII in the hydrobromination product was very small.

The diols required for the synthesis of 6-thiabicyclo[3.2.1]octane (XIII) and 2-thiabicyclo[2.2.2]-octane (XVII), *viz*, the 3- and 4-hydroxycyclohexanemethanols (XI and XIV), are readily obtainable, and XIII and XVII were therefore synthesized by the ditosylate route as indicated schematically (XI-XVII). These diols were prepared, in average yields of 69 and 63% respectively, as described by Owen *et al.*[9,10] Neither *trans*-3-hydroxycyclohexanemethanol nor its ditosylate can readily be separated from their respective admixtures with the corresponding *cis*-compounds,[9] so that a mixture of *cis*- and *trans*-ditosylates, obtained in almost theoretical yield by the usual method,[19] had to be



used for the preparation of XIII. The *trans*-isomer of 4-hydroxycyclohexanemethanol is easily separated from its admixture with the *cis*-isomer[10] however, so that the pure *trans*-ditosylate (XVI) was used for the preparation of XVII. Only a poor yield of XVI was obtained in a preliminary preparation carried out in the usual way,[19] and, following a suggestion by Haggis and Owen,[20] the majority of this ditosylate was prepared by reverse addition of the reactants.

The yields of XIII and XVII obtained on reaction of these ditosylates with sodium sulfide were very low (*ca.* 5%), the majority of the product being di- or poly-meric material. Consequently, since it appeared likely that the dibromide corresponding to the structure of the original diol would be the main hydrobromination product, it was considered worthwhile to investigate whether, despite the disadvantages already mentioned, the dibromide route might not prove to be on the whole more satisfactory than the ditosylate route. The yields of bicyclic sulfide were certainly increased to 15 and 12% based on the dibromides obtained from XI and XIV respectively, but surprisingly, this sulfide consisted in both instances almost entirely

(16) C. R. Noller and R. Adams, *J. Am. Chem. Soc.*, **48**, 2444 (1926).

(17) J. v. Braun, E. Kamp, and J. Kopp, *Ber.*, **70**, 1750 (1937).

(18) S. F. Birch, R. A. Dean, and E. V. Whitehead, *Chemistry & Industry* (London), 409 (1956) and a future publication in this series.

(19) E. C. Horning, *Org. Syntheses*, **Coll. Vol. 3**, 366 (1955).

(20) G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 389 (1953).

TABLE I
MELTING POINTS AND ANALYSES OF THE DERIVATIVES OF THE SULFIDES

Compound	Formula of derivative	M.P., °C., (corrected)	Analyses					
			Calcd.			Found		
			C	H	S	C	H	S
	$C_7H_{12}Cl_2HgS$	193–194[a]	21.0	3.0	8.0	21.3	3.0	8.1
2-Thiabicyclo[3.2.1]octane	$C_7H_{12}O_2S$	257[a]	52.5	7.6	20.0	52.3	7.7	20.1
	$C_8H_{15}IS$	210–211[a,b]	35.6	5.6	11.9	35.7	5.8	12.0
	$C_7H_{12}Cl_2HgS$	157–157.5[a]	21.0	3.0	8.0	21.1	3.3	8.2
6-Thiabicyclo[3.2.1]octane	$C_7H_{12}O_2S$	236–237	52.5	7.6	20.0	52.8	7.8	20.4
	$C_8H_{15}IS$	162.5–163.5[a,b]	35.6	5.6	11.9	35.7	5.6	12.4
	$C_7H_{12}Cl_2HgS$	226[a]	21.0	3.0	8.0	20.9	3.0	8.0
8-Thiabicyclo[3.2.1]octane	$C_7H_{12}O_2S$	281.5–282	52.5	7.6	20.0	52.3	7.8	20.2
	$C_8H_{15}IS$	242.5–243[a,b]	35.6	5.6	11.9	35.6	5.8	12.0
	$C_7H_{12}Cl_2HgS$	185–187[a]	21.0	3.0	8.0	21.3	3.2	7.9
2-Thiabicyclo[2.2.2]octane	$C_7H_{12}O_2S$	*ca.* 310	52.5	7.6	20.0	52.6	7.7	20.1
	$C_8H_{15}IS$	225–226[a,b]	35.6	5.6	11.9	34.9	5.3	12.3

[a] With decomposition. [b] Sealed tube plunged into bath at *ca.* 10° below m.p.

of XIII, and XVII was not present in detectable quantities in either product. This would seem to show that while with XI the hydrobromination complexes and reaction products do not tend to rearrange in such a way that *trans*-1-bromo-4-(bromomethyl)cyclohexane is formed, with XIV extensive rearrangements occur such that *trans*-1-bromo-3-(bromomethyl)cyclohexane is a major end product. Thus, while a quantity of XIII was obtained by this dibromide route, further amounts of XVII had to be prepared *via* the ditosylate. Specimens of XIII and XVII were purified by crystallization of their mercuric chloride complexes, followed by crystallization and sublimation of the regenerated sulfides.

All four sulfides are, like 3-thiabicyclo[3.2.1]-octane, wax-like solids with strong camphoraceous odors. 6- and 8-Thiabicyclo[3.2.1]octane melt at about the same temperature as 3-thiabicyclo[3.2.1]-octane (174–175°) and the melting point of 2-thiabicyclo [3.2.1] octane is only about 10° lower, while the melting point of 2-thiabicyclo[2.2.2]-octane is as high as 210–212°. Melting points of mixtures of the sulfides are indefinite, but are intermediate between those of the components of the mixtures, *i.e.* there is no true depression of the melting point. All five sulfides of the group have boiling points[21] within two or three degrees of 195° at atmospheric pressure. (The boiling points of 3-thiabicyclo[3.2.1]octane and 2-thiabicyclo-[2.2.2]octane[21] have not actually been determined, but their values can be deduced from data on the occurrence of the sulfides in fractions obtained on distillation of sulfide concentrates isolated from crude kerosene[5].)

Derivatives of the four sulfides described in this paper were prepared by methods described previously[6,22] and their melting points are given in Table I; the high melting points of the sulfones, especially that of 2-thiabicyclo[2.2.2]octane, are noteworthy. The infrared spectra[23] of these sulfides and of 3-thiabicyclo[3.2.1]octane have been obtained in the range 2–15 μ using a Grubb Parsons double beam spectrometer.

(21) Boiling point defined as temperature at which vapor pressure is 760 mm. 2-Thiabicyclo[2.2.2]octane sublimes when heated at atmospheric pressure and has no normal boiling point.

(22) E. V. Whitehead, R. A. Dean, and F. A. Fidler, *J. Am. Chem. Soc.* **73**, 3632 (1951).

(23) These spectra have been submitted to the A.P.I. Research Project 44 for inclusion in their catalog of spectral data.

EXPERIMENTAL

All melting points are corrected. Microanalyses are by Dr. Ing. A. Schoeller of Kronach/Oberfranken, Bambergerstrasse 20, Germany.

3-Thiabicyclo[8.2.1]-6-octene-8,8-dioxide (II) was obtained in 90–95% yield when 1,3-cycloheptadiene (I) (25 g.) (b.p. 120–121°/770 mm., n_D^{20} 1.4960), phenyl-β-naphthylamine (0.2 g.), and sulfur dioxide (86 g.) were reacted[2] at room temperature for 40 hr. The product, worked up in the usual way[2] and crystallized from ethanol, melted at 160.5–162°.

Anal. Calcd. for $C_7H_{10}SO_2$: C, 53.1; H, 6.4; S, 20.3. Found: C, 53.2; H, 6.5; S, 20.3.

8-Thiabicyclo[3.2.1]octane-8,8-dioxide (III) was obtained in theoretical yield by hydrogenating[2] II. The product was not distilled, but was crystallized from ether or benzene/cyclohexane. It melted at 281.5–282°.

8-Thiabicyclo[3.2.1]octane (IV). Reduction[2] of the sulfone (III) (1 mole) with lithium aluminum hydride (2 moles) gave 66% of the sulfide (IV) and 30% of unreduced sulfone (III). Crystallized to constant melting point from *n*-pentane and sublimed at 0.4 mm., 8-thiabicyclo[3.2.1]octane melted (sealed tube) at 176.5–178.5°, b.p. 194.5°/769 mm.

Anal. Calcd. for $C_7H_{12}S$: C, 65.6; H, 9.4; S, 25.0. Found: C, 65.6; H, 9.5; S, 25.0.

2-Cyclopentene-1-acetic acid was obtained in 65% yield by the method of Noller and Adams.[16] The diester was not isolated but was hydrolyzed and decarboxylated to give the required acid (b.p. 90°/2 mm.–90°1.2 mm., n_D^{20} 1.4682). The ester (V) obtained in 82% yield by continuous esterification of the acid, boiled at 95°/29 mm.–96°/27 mm., n_D^{20} 1.4480.

2-Cyclopentene-1-ethanol (VI) was prepared by reducing the ester (V) (258 g.) with lithium aluminum hydride (38 g.), yield 87%, b.p. 98°/30 mm., n_D^{20} 1.4722. (Hydrogenation of a portion of VI with a platinum black catalyst gave cyclopentanethanol in 87% yield, b.p. 96°/25 mm., n_D^{20} 1.4577).

Bromo-(2-bromoethyl)cyclopentanes (VII, VIII). Anhydrous hydrogen bromide was passed into a mixture of the alcohol (VI) (103 g.) and water (1 g.), at a maximum tem-

perature of 70° until no further increase in weight occurred. After working up the product in the usual way[6] it was distilled under reduced pressure when partial decomposition accompanied by evolution of hydrogen bromide took place. The following fractions were obtained: 1. b.p. <110°/5 mm., 44 g.; 2. b.p. 110°/5 mm.–112°/2.5 mm., 47 g., n_D^{20} 1.524; 3. b.p. 112°/2.5 mm.–98°/0.4 mm., 124 g., n_D^{20} 1.5332; residue 7 g. The third fraction was used for cyclization, a total of 264 g. being prepared. Hydrobromination of VI in the presence of ascaridole and under irradiation by ultraviolet light gave a similar product.

2-Thiabicyclo[3.2.1]octane (IX). The mixture of dibromides (VII, VIII) was reacted with sodium sulfide in the usual way[6] except that the reaction mixture was refluxed for 16 hr. The product was steam distilled and the distillate extracted with *n*-pentane; mercaptans present in the extract were oxidized with 10% aqueous potash and iodine, and after removal of the solvent the residue was distilled to give a semi solid product, b.p. 82–86°/19 mm., in 34% yield. Fractionation of this material under reduced pressure through a Bower and Cooke column[24] gave partial separation into liquid and solid fractions. These fractions were converted separately into their mercuric chloride complexes and fractional crystallization of these from ethanol yielded a constant melting derivative. The sulfide (6.8 g.) was regenerated from this complex with 15% hydrochloric acid: it melted at 165–166° (sealed tube), and after crystallization from acetic acid and sublimation the melting point was unchanged; b.p. 197°/774 mm.

Anal. Calcd. for $C_7H_{12}S$: C, 65.6; H, 9.4; S, 25.0. Found: C, 65.4; H, 9.4; S, 24.7.

The sulfide obtained from the remaining mercuric chloride complex was shown spectroscopically to consist of a mixture of 2-thiabicyclo[3.2.1]octane and *cis*-2-thiabicyclo[3.3.0]-octane; *trans*-2-thiabicyclo[3.3.0]octane could not be detected in the sample.

3-Hydroxycyclohexanemethanol (XI), (306 g., b.p. 117–119°/0.6 mm., n_D^{20} 1.4935) was prepared in average overall yield of 69% from ethyl *m*-hydroxybenzoate (564 g.), as described by Clarke and Owen.[9]

6-Thiabicyclo[3.2.1]octane (XIII). (a) *By the ditosylate[7] route.* A mixture of the ditosylates of *cis*- and *trans*-3-hydroxycyclohexanemethanol was obtained in almost theoretical yield by reaction of the diol (100 g.) with *p*-toluenesulfonyl chloride as described in *Organic Syntheses*,[19] except that the reaction mixture was allowed to stand overnight. The crude product, (which failed to solidify) was dried azeotropically by distilling off the solvent from its benzene solution, and dissolved in ethanol and reacted with sodium sulfide nonahydrate by the usual method.[3] The material steam distilled from the crude reaction product was dissolved in *n*-pentane and the solution was exhaustively extracted with 10 ml. portions of aqueous mercuric acetate (1 mole/liter), the extracts were added to excess aqueous sodium chloride and the sulfide was regenerated from the mercuric chloride complex by refluxing with 15% hydrochloric acid. Sublimation gave 4.5 g. (5%) of sulfide, the pure mercuric chloride complex of which melted at 157.5°.

(b) *By the dibromide route. cis*- and *trans*-3-Hydroxycyclohexanemethanol (85 g.) was hydrobrominated and the resultant dibromide (145 g., 87%, b.p. 84–89°/0.8 mm., n_D^{20} 1.5444) reacted with sodium sulfide by the general method described in an earlier paper.[6] The crude mercuric chloride complex of the sulfide gave pure material (49 g., m.p. 157.5°) after two crystallizations from ethanol. A *n*-pentane solution of the sulfide regenerated from this pure complex with 15% hydrochloric acid was washed with iodine in 10% aqueous caustic potash until mercaptan free and then with aqueous sodium thiosulfate until colorless. Sublimation of the residue from evaporation gave 6-thiabicyclo[3.2.1]-octane (10.8 g., 15%) which, after three crystallizations from acetic acid, melted (constantly) at 172.5–174° and boiled at 197°/769 mm.

Anal. Calcd. for $C_7H_{12}S$: C, 65.6; H, 9.4; S, 25.0. Found: C, 65.6; H, 9.6; S, 24.8.

This sulfide was shown by comparison of infrared spectra to be identical with the sulfide obtained from the ditosylate as described in section (a) above. Spectroscopic examination of the sulfide regenerated from the mercuric chloride complex recovered from the recrystallization mother liquors failed to detect the presence of any 2-thiabicyclo[2.2.2]-octane in this material.

4-Hydroxycyclohexanemethanol (XIV) (925 g., b.p. 120–122°/1.3 mm., n_D^{20} 1.4932) was prepared, in average overall yield of 63%, from ethyl *p*-hydroxybenzoate (1868 g.) as described by Owen and Robins.[10] A quantity (380 g.) of the *trans*-diol (XV) (m.p. 105–108°) was isolated from a portion (815 g.) of this *cis-trans* mixture, also as described by these authors.[10]

2-Thiabicyclo[2.2.2]octane (XVII). (a) *By the ditosylate route. trans*-4-Hydroxycyclohexanemethanol (165 g.) was added portionwise with stirring to a cooled solution of *p*-toluenesulfonyl chloride (5% excess) in pyridine and the mixture was allowed to stand overnight. The ditosylate was isolated in the usual way[19] and, crystallized twice from ethanol, it melted constantly at 94–95° (reported[10] m.p. 94–95°). A total of 932 g. of pure ditosylate was prepared in this way from 380 g. of diol.

A *n*-pentane solution of the product obtained on treatment of the pure ditosylate (300 g.) with sodium sulfide[3] was washed with iodine and 10% aqueous caustic potash until mercaptan free and then with aqueous sodium thiosulfate until colorless. The solution was evaporated and the solid sulfide (4 g., 5%) sublimed from the residue was converted to the mercuric chloride complex and crystallized to constant melting point (185–187.5°) from ethanol. 2-Thiabicyclo[2.2.2]octane (2.2 g., m.p. 208–210°) was regenerated by addition of this complex (7.5 g.) suspended in Carbito[25] (30 ml.) to a refluxing solution of sodium sulfide nonahydrate (33 g.) in water (50 ml.). This was combined with the sulfide (4.5 g.) obtained from 2 further 300 g. batches of ditosylate and the whole was crystallized from acetic acid and sublimed to give pure 2-thiabicyclo[2.2.2]octane melting at 210–212°.

Anal. Calcd. for $C_7H_{12}S$: C, 65.6; H, 9.4; S, 25.0. Found: C, 65.4; H, 9.4; S, 24.9.

(b) *Attempted preparation by the dibromide route.* The sulfide obtained by sodium sulfide treatment[6] of the dibromide (199 g., 92%, b.p. 100–104°/2.5 mm., n_D^{20} 1.5446) resulting from hydrobromination[6] of *cis*- and *trans*-4-hydroxycyclohexanemethanol (110 g.), was converted to the crude mercuric chloride complex and the material (12 g., 12%) regenerated by refluxing this complex with 15% hydrochloric acid was purified by crystallization from acetic acid. The pure sulfide proved to be identical (m.p. and infrared spectrum) with 6-thiabicyclo[3.2.1]octane and even the sulfide recovered from the recrystallization mother liquors did not contain sufficient 2-thiabicyclo[2.2.2]octane to be detectable by infrared spectroscopy.

Derivatives of the Sulfides. The mercuric chloride complexes, methiodides, and sulfones of all four sulfides were prepared by the usual methods, and their melting points and analyses are recorded in Table I.

Acknowledgment. The authors wish to thank the chairman and directors of The British Petroleum Company Limited for permission to publish these results and Messrs. N. G. McTaggart and A. R. West for the determination of the absorption spectra.

SUNBURY-ON-THAMES, ENGLAND

(24) J. R. Bower and L. M. Cooke, *Ind. Eng. Chem., Anal. Ed.*, **15**, 290 (1943).

(25) Union Carbide Chemicals Co. trade name; Carbitol is the monoethyl ether of diethylene glycol.

[CONTRIBUTION FROM THE NEW YORK QUININE AND CHEMICAL WORKS, INC.]

Monocarbamates of 1,2-Dihydroxy-3-aryloxypropanes

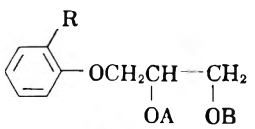
MANUEL M. BAIZER, JOHN R. CLARK, AND JOHN SWIDINSKY[1]

Received April 16, 1957

Ester interchange between diethyl carbonate and 1,2-dihydroxy-3-aryloxypropanes produces high yields of dioxolones which on treatment under mild conditions with ammonia in an alcohol give good yields of the carbamate of the primary alcohol group. In one case (Compound If) the isomeric carbamate (of the secondary alcohol group) was isolated from mother liquors and also synthesized by an unequivocal independent synthesis.

The rearrangement of derivatives of α-hydroxycarbamates is discussed. A method is provided for converting secondary carbamates to primary carbamates.

Monocarbamates of 1,2-dihydroxy-3-aryloxypropanes have recently emerged as a therapeutically useful group of compounds.[2-4] The presently most important members of this group have been formulated as Ia although no rigorous proof was presented that they are indeed Ia rather than their structural isomers Ib.



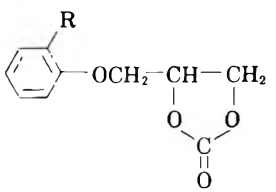
I

	A	B	R
a	H	—$CONH_2$	alkyl or alkoxyl
b	—$CONH_2$	H	alkyl or alkoxyl
c	H	H	alkyl or alkoxyl
d	H	—COCl	alkyl or alkoxyl
e	H	—$CONH_2$	methoxyl
f	—$CONH_2$	H	methoxyl

This investigation was undertaken in order to provide a satisfactory practical method for preparing the carbamates Ia and to determine by independent unequivocal synthesis whether the previous structural assignments have been correct.

Our results, reported here, are a new synthesis of Ia that is suitable for manufacturing purposes and a confirmation of the structure disclosed for the monocarbamate of 1,2-dihydroxy-3-(o-methoxyphenoxy) propane (Ie).[4] In addition we have discovered a hitherto unnoted rearrangement of carbamates Ie and If.

Synthesis. Monocarbamates of 1,2-dihydroxy-3-aryloxypropanes (Ic) have been prepared[2,4] by treating a solution of Ic with *one* mole of phosgene, which was assumed[5] to react preferentially with the primary alcohol group to yield the hydroxychlorocarbonates (Id) (not isolated); the latter were then converted by aqueous ammonia to Ia. Alternatively,[6] Ic was treated with phosgene under more severe conditions than above to yield the cyclic carbonate (or dioxolone) II, which, upon reaction



II R = alkyl or alkoxyl
IIa R = methoxyl

with liquid ammonia, yielded *the same monocarbamate as was obtained via the chlorocarbonate route.*

We have found that the dioxolones II are obtained in very high yield by ester interchange between Ic and diethyl carbonate in the presence of a catalytic amount of a metallic alkoxide.[7] The alkoxide may be added from an external source or may be formed *in situ, e.g.*, by dissolving sodium in molten Ic. Upon completion of the ester interchange, the alkoxide is destroyed by the addition of ammonium chloride and the excess diethyl carbonate is recovered by distillation. The residual crude cyclic carbonate is suspended in a suitable solvent (such as ethyl or isopropyl alcohol), ammonia gas is introduced, the system is closed and the mixture is stirred at room temperature for 8–16 hours. After the first several hours, the initial precipitate disappears and thereafter the somewhat turbid solution begins to deposit crystals copiously. Excess ammonia is expelled by heating, and from the cooled clarified solution[8] the crude product (60–80% yield) is recovered by filtration. Recrystallization from alcohols or ethyl acetate yields 60–65% of pure Ia.

(1) We wish to thank Dr. W. G. Bywater, S. B. Penick and Co., for reviewing this paper.

(2) H. L. Yale, E. J. Pribyl, W. Braker, F. H. Bergeim, and W. A. Lott, *J. Am. Chem. Soc.*, **72**, 3710 (1950).

(3) New and Nonofficial Remedies," J. B. Lippincott Co., 1956, p. 467.

(4) R. S. Murphey (to A. H. Robins Co., Inc.), U. S. Patent 2,770,649, Nov. 13, 1956.

(5) Reference (2), footnote 8.

(6) B. J. Ludwig and E. C. Piech, *J. Am. Chem. Soc.*, **73**, 5894 (1951).

(7) Other catalysts such as anhydrous potassium carbonate (*cf.* M. S. Morgan and L. H. Cretcher, *J. Am. Chem. Soc.*, **68**, 783 (1946)) are also effective.

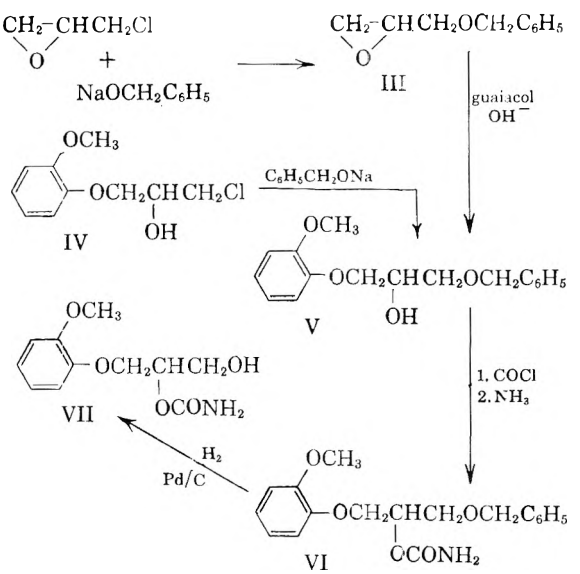
(8) An aliquot of the solution was taken to dryness *in vacuo*. The weight of the residue indicated quantitative conversion to monocarbamates. A sample of the residue was analyzed by Dr. Eric Smith, S. B. Penick and Co., using infrared spectroscopy and was found to contain 70–73% of Ic. All other infrared data reported here were likewise obtained by Dr. Smith.

The results of the ammonolysis of IIa were studied in detail. From the mother liquors remaining after the removal of pure Ie, melting in the range 93–97°, there was obtained by careful fractional crystallization, preferably from ethyl acetate, a quantity of isomeric carbamate, m.p. 117–119°, shown below to have the structure If. The higher-melting isomer was always obtained in minor yield, but its formation was not suppressed by conducting the ammonolysis at higher or lower temperatures or under pressure.[9]

The infrared spectrum of If differs substantially from that of Ie in the "fingerprint region." In particular If has a very strong absorption band at 10.17 μ which is completely absent in the spectrum of Ie.

Structural Investigation. As mentioned above, the reaction of one mole of phosgene with Ie was assumed to take place at the primary alcohol group and to lead from the chlorocarbonate to the primary monocarbamate. In order to confirm this structure, the synthesis of If pictured in Chart I was carried out.

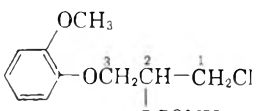
CHART I



V was prepared by either of two routes: (*a*) by condensation of epichlorohydrin with sodium benzylate followed by reaction of the resultant epoxide with guaiacol in the presence of a small amount of base;[10] (*b*) by condensation of Marle's chlorohydrin IV[10] with sodium benzylate. Route (*b*) gave the better yield of V. The identity of V from either source was verified by comparison of the refractive indices of the alcohols and the melting points and mixture melting points of the *p*-nitrobenzoates. Phosgenation of V followed by reaction of the unisolated intermediate chlorocarbonate with ammonia gave the benzyloxycarbamate VI. Hydrogenolysis in isopropyl alcohol at room temperature and atmospheric pressure led to VII, identical in melting point and infrared spectrum with If. The lower melting isomer is therefore the primary carbamate Ie as previously formulated.

Rearrangements. The rearrangement of β-glyceryl esters to α-glyceryl esters has been fairly extensively studied.[11] The acid-catalyzed rearrangement is considered to be an equilibration[11e,f] proceeding via a cyclic acetal intermediate. The preparation by independent synthesis[12] of certain analogous acetals has tended to support the mechanism proposed. However, the related rearrangements of propyl carbamates containing substituents on the carbon atom adjacent to the one bearing the carbamate function have not previously been reported.

We found that the *treatment of either Ie or If with thionyl chloride in pyridine led to one and the same chlorocarbamate*[13] for which we are suggesting the structure VIII on the basis of the fact that it reacts



VIII

with nitrous acid[14] to yield Marle's chlorohydrin IV, identified by its refractive index and by the melting point of its phenylurethane. Further, IV, on treatment with phosgene followed by ammonia, yields VIII. Since a rearrangement must have occurred during the reaction of Ie with thionyl chloride,[15] the validity of a degradative method for establishing the structure of α-hydroxycarbamates whose first step involves replacement of —OH by —Cl is open to serious question.[16,17]

(9) Experiments by D. Regenbogen, T. Swindlehurst, Jr., and K. K. Haber.

(10) E. R. Marle, *J. Chem. Soc.*, 316 (1912).

(11) (a) E. Fischer, *Ber.*, **53**, 1621 (1920); (b) H. Hibbert and N. M. Carter, *J. Am. Chem. Soc.*, **51**, 1601 (1929) and earlier literature cited therein; (c) B. F. Stimmel and C. G. King, *J. Am. Chem. Soc.*, **56**, 1724 (1934); (d) B. F. Daubert and C. G. King, *J. Am. Chem. Soc.*, **60**, 3003 (1938); (e) J. B. Martin, *J. Am. Chem. Soc.*, **75**, 5483 (1953); (f) P. E. Verkade and O. E. Van Lohuizen, *Koninkl. Med. Akad. Wetenschap., Proc., Ser. B.*, **56**, 324 (1953), *Chem. Abstr.*, **49**, 1557i (1955); (g) F. Aylward and P. D. S. Wood, *Chemistry and Industry*, 53 (1956).

(12) H. Hibbert and M. E. Greig, *Can. J. Research*, **4**, 254 (1931); *Chem. Abstr.*, **25**, 2973i (1931).

(13) Identity verified by infrared spectra.

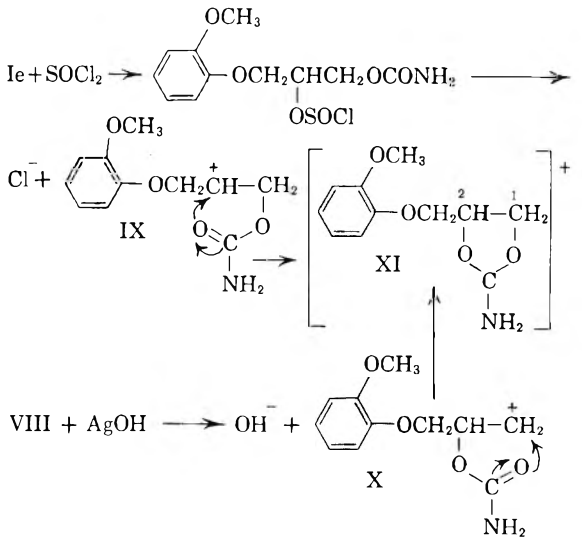
(14) It is taken for granted that in the nitrous acid reaction there is no disturbance of the bonds between C-1 and C-2 and their respective substituents so that further rearrangement during this deamination-decarboxylation is impossible.

(15) In a somewhat analogous situation which illustrates the migratory possibility of the chlorine atom, Suzuki and Inoue, *Proc. Imp. Acad. (Tokyo)*, **6**, 71 (1930), *Chem. Abstr.*, **24**, 4265 (1930) had found that both 1-chloro-2,3-dihydroxypropane and 2-chloro-1,3-dihydroxypropane give the same di-*p*-nitrobenzoyl derivative, namely 1,3-bis-*p*-nitrobenzoyl-2-chloropropane.

(16) H. Najer, P. Chabrier, and R. Giudicelli, *Bull. soc. chim. France*, 1142 (1954).

(17) M. M. Baizer, J. R. Clark and E. Smith, *J. Org. Chem.*, **22**, 1706 (1957).

A second shift occurs, at least in part, when VIII is treated with freshly prepared silver oxide in 50% isopropyl alcohol: a small yield of Ie was then the only definite product isolated from this reaction.[18] These rearrangements may be rationalized as indicated.



The acyclic carbonium ions IX-X which may be written to represent formally the initial products of reaction form a common cyclic transition cation, the aggregate of whose resonance forms can be represented by XI. When the environment contains Cl^-, attack appears to proceed predominantly at C-1; when OH^- is present, attack occurs at least in part at C-2.

In an effort to increase the overall yield of Ie from IIa attempts were made to rearrange If to Ie. When If (m.p. 117–119°) was heated under reflux in toluene containing a catalytic amount of *p*-toluenesulfonic acid, the melting point was lowered (94–112°) but upon recrystallization of the crude product only If could be recovered. When allowed to stand overnight at room temperature in chloroform saturated with hydrogen chloride, If was converted almost completely to its dioxolone; under the same conditions Ie yielded about 45% of the dioxolone and 42% of unchanged starting material. Neither If nor Ie reacted at room temperature with two moles of hydrogen chloride in isopropyl alcohol, but at 50–60° they were converted to the dioxolone in 33% and 40% yield respectively.[19] Obviously the carbamates were stable to small amounts of acid and in the presence of larger quantities lost ammonia and underwent recyclization.

The rearrangement of If with the aid of strong alkaline catalysts capable of supplying alkoxide or hydroxide ions, however, was successful. Stirring a suspension of If in isopropyl or ethyl alcohol overnight at room temperature with about two mole percent of catalyst in the presence of an ammonia atmosphere yielded about 60–65% of pure Ie.[20] Sodium ethoxide, sodium isopropoxide, sodium hydroxide, and benzyltrimethyl ammonium hydroxide were effective catalysts; piperidine was inoperative. After the rearrangement and removal of the pure Ie formed, the second crop material could again be rearranged to Ie in the same yield as above.

The virtual identity of the yield of Ie in a given period from either IIa or from If (or from Ie second crops), the observed liberation of ammonia during the rearrangement conducted in the absence of added gas, and the equilibration of Ie under similar conditions to a mixture from which 60–65% of Ie can be recovered strongly suggest that the rearrangement described here occurs *via* ring closure of the carbamates to IIa followed by ring-opening to give Ie and If in an approximately 7:3 ratio.

EXPERIMENTAL[21]

1-Carbamoxy-2-hydroxy-3-(o-methoxyphenoxy)propane (Ie). To 396.4 g. (2.0 mole) of molten (100°) 1,2-dihydroxy-3-(*o*-methoxyphenoxy)propane was added with stirring 5.6 g. (0.1 mole) of sodium methylate and 472 g. (4.0 mole) of diethyl carbonate. The mixture was heated with stirring, and the ethanol which formed distilled at 79–84°. When the internal temperature was 130°, heating was stopped, and 6 g. of ammonium chloride was added. The remainder of the ethanol and excess diethyl carbonate were then distilled *in vacuo* (25 mm.) to an internal temperature of 130°. The residue, crude dioxolone, IIa, was used without purification for the next step. A small amount of the residue was recrystallized from ethyl acetate; m.p. 68.4–69.0°.

Anal.[22] Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 59.04; H, 5.30.

The still warm (50°) crude molten IIa was mixed with 100 ml. isopropyl alcohol and added with stirring to a solution of 68 g. (4 mole) of ammonia in 2400 ml. of the alcohol. The mixture was stirred overnight at room temperature in a tightly stoppered flask. At first a dense almost unstirrable precipitate formed which dissolved and then reprecipitated. The 2-propanol and ammonia were removed *in vacuo* (120 mm.) on a steam bath. The residue was dissolved in 2400 ml. of hot ethyl acetate, treated with charcoal, and filtered. On cooling, 304 g. (63.4%) of Ie, m.p. 95–96.5° was obtained. No depression was observed in a mixture melting point with Ie prepared by Murphey's[4] procedure from 1,2-dihydroxy-3-(*o*-methoxyphenoxy)propane, phosgene, and ammonia. A second crop, 142 g. (28.4%), m.p. 90–105° was obtained. This substance was rearranged (see separate section on rearrangement) to yield 94 g. (19.5%) more of Ie, m.p. 94.5–96.0°. Another 8.4 g. (1.7%) was obtained by rearranging 15.4 g. (3.2%) of a third crop obtained from the mother liquors of the rearranged second crop; m.p. 94.5–96.0°. The total of Ie was 406.4 g. (84.6%).

Isolation of 1-hydroxy-2-carbamoxy-3-(o-methoxyphenoxy)-propane (I,). A kilogram of partly solvent-free (400 g. solid) mother liquor from several Ie preparations was recrystallized from 2 liters of ethyl acetate. The mother liquor was

(18) The reaction is complicated by the possibility that simultaneous dehydrohalogenation occurs.

(19) There was continuous evolution of carbon dioxide, indicating further decomposition of the dioxolone.

(20) The rearrangement also occurred when the mixture was heated under reflux for 24 hours, but in this case ammonia escaped and, although the yield of Ie was normal, no useful product could be obtained from the mother liquor.

(21) Melting points are corrected, boiling points are not.

(22) Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside, L. I., N. Y.

concentrated to 1200 ml. and chilled to give 113 g. of impure If, m.p. 116–118° which gave 85 g. m.p. 117–119° upon recrystallization from ethyl acetate.

Anal. Calcd. for $C_{11}H_{15}O_5N$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.96; H, 6.12; N, 5.98.

1-Carbamoxy-2-hydroxy-3-(o-methylphenoxy)propane (Mephenesin carbamate). In analogous manner 91 g. (0.5 mole) of 1,2-dihydroxy-3-(*o*-methylphenoxy)propane (Mephenesin), 1.4 g. of sodium methylate, 118 g. (1 mole) of diethyl carbonate were allowed to react. The crude dioxolone (II, R = CH_3) was again used without further purification. A sample of the dioxolone recrystallized from methanol melted at 95.4–96.0°.[23] To the crude dioxolone suspended in 300 ml. of dry toluene at 45° was added with stirring a solution of 17 g. (1 mole) of ammonia in 200 ml. of anhydrous 3 A alcohol. The mixture was stirred overnight at room temperature. The alcohol and ammonia were removed by distillation. The hot toluene solution was charcoaled and chilled to yield 101 g. (89.7%) of crude Mephenesin carbamates, m.p. 72–81°. For separation of 1-carbamoxy-2-hydroxy-3-(*o*-methylphenoxy)propane, the crude product was recrystallized from 505 ml. of 50% aqueous acetic acid to give 56.7 g. of a hydrate, m.p. 82–84°. Upon recrystallization from benzene with initial removal of water by azeotropic distillation, 54.8 g. (48.0%) of Mephenesin carbamate, m.p. 92–93.5° was obtained.[24]

Rearrangement of If to Ie. (*a*) To a mixture of 12.1 g. (0.05 mole) of If and 80 ml. of a saturated solution of ammonia in ethanol was added a solution of 0.056 g. (0.0025 g.-atom) of sodium in 20 ml. of anhydrous 3 A alcohol. The mixture was stirred overnight at room temperature in a tightly stoppered flask. The solid soon dissolved to form a cloudy solution. Ammonium chloride (0.2 g.) was added, the ethanol was removed, the residue dissolved in 50 ml. of hot 2-propanol, charcoaled, and chilled to give 7.7 g. (63.6%) of Ie, m.p. 94–96°; no depression in mixed melting point with Ie previously obtained. Similar results were obtained with isopropyl alcohol as a solvent, and with sodium hydroxide, and benzyltrimethylammonium hydroxide as the bases. No rearrangement occurred with piperidine or Dowex 1-X (hydroxide cycle).

(*b*) A mixture of 142 g. (0.59 mole) of second crop obtained in the initial Ie preparation described above, m.p. 90–105°, and a solution of 15 g. (0.88 mole) of ammonia and 0.56 g. (0.024 mole) of sodium in 1200 ml. of 2-propanol was stirred overnight at room temperature in a tightly stoppered flask. Ammonium chloride (0.8 g.) was added, and the 2-propanol and ammonia removed in vacuum (120 mm.) on a steam bath. The residue was dissolved in 700 ml. of hot ethyl acetate, charcoaled, and chilled to give 94 g. (66.1%) of Ie, m.p. 94.5–96.0°. From the mother liquor by concentration was obtained 15.4 g. of a third crop m.p. 114–116° which upon treatment with 1.8 g. of ammonia and 0.08 g. of sodium dissolved in 120 ml. of 2-propanol gave 8.4 g. (54.6%) of Ie, m.p. 94.5–96.0°.

Reaction of Ie and If with hydrogen chloride. (*a*) *In chloroform.* A mixture of 4.82 g. (0.02 mole) of Ie and 50 ml. of a saturated hydrogen chloride solution in chloroform was allowed to stand overnight at room temperature. After removal of chloroform and hydrogen chloride, the residue was recrystallized from benzene to give 2.0 g. (40%) of Ie, m.p. 92–94°. Evaporation of the mother liquor and recrystallization of the residue from 2-propanol yielded 2.0 g. (44%) of IIa, m.p. 66–67°; no depression in mixed melting point with previously obtained material. If gave mostly IIa; only a few crystals m.p. 108–112° were also isolated.

(*b*) *In 2-propanol.* A solution of 1.8 g. (0.044 mole) of hydrogen chloride in 32 ml. of 2-propanol and 4.82 g. (0.02 mole) of Ie was heated overnight at 55–60°. Ammonium chloride (0.91 g., 88.5%) was removed by filtration of the hot solution. Upon chilling, 1.5 g. (33.4%) IIa, m.p. (after recrystallization from 2-propanol) 68–70°, no depression in mixed melting point with previously obtained material. If gave 1.8 g. (40%) of IIa in a similar reaction.

1,2-Epoxy-3-benzyloxypropane (III). To 12.5 g. of fine sodium shot in 300 ml. of dry toluene was added 50.4 g. (0.5 mole) of benzyl alcohol. After stirring overnight at room temperature, the preparation of sodium benzylate was completed by refluxing until no more sodium remained. A thick suspension resulted to which 49.5 g. (0.52 mole) of epichlorohydrin was added after cooling to room temperature. The mixture was heated to 80° at which point a vigorous reaction started. The reaction subsided in 5–10 min., and reflux was continued for 1.5 hr. more. The mixture was cooled, water and dilute hydrochloric acid were added to neutrality, and the toluene layer separated. The aqueous was extracted with toluene. After drying (sodium sulfate) the toluene solution and distilling 14.7 g. (17.9%) of III, b.p. 76–81°/0.3–0.7 mm., n_D^{25} 1.5148–1.5150 was obtained.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.22; H, 7.37. Found: C, 73.25; H, 7.27.

1-Benzyloxy-2-hydroxy-3-(o-methoxyphenoxy)-propane (V). (*a*) To 2.48 g. (0.02 mole) of guaiacol in 10 ml. of toluene, in which 0.05 g. of sodium was dissolved, was added 1.64 g. (0.01 mole) of III in 10 ml. of toluene. After 7 hr. of reflux, the reaction mixture (cold) was extracted with 1*N* sodium hydroxide to remove excess guaiacol. The toluene solution gave upon distillation in high vacuum (Hickman still) 1.06 g. (36.8%) of V, n_D^{25} 1.5577; b.p. 120–130°/0.0005 mm. (bath temperature).

(*b*) To a solution of 0.67 g. (0.03 g. atom) of sodium in 25 ml. of dry benzyl alcohol was added 6.52 g. (0.03 mole) of 1-chloro-2-hydroxy-3-(*o*-methoxyphenoxy) propane (IV).[10] The mixture was heated to 110–120° for 24 hr., cooled, 100 ml. of ether added, and the salts filtered (1.92 g.; theory for sodium chloride, 1.76 g.). The ether solution was washed with water, dried (sodium sulfate) and distilled (Hickman still) to give 6.19 g. (71.5%) of V, b.p./0.5–5 μ 125–145° (bath temperature), n_D^{25} 1.5576–1.5594.

A sample was redistilled for analysis; b.p./1 μ 120° (bath temperature); n_D^{25} 1.5572.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 72.31, 72.06; H, 7.14, 7.10.

This substance was somewhat impure. The products from both reactions gave the same *p*-nitrobenzoate with *p*-nitrobenzoyl chloride and pyridine; m.p. 73–75°; no depression in mixed melting point.

Anal. Calcd. for $C_{24}H_{23}O_7N$: C, 65.89; H, 5.30; N, 3.20. Found: C, 65.08; H, 5.09; N, 3.27.

1-Benzyloxy-2-carbamoxy-3-(o-methoxyphenoxy)propane (VI). To a solution of 1.18 g. (0.012 mole) of phosgene in 15 ml. of dry toluene was added with stirring at 0–5° in 1 hr. 2.88 g. (0.01 mole) of V and 1.70 g. (0.014 mole) of dimethylaniline in 10 ml. of dry toluene. The mixture was stirred for 2.5 hr. at 0–5°, 10 ml. of ice water added, and the toluene layer removed. It was washed with 10 ml. of cold (5°) 2% hydrochloric acid, 10 ml. of ice water, and stirred with 2.2 g. (0.04 mole) of concentrated aqueous ammonia for 2 hr. at 0–10° and for 1 hr. at 25°. The toluene solution was washed with water, dried (sodium sulfate), and the toluene removed. The residue was triturated with hexane to give 3.4 g. of crystals m.p. 50–64°. Upon two recrystallizations from diisopropyl ether, 1.75 g. (52.8%) of VI, m.p. 74.5–76.0° was obtained.

Anal. Calcd. for $C_{18}H_{21}O_5N$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.20; H, 6.25; N, 4.33.

1-Hydroxy-2-carbamoxy-3-(o-methoxyphenoxy)propane (If). A solution of 0.29 g. (0.88 millimole) of VI in 18 ml. of 2-propanol was hydrogenated over 0.15 g. of 15% Pd/C at room temperature and atmospheric pressure. After 3 hr., 21.6 ml. (theory 19.7 ml.) of hydrogen was absorbed. The mixture was filtered and concentrated to a small volume. Upon cooling, 0.16 g. (76%) of crude If, m.p. 104–116° crystallized; m.p. 117–119° upon recrystallization from ethyl acetate. No depression in mixture melting point with

(23) Reported[6] 96–97°.

(24) Reported[6] 93–94°.

If isolated from Ie reaction mixtures was observed. The infrared absorption spectra of both were identical.[25]

1-Chloro-2-carbamoxy-3-(o-methoxyphenoxy)propane (VIII). (*a*) *From Ie.* To a mixture of 120.6 g. (0.50 mole) of Ie, 47.5 g. (0.50 mole) of dry pyridine, and 500 ml. of dry benzene was added with stirring at 0–10° in 1 hr. 65.4 g. (0.55 mole) of thionyl chloride. The mixture was then slowly heated to reflux until the evolution of sulfur dioxide stopped (constant internal temperature) and for 30 min. more. Water (200 ml.) was added to the cooled (25°) reaction mixture. Two liquid phases which crystallized rapidly formed. After filtration and washing with water and benzene, 111.4 g. (87.6%) of VIII, m.p. 105–106° was obtained.

(*b*) *From If.* To an ice cooled solution of 2.41 g. (0.01 mole) of If in 1.10 g. (0.014 mole) of dry pyridine was added 1.5 g. (0.0125 mole) of thionyl chloride. After 1 hr. at room temperature and several minutes on the steam bath, water was added to the cooled reaction mixture. The crude product was filtered and recrystallized from 2-propanol to give 1.67 g. (64.5%) of VIII, m.p. 104–104.5°; m.p. 105.5–106.5° after recrystallization (2-propanol).

(*c*) *From IV.* To a stirring solution 20 g. (0.0923 mole) of IV in 135 ml. of dry toluene at 20° was added 9.9 g. (0.10 mole) of phosgene in 100 ml. of dry toluene. After 1 hr. at room temperature, 12.1 g. (0.10 mole) of dimethylaniline in 75 ml. of toluene was added below 20°. The toluene solution was washed with ice water, ice cold 5% hydrochloric acid, ice water, and added, at 0–5°, to 170 ml. of concentrated aqueous ammonia. After 4 hr. at 0–5°, the product, 4 g. (16.6%), was filtered and recrystallized twice from 2-propanol; m.p. 105–106.5°.

All three preparations showed no depressions in mixed melting points.

All gave the same infrared absorption spectra.

Anal. Calcd. for $C_{11}H_{15}O_4ClN$: Cl, 13.65; N, 5.39. Found: Cl, 13.58; N, 5.5[illegible].

Reaction of VIII with nitrous acid. To a solution of 6.8 g. (0.026 mole) of VIII in 50 ml. of acetic acid was added with stirring at 80°C in 30 min. 5 g. of sodium nitrite in 10 ml. of water. The mixture was poured into 250 ml. of water, and extracted with benzene. The benzene was removed, and the residue recrystallized from fresh benzene to give 2.2 g. (32.4%) of unchanged VIII, m.p. 104–106° C. The mother liquor was distilled (Hickman still) to give 1.7 g. (30.7%) of IV, b.p./1 μ 90–100° (bath temperature), n_D^{25} 1.5430. A phenyl urethane m.p. 118.5–119.5° was obtained with phenyl isocyanate; no mixed melting point depression with the urethane from IV obtained by Marle's[10] method, m.p. 119.5–120.5°.

Reaction of VIII with silver hydroxide. A mixture of 5.6 g. (0.02 mole) of VIII and freshly precipitated silver hydroxide (from 3.4 g., 0.02 mole, of silver nitrate) in 60 ml. of 50% 2-propanol was refluxed for 4 hr. After filtration, removal of solvent, and benzene recrystallization, 1.0 g. of crystals m.p. 78–88° was obtained. Upon recrystallization from 2-propanol, 0.5 g. of Ie m.p. 94–96°C was obtained. No depression in mixed melting point with Ie previously prepared was observed.

(25) A Perkin-Elmer Model 21 was used.

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[CONTRIBUTION FROM THE MALLINCKRODT CHEMICAL LABORATORY AT HARVARD UNIVERSITY]

Cycloalkyl- and Secondary Alkyltin Compounds and Their Cleavage by Iodine in Benzene Solution

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The preparation of (cyclo-C_5H_9)$_2$SnR_2 and (cyclo-C_6H_{11})$_2$SnR_2 (R = Me, *n*-Bu, C_6H_5), (sec.-Bu)$_2$SnMe$_2$, (iso-Pr)$_2$SnR_2 (R = Me, *n*-Bu), and *n*-Bu$_2$SnMe$_2$ is described. These compounds were cleaved by the action of one equivalent of iodine in refluxing benzene solution to give mixtures of both possible cleavage products, except in the case of those compounds which contained phenyl groups. In the latter compounds only phenyl cleavage was observed. Twelve new organotin iodides of formula $R_2R'SnI$ are described.

Only two publications have thus far been concerned with cycloalkyltin compounds.[2,3] Similarly, organotin compounds containing secondary alkyl groups have been the subject of only a small number of studies.[4–6]

Little is known of the position of cycloalkyl and secondary alkyl groups in the cleavage series for organotin compounds. It has been established that the phenyl group is cleaved in preference to the cyclohexyl group by the action of concentrated hydrochloric acid on (cyclo-C_6H_{11})$_2$Sn(C_6H_5)$_2$,[3] thus showing that the latter group behaves like an aliphatic group. However, no experiments have been reported which determine the place of a cycloalkyl group in the aliphatic organotin cleavage series. It was stated by Luitjen and van der Kerk (ref. 6, p. 80) that secondary alkyl groups are cleaved from a tin atom prior to *n*-alkyl groups, but a quantitative product study of only one reaction[4]

$$(n\text{-}C_4H_9)_3SnC_4H_9\text{-}sec. + I_2 \longrightarrow (n\text{-}C_4H_9)_3SnI + sec.\text{-}C_4H_9I$$

appears to provide experimental proof for this generalization.

We now wish to report the preparation of a number of cyclopentyl-, cyclohexyl-, and secondary alkyltin compounds and the results of the cleavage of

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(2) E. Krause and R. Pohland, *Ber.*, **57**, 542 (1924).

(3) T. S. Bobashinskaya and K. A. Kocheshkov, *J. Gen. Chem.* (*U.S.S.R.*), **8**, 1850 (1938).

(4) Z. M. Manulkin, *J. Gen. Chem.* (*U.S.S.R.*), **14**, 1047 (1944).

(5) F. Caujolle, M. Lesbre, D. Meynier, and A. Blaizot, *Compt. rend.*, **240**, 1732 (1955).

(6) J. G. A. Luitjen and G. J. M. van der Kerk, *Investigations in the Field of Organotin Chemistry*, Tin Research Institute, Greenford, England, 1955, p. 105.

TABLE I

TETRAORGANOTIN COMPOUNDS PREPARED BY THE GRIGNARD METHOD

Compound	B.P. °C.	B.P. Mm. Hg	n_D^{25}	d_4^{25}	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
(Cyclo-C_5H_9)$_2$SnMe$_2$	76–77	0.3	1.5109	1.231	50.21	50.20	8.43	8.48
(Cyclo-C_5H_9)$_2$SnBu-*n*$_2$	128	0.3	1.5067	1.127	58.24	58.53	9.78	9.08
(Cyclo-C_5H_9)$_2$Sn(C_6H_5)$_2$	M.p.	49–50.2°			64.26	64.41	6.86	6.82
(Cyclo-C_6H_{11})$_2$SnMe$_2$	101–102	0.6–0.7	1.5184	1.208	53.37	53.16	8.96	8.72
	98	0.4						
(Cyclo-C_6H_{11})$_2$SnBu-*n*$_2$	143	0.45	1.5126	1.119	60.17	60.08	10.10	10.08
n-Bu$_2$SnMe$_2$	70	4.4	1.4640	1.124	45.67	45.92	9.20	9.38
sec.-Bu$_2$SnMe$_2$	68	5.5	1.4738	1.143	45.67	45.92	9.20	9.24
iso-Pr$_2$SnMe$_2$	68	29.0	1.4621	1.161	40.90	41.16	8.58	8.52
iso-Pr$_2$SnBu-*n*$_2$	102	2.9	1.4756	1.074	52.69	52.42	10.11	10.07

these compounds by the action of iodine in refluxing benzene solution.

The compounds (cyclo-C_5H_9)$_2$SnR$_2$ and (cyclo-C_6H_{11})$_2$SnR$_2$ (R = Me, n-Bu, C_6H_5), (sec.-C_4H_9)$_2$-SnMe$_2$, (iso-C_3H_7)$_2$SnR$_2$ (R = Me, n-Bu), and (n-C_4H_9)$_2$SnMe$_2$ were prepared by the reaction of the appropriate Grignard reagent with the various R$_2$-SnCl$_2$ compounds (R = Me, n-Bu, C_6H_5) in refluxing tetrahydrofuran (THF), which is now the solvent of choice in this laboratory for the preparation of tetraorganotin compounds.[7] The compounds prepared in this manner are listed in Table I, together with their physical constants and analytical data.

In several publications of Manulkin,[4,8] as well as in the work of Luitjen and van der Kerk (ref. 6, p. 120), it was reported that in the cleavage of mixed tetraorganotin compounds of types R$_2$SnR$'_2$ or R$_3$SnR$'$ with one equivalent of iodine in refluxing diethyl ether solution a preference is shown for only one of the two different groups present in the molecule. Thus of the two possible reactions, (a) and (b),

$$R_2SnR_2' + I_2 \longrightarrow \begin{cases} R_2R'SnI + R'I & (a) \\ RR'_2SnI + RI & (b) \end{cases}$$

only one was observed, and no mixtures of products were reported. However, Luitjen and van der Kerk pointed out (ref. 6, p. 80) that under more vigorous reaction conditions a mixture of the two possible products may well be obtained.

The results of our cleavage study, summarized in Table II, show that this is indeed the case. When the iodine cleavage reaction is carried out at the temperature of the refluxing benzene solution, a mixture of the two possible products results.[9] Exceptions to this generalization are provided when one of the groups is phenyl, in which case only phenyl cleavage occurs, or when one of the groups is trimethylsilylmethyl,[7b] where the other R group is cleaved and no attack on the Me$_3$SiCH$_2$-Sn link occurs even at 175° in the compounds (Me$_3$SiCH$_2$)$_2$-SnMe$_2$ and (Me$_3$SiCH$_2$)$_2$SnBu-n$_2$.

TABLE II

CLEAVAGE OF SOME TETRAORGANOTIN COMPOUNDS BY IODINE IN BENZENE

Compound	Cleavage Products, Yield, %
(Cyclo-C_5H_9)$_2$SnMe$_2$	Cyclo-C_5H_9I (36.0), cyclo-C_5H_9-Me$_2$SnI (33.8), (Cyclo-C_5H_9)$_2$-MeSnI (45.6)
(Cyclo-C_5H_9)$_2$SnBu-*n*$_2$	Cyclo-C_5H_9(*n*-Bu)$_2$SnI (39.3) + inseparable mixture of both tin cleavage products
(Cyclo-C_5H_9)$_2$Sn(C_6H_5)$_2$	C_6H_5I (91.6)[a]
(Cyclo-C_6H_{11})$_2$SnMe$_2$	Cyclo-C_6H_{11}I (45.4), cyclo-C_6H_{11}-Me$_2$SnI (44.2), (cyclo-C_6H_{11})$_2$-MeSnI (45.1)
(Cyclo-C_6H_{11})$_2$SnBu-*n*$_2$	Cyclo-C_6H_{11}(*n*-Bu)$_2$SnI (54.2), (Cyclo-C_6H_{11})$_2$(*n*-Bu)SnI (36.8)
(Cyclo-C_6H_{11})$_2$Sn(C_6H_5)$_2$	C_6H_5I (88.0)
iso-Pr$_2$SnMe$_2$	*iso*-PrMe$_2$SnI (50.6), *iso*-Pr$_2$MeSnI (23.4)[b]
sec.-Bu$_2$SnMe$_2$	*sec.*-BuMe$_2$SnI (25.0), *sec.*-Bu$_2$MeSnI (56.1)[b]
n-Bu$_2$SnMe$_2$	*n*-BuI (21.5), *n*-BuMe$_2$SnI (27.6), *n*-Bu$_2$MeSnI (65.5)

[a] Reaction with two equivalents of iodine. [b] Low total yield due to appreciable intermediate fraction in the distillation.

A study of Table II shows that no general pattern emerges from the data obtained. In the case of the mixed alkyl(cycloalkyl)tin compounds, the differences in the yields obtained of the two possible products is too small to permit any firm conclusions to be drawn. We can at this time offer no explanation for the apparent great difference in the rate of cleavage of the structurally similar isopropyl and secondary butyl groups.

These cleavage reactions were carried out in refluxing benzene solution because a preliminary experiment showed that no appreciable reaction occurred between iodine and dicyclohexyldimethyltin in diethyl ether solution during a 17-hour reflux period. The cleavage of di-*n*-butyldimethyl served

(7) (a) D. Seyferth and F. G. A. Stone, *J. Am. Chem. Soc.*, **79**, 515 (1957); (b) D. Seyferth, *J. Am. Chem. Soc.*, in press. (c) See alsoS . D. Rosenberg, A. J. Gibbons, and H. E. Ramsden, *J. Am. Chem. Soc.*, **79**, 2137 (1957).

(8) Z. M. Manulkin, *J. Gen. Chem.* (*U.S.S.R.*), **13**, 42, 46 (1943).

(9) This observation would seem to cast some doubt on the results claimed for the cleavage of *n*-Bu$_2$(*sec.*-Bu)Sn,[4] which was carried out in refluxing xylene solution.

TABLE III

ORGANOTIN IODIDES PREPARED BY CLEAVAGE WITH IODINE

Compound	B.P. °C.	B.P. Mm. Hg	n_D^{25}	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Cyclo-$C_5H_9Me_2SnI$	77	0.5	1.5758	24.38	24.50	4.38	4.27
$(Cyclo\text{-}C_5H_9)_2MeSnI$	115	0.7	1.5836	33.12	32.96	5.31	5.43
Cyclo-$C_5H_9(n\text{-}Bu)_2SnI$	125	0.4	1.5497	36.40	36.52	6.35	6.16[a]
Cyclo-$C_6H_{11}Me_2SnI$	86	0.65	1.5717	26.77	27.04	4.78	4.85
$(Cyclo\text{-}C_6H_{11})_2MeSnI$	134	0.4	1.5786	36.57	36.67	5.90	5.61[b]
Cyclo-$C_6H_{11}(n\text{-}Bu)_2SnI$	136	0.6	1.5494	37.96	37.95	6.60	6.42
$(Cyclo\text{-}C_6H_{11})_2(n\text{-}Bu)SnI$	160	0.7	1.5630	40.97	41.22	6.66	6.65
$n\text{-}BuMe_2SnI$	88–89	5.4	1.5467[c]	21.65	21.98	4.54	4.73
$n\text{-}Bu_2MeSnI$	82	0.35	1.5375	28.83	28.91	5.65	5.79
sec.-$BuMe_2SnI$	84	5.5	1.5510	21.65	22.39	4.54	4.74
sec.-Bu_2MeSnI	71	0.25	1.5498	28.83	28.64	5.65	5.54
iso-$PrMe_2SnI$	77–78	9.2	1.5553	18.84	19.02	4.11	4.11
iso-Pr_2MeSnI	96	7.6	1.5518	24.24	24.01	4.94	4.78

[a] % I: calcd., 29.59; found, 29.48. [b] % I: calcd., 29.73; found, 29.70. [c] Manulkin[8] reports b.p. 118–120° at 25 mm., n_D^{20} 1.5478.

to show that the more vigorous conditions and not the structure of the organotin reactants, which in all other cases contained bonds between tin and a secondary carbon atom, were responsible for the formation of a mixture of both possible cleavage products.

It seems clear that further experiments are needed in order to place cycloalkyl and secondary alkyl groups in the organotin cleavage series. It would be advisable to use milder reaction conditions, and it is hoped that cleavage with hydrogen bromide at low temperature may provide more conclusive results.

The organotin iodides which resulted from these cleavage reactions are listed in Table III.

EXPERIMENTAL[10]

Starting materials. Dimethyltin dichloride was prepared by the method of Smith and Rochow[11] and diphenyltin dichloride by the disproportionation of tetraphenyltin with tin(IV) chloride at 190°. Di-*n*-butyltin dichloride was obtained from Metal and Thermit Corp., Rahway, N. J. Tetrahydrofuran was distilled from potassium hydroxide pellets and subsequently from lithium aluminum hydride prior to use.

Preparation of tetraorganotin compounds. The preparation of dicyclohexyldimethyltin is given as an example of the procedure used.

Cyelohexylmagnesium chloride was prepared from 50 g. (0.42 mole) of cyclohexyl chloride and 9.7 g. (0.4 g.-atom) of magnesium turnings in 200 ml. of THF. Addition of a few drops of ethyl bromide served to initiate attack on the magnesium. To the Grignard solution was added 35 g. (0.16 mole) of dimethyltin dichloride in 70 ml. of THF at such a rate that a gentle reflux was maintained. After the addition was completed, the reaction mixture was stirred and heated at reflux for 22 hr. The mixture was then cooled to room temperature and hydrolyzed with 60 ml. of saturated ammonium chloride solution. The organic layer was decanted and the salts were washed with three portions of diethyl ether, the washings being added to the organic layer. Distillation of the organic layer, after removal of the solvents at atmospheric pressure, gave 41.3 g. (82%) of dicyclohexyldimethyltin, b.p. 98° at 0.45 mm. to 101° at 0.6 mm.

Experimental details of the other preparations are given in Table IV.

TABLE IV

TETRAORGANOTIN COMPOUNDS BY THE GRIGNARD METHOD. EXPERIMENTAL

Tin Halide	Moles	Alkyl Halide	Moles	Yield of R_2SnR_2', %
Me_2SnCl_2	0.16	Cyclo-C_5H_9Br	0.4	51.2
$n\text{-}Bu_2SnCl_2$	0.148	Cyclo-C_5H_9Br	0.4	83.5
$(C_6H_5)_2SnCl_2$	0.145	Cyclo-C_5H_9Br	0.4	81.7
Me_2SnCl_2	0.16	Cyclo-$C_6H_{11}Cl$	0.4	82.0
Me_2SnCl_2	0.16	Cyclo-$C_6H_{11}Br$	0.4	69.0
$n\text{-}Bu_2SnCl_2$	0.148	Cyclo-$C_6H_{11}Br$	0.4	71.5
$(C_6H_5)_2SnCl_2$	0.145	Cyclo-$C_6H_{11}Br$	0.4	82.0
$n\text{-}Bu_2SnCl_2$	0.312	CH_3Br	1.0	90.0
Me_2SnCl_2	0.34	*sec.*-C_4H_9Br	1.0	86.5
Me_2SnCl_2	0.34	*iso*-C_3H_7Br	1.0	76.6
$n\text{-}Bu_2SnCl_2$	0.312	*iso*-C_3H_7Br	1.0	88.1

Crude dicyclopentyldiphenyltin was obtained as an orange oil after removal of the solvent. It was crystallized from a methanol-ethanol mixture at −78°. Dicyclohexyldiphenyltin similarly was obtained as an oil. Addition of ethanol caused crystallization to give a white solid, m.p. 109–113°. Recrystallization from ethanol gave pure material, m.p. 118–120° (lit.[3] m.p. 119–120°).

Iodine cleavage reactions. The cleavage of dicyclohexyldimethyltin is described to illustrate the procedure used. To a solution of 34.0 g. (0.108 mole) of dicyclohexyldimethyltin in 300 ml. of benzene was added 27.45 g. (0.108 mole) of iodine. The iodine was completely consumed at the end of a reflux period of 1 hr. The benzene was then distilled at atmospheric pressure. Fractional distillation at reduced pressure gave: (1) cyclohexyl iodide, b.p. 42° at 1 mm., n_D^{25} 1.5462 (lit.[12] n_D^{20} 1.5470), 10.3 g.; (2) a small intermediate cut; (3) cyclohexyldimethyltin iodide, b.p. 86° at 0.65 mm., 17.1 g.; (4) a small intermediate cut; (5)

(10) Analyses were performed by the Schwarzkopf Microanalytical Laboratories, Woodside 77, N. Y. Melting points were determined using a Hershberg melting point apparatus.

(11) A. C. Smith, Jr., and E. G. Rochow, *J. Am. Chem. Soc.*, **75**, 4103 (1953).

(12) P. G. Stevens, *J. Am. Chem. Soc.*, **56**, 450 (1934).

dicyclohexylmethyltin iodide, b.p. 136–140° at 0.65 mm., 20.8 g.

In the cleavage of dicyclopentyldimethyltin the cyclopentyl iodide isolated was characterized: b.p. 41–43° at 6.8 mm., n_D^{25} 1.5465 (lit.[13] n_D^{25} 1.5457).

Dicyclopentyldiphenyltin was treated with two equivalents of iodine and dicyclohexyldiphenyltin with one equivalent. The iodobenzene resulting from the cleavage was recovered by distillation. The organotin cleavage products were not isolated.

(13) M. T. Rogers and J. D. Roberts, *J. Am. Chem. Soc.*, **68**, 843 (1946).

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[CONTRIBUTION FROM THE RAHWAY RESEARCH LABORATORY OF THE METAL AND THERMIT CORP.]

Preparation of Vinylmagnesium Chloride and Some Homologs[1]

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Vinylmagnesium chloride and several of its homologs were prepared. Among the homologs were 1-propenyl, 2-propenyl, 1-but-1-enyl, 2-but-2-enyl, 4-methyl-2-pent-1-enyl, and 1-cyclohexenyl magnesium chlorides. Several characterizing reactions of vinylmagnesium chloride were carried out.

Both vinyl chloride and vinyl bromide have long been considered to be unreactive toward magnesium to form vinylmagnesium halides. Krestinsky[2] reported a lack of success in preparing vinylmagnesium bromide in ether. Austerweil,[3] however, reported a successful Wurtz reaction of vinyl bromide with 2-chloropropene to form isoprene. A patent[4] issued to the General Electric Co. showed a more recent use of vinylmagnesium bromide in ether to form vinylsilanes. Quite recently, Normant[5] has shown in excellent researches the attaining of good results using tetrahydrofuran as solvent for the preparation of vinylic magnesium bromides in high yield. In many subsequent papers Normant and co-workers have shown the use of several vinylic magnesium bromides to prepare olefinic derivatives.[6–16] However, Braude in attempts to repeat Normant's preparation of 1-isobutenylmagnesium bromide reported complete lack of success.[17]

This article is in part confirmation of Normant's preparation of vinylic magnesium bromides. Since Normant has not shown the generality of this preparation by extending it to vinylic chlorides,[18] we would like to do so here in reporting work done independently.[19,20]

Vinylmagnesium chloride was prepared by passing vinyl chloride into tetrahydrofuran and active magnesium. The Gilman titration[21] showed a 98.5% yield of Grignard reagent and recovery of magnesium showed a 94.5% consumption. Carbonation yielded acrylic acid. These results appear to be the first preparation of vinylmagnesium chloride.

Vinyl chloride is remarkably soluble in tetrahydrofuran and this property may be used to advantage in preparing vinylmagnesium chloride in techniques similar to those used for arylmagnesium

(1) Parts of this paper were presented at the 130th National Meeting of the AMERICAN CHEMICAL SOCIETY, Atlantic City, September, 1956.

(2) W. Krestinsky, *Ber.*, **55B**, 2770–2774 (1922).

(3) G. Austerweil, German Patent **245,180** (1912); [*Chem. Abstr.* **6**, 2334 (1912)].

(4) J. Pyle, U. S. Patent **2,448,391** (1948); [**43**, 1223 (1949)].

(5) H. Normant, *Compt. rend.*, **239**, 1510 (1954).

(6) H. Normant, *Compt. rend.*, **239**, 1811 (1954).

(7) H. Normant, *Compt. rend.* **240**, 314 (1955).

(8) H. Normant, *Compt. rend.*, **240**, 440 (1955).

(9) H. Normant, *Compt. rend.*, **240**, 631 (1955).

(10) H. Normant, *Compt. rend.*, **240**, 1111 (1955).

(11) H. Normant, *Compt. rend.*, **240**, 1435 (1955).

(12) J. Ficini, *Bull. soc. chim. France*, 119 (1956).

(13) H. Normant and C. Crisan, *Compt. rend.* **240**, 1946 (1955).

(14) H. Normant and P. Maitte, *Bull. soc. chim. France*, 951, 1439 (1956).

(15) H. Normant and J. Ficini, *Bull. soc. chim. France*, 1441 (1956).

(16) a. V. Levy and H. Normant, *Compt. rend.*, **242**, 202 (1957); b. H. Normant and G. Martin, *Bull. soc. chim. France*, 429, 728 (1957).

(17) E. A. Braude, *J. Chem. Soc.*, 3324 (1955).

(18) *Chem. Abstr.*, **50**, 228 (1956) the abstract of ref. 5 states vinylmagnesium chlorides can be made, which is true, although Normant did not so state in ref. 5.

(19) In extensive private communications with Normant during 1955 it was determined that his work and ours were initiated at about the same time, very much prior to 1954.

(20) a. This work is covered by patent applications. b. H. E. Ramsden and A. E. Balint, Brit. Pat. **777,158** (June 19, 1957).

(21) H. Gilman, H. A. Zoellner, and J. B. Dickey, *J. Am. Chem. Soc.* **51**, 1576 (1929).

chlorides.[22] Addition of the vinyl chloride–tetrahydrofuran solution to magnesium, activated by ethyl bromide in the presence of a few milliliters of the solution, leads to a rapid initiation and reaction to give high yields (above 90% consistently) of vinylmagnesium chloride, in a few hours time. However, purity of the vinyl chloride is essential and particularly important is very low contamination by the phenol[23] usually used to stabilize the vinyl chloride.

Vinylmagnesium chloride in tetrahydrofuran is relatively stable. It has been stored for as much as a month with no loss of activity. No polymerization occurs during either preparation or storage. However, if the tetrahydrofuran is removed by vacuum distillation without a concomitant replacement by another solvent, a violet decomposition reaction sets in when the solution becomes quite concentrated. In one such reaction, a serious fire resulted when the rapidly rising internal pressure blew out the thermometer well. Use of a displacing solvent such as toluene or cumene avoids this decomposition.

In its reactions, vinylmagnesium chloride appears to be at least as reactive as ethylmagnesium chloride. Reactions with carbonyl functions, as in aldehydes, ketones, and esters, with metal salts such as tin, lead, silicon,[24] antimony, aluminum, and other metal and metalloid halides, with olefin oxides, alkyl halides, and with other reactive molecules have been carried out.

With paraformaldehyde and with ethylene oxide, vinylmagnesium chloride yields the expected allyl alcohol and 3-buten-1-ol. It gives a strong positive reaction in the well known Gilman Color Test I.[25]

Several compounds prepared using vinylmagnesium chloride are identical to compounds prepared by Normant with vinylmagnesium bromide. A comparison of yields obtained with vinylmagnesium chloride and vinylmagnesium bromide is shown in Table I. They illustrate that the two reagents give about the same yields of products.

TABLE I

Compound Prepared	Yields, % Vinylmagnesium chloride	Yields, % Vinylmagnesium bromide
Phenylvinylcarbinol	54 (85)[a]	67[7]
Propylvinylcarbinol	75	85[7]
Dimethylvinylcarbinol	79.5[b]	74[7]
Divinylcarbinol	68.5 (90)[a]	60[10]
Linalool	80.5	83[9]

[a] The yields in parentheses have been obtained in more recent work. [b] The dimethylvinylcarbinol easily dehydrated to form isoprene.

In agreement with Normant,[5] we have found that 2-methyltetrahydrofuran and tetrahydropyran are suitable solvents for this preparation. Dihydropyran and ethyl tetrahydrofurfuryl ether also function as effective solvents, although the dihydropyran is too unstable to be useful in further reactions.

In addition to vinyl chloride several other homologs were tried to test the generality of the preparation. These compounds and the yields of Grignard reagents prepared from them are summarized in Table II.

TABLE II

Reactant	Grignard Yield,[a] %
1-Chloropropene-1	10
2-Chloropropene	24
1-Chlorobutene-1	15
2-Chlorobutene-2	50
1,1-Dichloropropene-1	27[b]
2 Chloro-4-methylpentene-1	88
1 Chlorocyclohexene-1	19

[a] Determined by Gilman titration.[21] [b] Accompanied by an evolution of gas.

With these compounds it is rather interesting that yields with non-terminal chlorines (*i.e.*, those on secondary carbons) are higher than with terminal chlorines. Also, of interest is their apparent lower reactivity than that of vinyl chloride. This appears somewhat contrary to experience with the bromo compounds[26] where the higher homologs are more amenable to forming Grignard reagents.

EXPERIMENTAL

All reactions were carried out in a static atmosphere of dry nitrogen. The vinyl chloride is the commercial grade as supplied by the Matheson Co. The magnesium turnings are those commercially available from the Dow Chemical Co. Tetrahydrofuran was used as supplied by the DuPont Co. Tetrahydrofuran should be free of peroxides and water. Stabilized material as supplied by DuPont is peroxide-free and functions as well as carefully purified tetrahydrofuran.[22] Constant care is necessary to guard against the hazard of peroxides with this solvent.

Yields of Grignards were determined by a modification of the Gilman titration reported elsewhere.[21] Melting points as given were determined on the Fisher Johns apparatus and the point of total melting is given here. All compounds were recrystallized several times to give as narrow a range of melting as possible. Boiling points were obtained during distillation through a 15-inch glass-helices-packed column with a variable take-off head.

Vinylmagnesium chloride. Preparation method I. Into a 1000-ml., 3-neck flask, equipped with stainless steel anchor stirrer, thermometer, 3-way Y adapter with a gas inlet tube (dipping under the liquid surface), and reflux condenser topped by a static nitrogen atmosphere system, were placed

(22) H. E. Ramsden, A. E. Balint, W. R. Whitford, J. J. Walburn, and R. Cserr, *J. Org. Chem.*, **22**, 1202 (1957).

(23) Private communication from the Matheson Co. (1954).

(24) S. D. Rosenberg, J. J. Walburn, T. D. Stankovich, A. E. Balint, and H. E. Ramsden, *J. Org. Chem.*, **22**, 1200 (1957).

(25) H. Gilman and F. Schultz, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(26) M. S. Kharasch and O. Reinmuth, *Grignard Reaction of Nonmetallic Substances*, Prentice-Hall, New York, 1954, p. 37.

magnesium turnings (1 g.-atom) and 300 ml. of tetrahydrofuran. After the system had been flushed out with nitrogen, an iodine crystal and 2 ml. of ethyl bromide were added to activate the magnesium, and vinyl chloride was passed in through the gas inlet tube. Intermittent heat from an infrared lamp was applied. After 35 min. the temperature was 35° and a light green color appeared, deepening to a deep green, gradually changing to blue, and finally to murky white. The temperature, meanwhile, increased to 42°. After 51 min. the temperature had reached 52° (without any external heating after the temperature had reached 35°). Heat was applied to bring the mixture to reflux. A deep brown color began developing and the heating was continued for 2.5 hr., after which the reaction was stopped overnight. In the morning the reaction mixture was rapidly heated to 50° and heating removed. Reaction of vinyl chloride with the magnesium maintained the temperature between 50 and 52° until completion of reaction 3.75 hr. later when the temperature fell sharply. The reaction mixture was diluted with tetrahydrofuran to 1000 ml. in a volumetric flask and 20-ml. aliquots titrated by a modification of the Gilman titration[21] (addition to 50 ml. portions of 0.5*N* H_2SO_4 and the excess H_2SO_4 back titrated using 0.2*N* NaOH and bromo-cresol purple indicator) to obtain a yield of 98.5%. Magnesium (1.38 g.) was recovered, indicating use of 94.5% of the magnesium.

Vinylmagnesium chloride. Preparation method II (preferred technique). A. *Preparation of solution.* Vinyl chloride gas was passed into tetrahydrofuran (984.0 g.; 13.67 moles) in a weighed 2-neck flask, equipped with a Scott condenser (cooled by Dry Ice–acetone mixture) and a gas inlet tube, until about 3.5 moles were absorbed (actually 239.4 g. were absorbed).

B. *Preparation of Grignard.* Ethyl bromide (4 ml.) was added to a mixture of 3.0 g.-atoms (72.9 g.) of magnesium turnings and 15 ml. of the vinyl chloride–tetrahydrofuran solution in a 3000-ml. 3-neck flask equipped with a stainless steel anchor stirrer, thermometer, Scott condenser (cooled with Dry Ice–acetone), and a large capacity dropping funnel. Initiation was immediate; the vinyl chloride solution was then added as rapidly as possible, controlling the temperature of reaction at about 50° by the rate of addition. After completion of addition, the mixture was heated for 0.75 hr. at 50° and then cooled. This was used as a stock solution. Titration of a 10 ml. sample showed it to contain 22.6 mil. equiv. of vinylmagnesium chloride. The yield in this procedure varies from 90–98% depending on the technique.

Allyl alcohol. Trioxymethylene (90.1 g.; 1 mole) was slurried in 150 ml. of tetrahydrofuran in a cooled stirred flask. To this slurry was added 442 ml. (equivalent to 1 mole) of the stock solution of vinylmagnesium chloride. Stirring was continued for 2.0 hr. at which time a negative Color Test I was obtained. Sulfuric acid (28 ml. concd. H_2SO_4 and 100 ml. H_2O) was then added and the mixture filtered. The precipitate was slurried in 250 ml. tetrahydrofuran and filtered. The filtrates were combined and distilled. After removal of solvent, a large (60 ml.) fore-cut boiling 66–86° was obtained and a 10 ml. fraction boiling at 97–99° (n_D^{25} 1.4125) was obtained. Allyl alcohol has n_D^{20} 1.4134.[27]

A repetition of this procedure gave 30.3% yield, α-naphthylurethane, m.p. 107° (Lit. 109°[28]); phenylurethane, m.p. 70° (Lit. 70°[28]).

Carbonation. A solution of vinylmagnesium chloride in tetrahydrofuran (from 1.0 g.-atom of magnesium and prepared by gaseous method) was added to a large excess of powdered Dry Ice. After evaporation of the Dry Ice, 1.1 moles of hydrochloric acid (37% solution), 500 ml. water, and 500 ml. of ethyl ether were added and the two layers separated. The aqueous layer was extracted three times with 100-ml. portions of ether, the extracts combined with the organic layer, and the whole distilled. Twenty milliliters of acrylic acid (with n_D^{22} 1.4223)[27] was obtained, boiling at about 140°.

Repetition of this procedure using vacuum distillation yielded 37.0 g. (52.6%) of acrylic acid; b.p. 81° (88 mm.).

3-Butenol-1. To vinylmagnesium chloride (1 g. atom magnesium and 1 mole vinyl chloride in 3.0 moles tetrahydrofuran) was added 1 mole (44 g.) of ethylene oxide in 150 ml. of tetrahydrofuran at 20°. After 1 hr. further stirring, the solvent was evaporated under an aspirator vacuum, the paste treated with 550 ml. of water and 100 ml. of 37% HCl. The organic layer was separated and combined with two 100-ml. ethyl ether extracts of aqueous layer. This solution was neutralized by saturated $NaHCO_3$ solution, and dried over K_2CO_3. Solvents were removed under vacuum (0.2 g. hydroquinone added) and the residue fractionated through a Todd column. The product fraction which came over at 50° (40 mm.) weighed 48.3 g. (67.1%); n_D^{20} 1.4221; phenylurethan, m.p. 21°. The literature gives n_D^{20} 1.422;[29] phenylurethane, m.p. 23.5–24.5.[30]

Phenylvinylcarbinol. To a stirred solution of 1 mole of vinylmagnesium chloride in tetrahydrofuran was added, dropwise, 104.5 g. (0.9 mole) of freshly distilled benzaldehyde (Matheson). Stirring was continued for 1 hr., the mass was cooled and hydrolyzed by addition of saturated ammonium chloride solution. The layers were separated, the organic layer treated with dilute sodium bicarbonate solution and distilled at atmospheric pressure until the tetrahydrofuran was removed. The residue was distilled under reduced pressure to yield 73.5 g. (60%) of phenylvinyl carbinol; b.p. 76–77° (3 mm.);[15] n_D^{25} 1.5417 (lit.[31] $n_D^{14.5}$ 1.5464); *p*-nitrobenzoate, m.p. 47° (lit.[32] d. 48°).

Propylvinylcarbinol. To eight-tenths mole vinylmagnesium chloride was added, dropwise, 58 g. (0.8 mole) of *n*-butyraldehyde at 0–10°. Stirring was continued for 1 hr. After hydrolysis with 200 ml. of saturated ammonium chloride solution, the organic layer (and two 100-ml. portions of tetrahydrofuran used to extract the aqueous phase) was distilled to remove tetrahydrofuran and then distilled at about 100 mm. The fraction boiling at 77–79° (96 mm.) weighed 60.3 g. (75%); Iodine no. 246 (calcd. 254); n_D^{25} 1.4272. (Lit.[7] n_D^{18} 1.4297); *p*-Nitrobenzoate, m.p. 59° (lit.[33] 60–62°).

Dimethylvinylcarbinol and isoprene. To vinylmagnesium chloride (prepared from 2 moles vinyl chloride, 2.0 g. atoms of magnesium, and 6.0 moles of tetrahydrofuran) was added 116.0 g. (2.0 moles) of acetone and the mixture was stirred for 1 hr. After hydrolysis with 166 ml. of 12*N* hydrochloric acid in 500 ml. of water, the organic layer (and two 100-ml. portions of xylene used to extract the aqueous phase) was fractionated in a Todd column. A fraction distilling at 95–96° was obtained, weighing 135.7 g. (79.5%); n_D^{25} 1.4189 (Lit.[34] n_D^{20} 1.4125); d_4^{20} 0.8270, (lit.[35] 0.8255).

This fraction was distilled from 12 g. aniline hydrobromide

(27) Handbook of Chemistry and Physics, 31st ed., Chemical Rubber Publishing Co., Cleveland, Ohio.

(28) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, 3rd ed., John Wiley and Sons, Inc., New York, 1948, p. 226.

(29) H. Waldman and R. Petri, *Chem. Ber.*, **83**, 287 (1950).

(30) I. Heilbron, *Dictionary of Organic Compounds*, **Vol. I**, Oxford University Press, New York, 1953, p. 55.

(31) E. A. Braude, E. R. H. Jones, and E. S. Stern, *J. Chem. Soc.*, 401 (1946).

(32) I. Heilbron, *Dictionary of Organic Compounds*, **Vol. IV**, p. 98–99.

(33) I. Heilbron, *Dictionary of Organic Compounds*, **Vol. II**, p. 678.

(34) I. N. Nazarov, V. N. Rakcheeva, and L. I. Shmonina, *Zhur. Obshchet. Khim.* 22, 442 (1952 [*Chem. Abstr.*, 47, 5370a (1953)].

(35) F. J. Soday, U. S. Patent 2,382,031; [*Chem. Abstr.*, 40, 3469 (1946)].

TABLE III

Reactant, Wt., Moles	Magnesium, G.-Atoms	Reaction Time, Hr.		Yield, % (by Titration)	Remarks
		Addition	After addition		
2-Chloropropene 76.5 g. (1.0)	24.3 g. (1.0)	1.0	25.5	24	Heated throughout. Mg used, 8.3 g. (34.3%)
1-Chlorobutene-1[a] 40.6 g. (0.45)	11.6 g. (0.45)	7.0	16.3	14.8	Heated throughout. Mg used, 25.8%
2-Chlorobutene-2[b] 45.3 g. (0.5)	12.2 g. (0.5)	3.0	5.3	49.7	Heated throughout. Mg used, 56.5%
2-Chloro-4-methylpentene-1[c] 59.3 g. (0.5)	12.2 g. (0.5)	1.25	2.25	87.8	Heated throughout. Mg used, 93.3%
1-Chlorocyclohexene 58.3 g. (0.5)	12.2 g. (0.5)	1.66	13.2	19.2	Heated throughout. Mg used, 28.7%
1,1-Dichloropropene (1.0) 111.0 g.	24.3 g. (1.0)	1.66	1.25	26.7[d]	

[a] Prepared by KOH/ethylene glycol dehydrochlorination of 1,1 dichloropropane.[40] [b] Prepared from methyl ethyl ketone and PCl_5.[40] [c] Prepared from methyl isobutyl ketone and PCl_5;[40] b.p. 37–39.5 (65 mm). [d] Negative color test. Allene or methylacetylene was given off copiously; this material formed a bromide of 87% Br content; n_D^{25} 1.5121.

under a 4-inch packed column. Material boiling at 33–36° was removed to yield 64.7 g. (47.5% based on magnesium, 58.5% based on dimethylvinylcarbinol) of isoprene; n_D^{20} 1.4211 (lit.[36] 1.4216); tetrabromide, b.p. 157° (lit.[37] 155–160).

Divinylcarbinol. To 1.0 mole of vinylmagnesium chloride in tetrahydrofuran was added 27.0 g. (0.45 mole) of methyl formate at 0–5°. After 1.0 hr. further stirring, 250 ml. of saturated ammonium chloride solution was added. The organic layer (and three 75-ml. portions of tetrahydrofuran used to extract the aqueous layer) was distilled (0.1 g. hydroquinone added) at 100 mm. to remove tetrahydrofuran. The fraction boiling at 56° (80 mm.) weighed 20.9 g. (55%). Five more grams were obtained on refractionating the forerun to bring the total yield to 25.9 g. (68.5%); n_D^{17} 1.4474 (Lit.[38] n_D 1.4400); α-naphthylurethane; m.p. 100° (lit.[37] 100–101°). Repetitions of this procedure have given yields of 90%.

Linalool. Two moles (252.0 g.) of methyl heptenone (2-methylhept-2-en-6-one from Trubek Laboratories) were added to vinylmagnesium chloride (prepared from 53.5 g., 2.2 g.-atoms, of magnesium, 137.5 g., 2.2 moles, of vinyl chloride, and 475 g., 6.6 moles, of tetrahydrofuran), which had been freed of magnesium particles by filtration, over a period of 1.5 hr. at a temperature of 30–35°. After 1 hr. of further stirring, the mixture was cooled and hydrolyzed with 172 ml. of 37% hydrochloric acid and 522 ml. of water. The organic layer was washed with 200 ml. of saturated sodium bicarbonate solution and with water, dried over anhydrous sodium sulfate, filtered, and vacuum-distilled. A fraction was obtained (b.p. 65–68° at 6 mm.) which weighed 246.7 g. (80.5%); n_D^{22}, 1.4609 (lit.[39] n_D^{20} 1.462). A further 29.5 g. (9.6%) was recovered from forerun and holdup.

1-Propenylmagnesium chloride. A solution of 1-chloropropene (76.5 g., 1 mole) in 3.0 moles of tetrahydrofuran was added dropwise to 24.3 g. (1 g.-atom) of magnesium turnings (activated by 2 ml. of ethyl bromide and 15 ml. of the solution). Heating at reflux was necessary for the 5.5 hr. required for addition and for 17.5 hr. afterwards. A yield of 9.3% (titration) was obtained.

Homologs preparations. Preparations of the homologs are summarized in Table III because of their similarity to the preparation of 1-propenylmagnesium chloride. The tetrahydrofuran was always used in the ratio of 3 moles to one of chloride.

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(36) I. Heilbron, **Vol. III,** p. 106.
(37) Beilstein, **Vol. I,** p. 138.
(38) I. Heilbron, **Vol. IV,** p. 61.
(39) P. Z. Bedoukian, *Perfumery Synthetics and Isolates*, D. Van Nostrand Co., Inc., New York, 1951., p. 292.
(40) T. L. Jacobs, *Org. Reactions*, **V,** 20 (1949).

[CONTRIBUTION FROM THE EAHWAY RESEARCH LABORATORY OF THE METAL AND THERMIT CORP.]

Preparation of Some Arylchlorosilanes with Arylmagnesium Chlorides[1]

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Diphenyldichlorosilane, phenylmethyldichlorosilane, phenylvinyldichlorosilane, phenyltrichlorosilane, *p*-chlorophenyltrichlorosilane, bis-*p*-chlorophenyldichlorosilane, bis-*p*-methoxyphenyldichlorosilane, and bis-*p*-ethylphenyldichlorosilane have been prepared by the reaction of arylmagnesium chlorides with appropriate silicon chlorides.

Since 1904 when the use of a Grignard reagent to prepare organosilicon compounds was reported by Kipping[2] and Dilthey,[3] this method of synthesis of organosilanes has undergone considerable refinement in techniques, and has become a very versatile and popular method for the preparation of these compounds on a laboratory scale. The development of arylmagnesium chloride reagents in this laboratory[4] has afforded the opportunity of preparing arylchlorosilanes utilizing comparatively inexpensive chlorobenzene and some of its derivatives.

As in almost any reaction of a Grignard reagent with silicon tetrachloride to form partially substituted arylchlorosilanes, it was found that a group of successive substitution products was formed.[5] By choosing proper reaction concentrations and temperatures it was possible, in most cases, to produce the desired arylchlorosilanes in good yields. Diphenyldichlorosilane was prepared in a 77% yield by the addition of 2.0 equivalents of phenylmagnesium chloride to 0.9 equivalent of silicon tetrachloride. Using virtually identical conditions,

$$C_6H_5MgCl + SiCl_4 \xrightarrow[\text{Reflux}]{\text{Heptane}} (C_6H_5)_2SiCl_2$$

it was possible to prepare bis-*p*-chlorophenyldichlorosilane, bis-*p*-methoxyphenyldichlorosilane, and bis-*p*-ethylphenyldichlorosilane from the appropriate arylmagnesium chloride[4] in tetrahydrofuran and silicon tetrachloride in heptane.

The preparation of phenyltrichlorosilane by the addition of 2.0 equivalents of phenylmagnesium chloride to 2.2 equivalents of silicon tetrachloride led to the formation of a fair amount of diphenyldichlorosilane (17%) as well as the desired product (47%). The use of a larger amount of silicon tetrachloride did not seem to change the product balance and, indeed, it complicates the solvent recovery problem because of the proximity of the boiling points of silicon tetrachloride (57.6°) and tetrahydrofuran (65.5°). A similar problem was encountered in the preparation of phenylvinyldichlorosilane.

It was found that greater advantage of the concentration effect could be taken if the tetrahydrofuran were displaced from the stock phenylmagnesium chloride solution by the use of toluene. Toluene was added to the stock solution and most of the tetrahydrofuran removed by distillation. The addition of 2.0 equivalents of phenylmagnesium chloride in toluene to 4.0 equivalents of methyltrichlorosilane in toluene resulted in the preparation of phenylmethyldichlorosilane in a 73% yield, accompanied by a 51% recovery of methyltrichlorosilane.

A hydrocarbon solvent was used in all the reactions to limit the solubility of the magnesium chloride in the reaction solution and to yield a salt from which the solution could be filtered easily. Heptane, when used in the concentrations reported, accomplished both of these tasks very well. The filtered solutions were distilled to virtual dryness leaving only a small amount of salt as residue. In the reactions reported here tetrahydrofuran as received from the du Pont Company, purified virgin tetrahydrofuran and purified recovered tetrahydrofuran were used as solvents in the preparation of the arylmagnesium chlorides. No difference was noted in the behavior of the reactions in comparative duplicate runs provided the solvents were maintained anhydrous. In our hands, tetrahydrofuran exhibited no unusual behavior or hazard provided standard safety precautions were observed.

EXPERIMENTAL

Phenyltrichlorosilane. In a 5.0-l. flask was placed 374.0 g. (2.2 moles) of silicon tetrachloride in 2.0 l. of heptane. Then phenylmagnesium chloride[4] in tetrahydrofuran solution from a 2.0-mole run was added, by means of a dropping funnel, at the rate of 0.5 l. per hr. Excellent stirring and a pot temperature of 40–50° were maintained throughout the addition. After completion of the addition, the mix was refluxed for 2.0 hr. and then allowed to cool to room temperature while the suspended salt settled.

The reaction solution was filtered from the salt *via* a gas dispersion tube[6] to a 5.0-l. flask. Nitrogen pressure of 2–5 lb./in.^{2} was used to force the solution through the dispersion tube. The salt cake was washed with two 250-ml. portions of heptane and the washings were transferred to

(1) This paper was presented before the 130th Meeting of the AMERICAN CHEMICAL SOCIETY at Atlantic City, N. J., September 1956.

(2) F. S. Kipping, *Proc. Chem. Soc.*, **20**, 15 (1904).

(3) W. Dilthey, *Ber.*, **37**, 319 (1904).

(4) H. E. Ramsden, A. E. Balint, W. R. Whitford, J. J. Walburn, and R. Cserr, *J. Org. Chem.*, **22**, 1202 (1957).

(5) See E. G. Rochow, *An Introduction to the Chemistry of the Silicones*, John Wiley and Sons, Inc., New York, 1951, p. 35, for a brief discussion of this problem.

(6) Scientific Glass Apparatus Co., Bloomfield, N. J., Catalogue No. G5420.

TABLE I

PREPARATION OF SOME ARYLCHLOROSILANES

Reactants: Arylmagnesium Chloride	Reactants: Silicon Chloride	Products (Yield)	B.P./mm.	Analysis, % Cl[a]: Calcd.	Analysis, % Cl[a]: Found
C_6H_5MgCl	$SiCl_4$	$C_6H_5SiCl_3$ (47%)	54–57°/0.4	50.4	50.3
		$(C_6H_5)_2SiCl_2$ (17%)	123–126°/2.0	28.0	27.8
C_6H_5MgCl	$SiCl_4$	$(C_6H_5)_2SiCl_2$ (77%)			
		$C_6H_5SiCl_3$ (8%)			
C_6H_5MgCl	CH_3SiCl_3	$CH_3(C_6H_5)SiCl_2$ (73%)	55–58°/1.0	37.0	36.8
		$CH_3(C_6H_5)_2SiCl$ (5%)	112–115°/1.0	15.3	15.1
C_6H_5MgCl	$CH_2{=}CHSiCl_3$	$CH_2{=}CH(C_6H_5)SiCl_2$ (56%)	84–87°/1.5	34.9	34.7
		$CH_2{=}CH(C_6H_5)_2SiCl$ (15%)	133–136°/1.5	14.5	14.3
p-ClC_6H_4MgCl	$SiCl_4$	p-$ClC_6H_4SiCl_3$ (32%)	88–91°/1.5	57.7	57.4
		$(p$-$ClC_6H_4)_2SiCl_2$ (21%)	178–181°/1.5	44.0	44.1
p-ClC_6H_4MgCl	$SiCl_4$	$(p$-$ClC_6H_4)_2SiCl_2$ (39%)			
		p-$ClC_6H_4SiCl_3$ (18%)			
p-$CH_3OC_6H_4MgCl$	$SiCl_4$	$(p$-$CH_3OC_6H_4)_2SiCl_2$ (44%)	194–197°/1.5	22.6	22.8
		p-$CH_3OC_6H_4SiCl_3$ (24%)	94–97°/1.0	44.0	44.2
p-$C_2H_5C_6H_4MgCl$	$SiCl_4$	$(p$-$C_2H_5C_6H_4)_2SiCl_2$ (62%)[b]	163–166°/1.8	22.9	22.7
		p-$C_2H_5C_6H_4SiCl_3$ (13%)	94–97°/1.0	44.4	44.2

[a] % Cl found by hydrolysis and titration with $AgNO_3$ solution. [b] n_D^{20} 1.5694; d_D^{20} 1.1422.

the 5.0-l. flask. The unreacted silicon tetrachloride, tetrahydrofuran, and heptane were removed from the filtrate by distillation at 1.0 atm. The residue was transferred to a 500-ml. flask and distilled under reduced pressure to yield the following fractions.

(1) b. 54–57°/0.4 mm., 198.5 g. (47.0%) of phenyltrichlorosilane.

(2) b. 95–105°/1.0 mm., 10.0 g. (7.0%) of biphenyl.

(3) b. 123–126°/2.0 mm., 42.4 g. (17.0%) of diphenyldichlorosilane.

Phenylvinyldichlorosilane. In a 5.0-l. flask was placed 324.0 g. (2.0 moles) of vinyltrichlorosilane in 2.0 l. of heptane. Then phenylmagnesium chloride in tetrahydrofuran solution from a 2.0-mole run was added at the rate of 0.25 l. per hr. Excellent stirring was maintained. After completion of the addition, the mix was refluxed for 1.0 hr. and then allowed to cool while the salt settled.

The solution was filtered, the salt washed, and the solvents stripped at 1.0 atm. The residue was distilled under reduced pressure to yield 228.2 g. (56%) of phenylvinyldichlorosilane, b. 84–87°/1.5 mm., and 35.9 g. (15%) of diphenylvinylchlorosilane, b. 133–136°/1.5 mm.

Phenylmethyldichlorosilane. In a 5.0-l. flask was placed 598.0 g. (4.0 moles) of methyltrichlorosilane in 2.0 l. of toluene. Then phenylmagnesium chloride in toluene solution[7] from a 2.0-mole run was added at the rate of 0.75 l. per hr. Excellent stirring and a pot temperature of 40° were maintained. After completion of the addition, the mixture was stirred for 2.0 hr. and then the salt was allowed to settle.

The solution was filtered, the salt was washed with toluene, and the unreacted methyltrichlorosilane and toluene were removed at 1.0 atm. The residue was distilled under reduced pressure to yield 277.0 g. (73%) of phenylmethyldichlorosilane, b. 55–58°/1.0 mm., and 12.0 g. (5%) of diphenylmethylchlorosilane, b. 112–115°/1.0 mm.

The solution of methyltrichlorosilane in toluene was carefully fractionally distilled to yield 305.0 g. (51%) of methyltrichlorosilane distilling at 63–70°.

Perchlorophenylmagnesium chloride. In a 2.0-l. flask were placed 142.4 g. (0.5 mole) of hexachlorobenzene 48.7 g. (2.0 g.-atom) of magnesium turnings, 500 ml. of tetrahydrofuran, and one crystal of iodine. The flask was warmed gently and 2.0 ml. of ethyl bromide added. At the first sign of initiation, the heat source was removed and the flask was immersed in a cold water bath. The initiation phase of the reaction is extremely vigorous and it is essential that a water condenser with a large liquid capacity be used. Once the initiation phase was completed, 427.2 g. (1.5 moles) of hexachlorobenzene was added via a solid addition funnel as fast as the reflux rate would allow. When all of the solid had been added, the water bath was removed and the solution was stirred for 1.0 hr. At this time all of the magnesium had been consumed and the perchlorophenylmagnesium chloride was ready for use. The yield, as ascertained by hydrolysis to pentachlorobenzene, was 1.2 moles (60.0%), m.p. 84–86°.

Acknowledgment. The authors would like to thank Dr. Marie Farnsworth and her co-workers in the Physical and Analytical Section of this laboratory for their assistance throughout this work.

RAHWAY, N. J.

(7) This technique was outlined in the discussion.

[CONTRIBUTION FROM THE ROHM & HAAS CO., REDSTONE ARSENAL RESEARCH DIVISION]

Reaction of Dypnone with Certain Organometallic Reagents

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The hydrocarbons derived from the products of 1,2 addition of phenyllithium and of the phenyl, methyl, and ethyl Grignard reagents to dypnone have been examined and their structures assigned on the basis of their spectral properties.

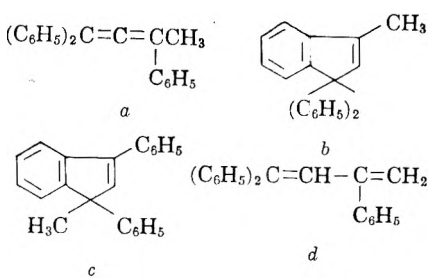
Recently, in connection with another investigation, an authentic sample of 2,2-diphenylbutyrophenone (II) was required. The method of preparing this material involved the 1,4-addition of phenylmagnesium bromide to dypnone (I).[1]

$$\underset{\text{I}}{C_6H_5(CH_3)C{=}CHCOC_6H_5} + C_6H_5MgBr \longrightarrow \underset{\text{II}}{CH_3C(C_6H_5)_2CH_2COC_6H_5}$$

In addition to the desired ketone an unsaturated hydrocarbon which was derived from 1,2-addition of the Grignard reagent also was obtained. As no 1,2-addition products with dypnone have been characterized, a reinvestigation of this reaction has been carried out.

During his classic studies of conjugate addition, Kohler[1] reported that dypnone underwent both 1,2- and 1,4-addition to approximately the same extent with the ethyl and phenyl Grignard reagents. The 1,2-addition product was not isolated, but it was stated that hydrocarbon mixtures often were obtained. A subsequent report[2] of this reaction also reported only isolation of the 1,4-adduct.

In the present study a $C_{22}H_{18}$ hydrocarbon was isolated in addition to the previously identified ketone when dypnone was treated with phenylmagnesium bromide. This compound was identical with the hydrocarbon obtained upon acid-catalyzed dehydration of 1,1,3-triphenylbut-1-en-3-ol (III).[3] Assuming no rearrangement (other than double bond migration) in the dehydration of the intermediate alcohol IV, four structures may be considered for the hydrocarbon: (*a*) 1,1,3-triphenyl-3-methylallene; (*b*) 1,1-diphenyl-3-methylindene; (*c*) 1,3-diphenyl-1-methylindene; or (d) 1,1,3-triphenyl-1,3-butadiene. The allene[3] and the 1,3-diphenyl-1-methylindene[4] are known and may be ruled out on the basis of melting point.



a *b* *c* *d*

The isomeric indene (b) was prepared by dehydration of the carbinol resulting from the reaction of methylmagnesium bromide with 3,3-diphenylindanone. This compound proved to be quite different from the hydrocarbon under study. Logically, then, the structure of the material should be that of 1,-1,3-triphenyl-1,3-butadiene (d). Ziegler and Sauermilch[3] recognized the probability that this was the structure of their product, but were reluctant to assign this structure unequivocally since they were unable to effect hydrogenation of the material. They mentioned the possibility of some rearrangement occurring.

$$\underset{\text{III}}{(C_6H_5)_2C{=}CH{-}\overset{\overset{OH}{|}}{\underset{\underset{C_6H_5}{|}}{C}}{-}CH_3} \xrightarrow{H^+} \underset{\text{IV}}{(C_6H_5)_2C{=}CH{-}\overset{\overset{C_6H_5}{|}}{C}{=}CH_2} \xleftarrow{H^+} C_6H_5C{=}CH{-}\overset{\overset{OH}{|}}{\underset{\underset{C_6H_5}{|}}{C}}C_6H_5$$

In this study it was found that the hydrocarbon could be reduced to a $C_{22}H_{22}$ hydrocarbon which was not capable of further reduction. Chromic acid oxidation of the $C_{22}H_{18}$ hydrocarbon yielded benzophenone as the only isolable product. This experiment, while not definitive, showed that two terminal phenyl groups were present as expected of a 1,2-adduct and also that these groups had not rearranged during the dehydration process. The infrared spectrum of the hydrocarbon shows a band of medium intensity at 898 cm.$^{-1}$ which is attributable to the CH out-of-plane wagging vibrations characteristic of the group $R_2C{=}CH_2$.[5] Quantitative infrared analysis demonstrated that the compound contained three monosubstituted phenyl groups.[6] The only structure compatible with all

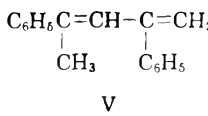
(1) E. P. Kohler, *Am. Chem. J.*, **38**, 511 (1907).
(2) Y. de Schuttenbach, *Ann. chim.*, **6**, 53 (1936).
(3) K. Ziegler and W. Sauermilch, *Ber.*, **63B**, 1851 (1930).
(4) C. F. Koelsch and P. R. Johnson, *J. Am. Chem. Soc.*, **65**, 567 (1943).
(5) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 44.
(6) This analysis was carried out by measurement of the band area of the C—H out-of-plane deformation band at 700–710 cm.$^{-1}$ The standard used was 1,1,3-triphenyl-1-butene.[3]

these features is that of 1,1,3-triphenyl-1,3-butadiene (d).

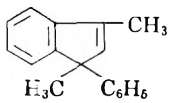
The ultraviolet spectrum of this diene is worth special mention. It had the following characteristics: λ_{max} 252, ϵ_{max} 16,000. This wave length maximum is comparable to those of styrene (λ_{max} 244) and 1,1-diphenylethylene (λ_{max} 250) rather than to that of 1-phenylbutadiene (λ_{max} 280). Such a lowering is to be attributed to steric interference to planarity caused by the interaction between the phenyl groups in positions 1 and 3 quite similar to that recently discussed[7] for other substituted dienes.

Since lithium reagents ordinarily produce predominantly 1,2-adducts, the reaction of dypnone with phenyllithium was investigated. As expected, only a trace of the 1,4-adduct was obtained. The 1,2 product IV was converted to different hydrocarbons depending upon the method employed in decomposing the reaction mixture. This sensitivity to the dehydration conditions probably accounts for the hydrocarbon mixtures reported by Kohler.[1] When it was decomposed with cold ammonium chloride solution and the intermediate carbinol isolated and then dehydrated with an acetic acid–sulfuric acid mixture, a mixture of the two indenes, (*b*) and (*c*), was obtained. This structural assignment was made on the basis of elementary analysis and the close similarity of the ultraviolet spectrum of the mixture to that of authentic 1,1-diphenyl-3-methylindene. A similar mixture of these indenes was obtained upon acid isomerization of 1,1,3-triphenyl-3-methylallene.[3] When the reaction mixture was hydrolyzed directly with hydrochloric acid as in the Grignard reaction, 1,1,3-triphenyl-1,3-butadiene was produced.

The reaction of dypnone with the methyl and ethyl Grignard reagents was also examined. With the ethyl reagent approximately equal amounts of the 1,4-adduct, 2-phenyl-2-methylvalerophenone, and of the product of 1,2-addition, 2,4-diphenyl-2,4-hexadiene[8], were isolated; the nature of the hydrocarbon was not affected by the method of dehydration. The structure of the diene was inferred from its elementary analysis and the similarity of its ultraviolet spectrum (λ_{max} 253, ϵ_{max} 15,900) to that of the triphenylbutadiene. The methyl Grignard reagent produced only a 1,2-adduct, but the structure of the derived hydrocarbon was dependent upon the conditions of dehydration. Hydrolysis of the reaction mixture with cold hydrochloric acid produced a mixture of the carbinol and 2,4-diphenyl-1,3-pentadiene (V), identified by its elementary analysis and infrared (strong terminal methylene deformation band at 898 cm.$^{-1}$) and ultraviolet spectra (λ_{max} 249, ϵ_{max} 17,300). When the carbinol was isolated and heated in an acetic acid–sulfuric acid mixture, 1-phenyl-1,3-dimethylindene (VI) was produced. This structure was proven by independent synthesis. In an effort to synthesize 2,4-diphenyl-1,3-pentadiene, the reaction between magnesium and β-bromo-α-methylstyrene was examined in the hope of producing a Grignard reagent. The mixture was heated under reflux until all

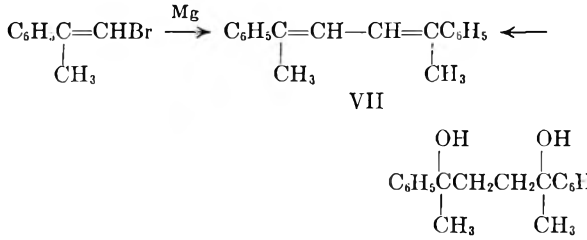


V



VI

the metal had disappeared and then acetophenone was added. In working up the reaction mixture, it became evident that no attack on the acetophenone had occurred and only 2,5-diphenyl-2,4-hexadiene (VII) was obtained. This hydrocarbon was identified by its elementary analysis, the close similarity of its ultraviolet spectrum to that of *trans,trans*-1,4-diphenylbutadiene, and its identity with the hydrocarbon produced by dehydration of 2,5-diphenyl-2,5-hexanediol. This coupling reaction is analogous to that reported in the reaction of β-bromostyrene with magnesium wherein *trans,trans*-1,4-diphenylbutadiene was produced.[9]



VII

EXPERIMENTAL

Reaction of dypnone with phenylmagnesium bromide. To 35 ml. of a 3*M* solution of phenylmagnesium bromide[10] in 100 ml. of dry ether was added 11.0 g. (0.05 mole) of dypnone in 50 ml. of dry ether. The resulting mixture was heated under reflux 4 hr. and then poured onto ice and hydrochloric acid. Upon drying and concentrating the organic extracts an oily mushy material remained which dissolved partially in boiling ethanol. The hot ethanol was decanted and allowed to cool. A white solid precipitated and was collected, m.p. 99–102°; yield 6.0 g. (40%). Upon recrystallization from ethanol it melted at 104–105°. 2,2-Diphenylbutyrophenone is reported[1] to melt at 103°. The compound formed an oxime, m.p. 163–165° (lit.[1] m.p. 161°) and a yellow *2,4-dinitrophenylhydrazone*, m.p. 183–185°.

Anal. Calcd. for $C_{28}H_{24}N_4O_4$: C, 69.99; H, 5.03. Found: C, 70.39; H, 5.26.

The ethanol-insoluble material crystallized from an ethanol-benzene mixture to give small crystals, m.p. 165–166°; yield 3.9 g. (28%). This material is assigned the structure of *1,1,3-triphenyl-1,3-butadiene.*

(7) E. A. Braude and E. Evans, *J. Chem. Soc.*, 3333 (1956).

(8) This structure rather than the isomeric one containing a terminal double bond is preferred because of the absence of any infrared band in the 880–920 cm.$^{-1}$ region comparable to that present in the spectrum of 2,4-diphenylpentadiene (see below).

(9) H. Rupe and H. Proske, *Ber.*, **43**, 1231 (1910).

(10) Obtained from Arapahoe Chemical Co., Boulder, Colo.

Anal. Calcd. for $C_{22}H_{18}$: C, 93.58; H, 6.42. Found: C, 93.42; H, 6.45.

Reduction of 1,1,3-triphenyl-1,3-butadiene. The hydrogenation was conducted at room temperature (23–25°) in a Parr hydrogenation apparatus employing 1.5 g. of 1,1,3-triphenyl-1,3-butadiene and 0.2 g. of platinum oxide in 90 ml. of a 1:1 mixture of acetic acid and ethyl acetate under 50 pounds of hydrogen for 12 hr. Upon filtering the catalyst and concentrating the solvents, a white hydrocarbon was obtained which was recrystallized from ethanol, m.p. 115–117°.

Anal. Calcd. for $C_{22}H_{22}$: C, 92.26; H, 7.74. Found: C, 92.15; H, 7.70.

This material is assigned the structure of *1,1,3-triphenylbutane.*

1,1-Diphenyl-3-methylindene. To 15 ml. of a 4*M* solution of methylmagnesium bromide[10] in 100 ml. of dry ether was added slowly a solution of 7.4 g. (0.026 mole) of 3,3-diphenyl-1-indanone[11] in 50 ml. of dry benzene. The mixture was heated under reflux for 3 hr. and then decomposed with ice and hydrochloric acid. Upon drying and concentrating the organic extracts, a yellow oil whose infrared spectrum indicated that it was the desired indanol was obtained. This oil was dissolved in 25 ml. of glacial acetic acid containing 1 ml. of sulfuric acid and the solution was heated under reflux 2 hr. and then poured on ice. The white solid that separated was collected and recrystallized from ethanol to give tiny white flakes, m.p. 119–120°; yield 4 g. (55%). Ultraviolet maxima: λ_{max} 225, 265; ϵ_{max} 23,400, 6600.

Anal. Calcd. for $C_{22}H_{18}$: C, 93.58; H, 6.42. Found: C, 93.61; H, 6.42.

Reaction of phenyllithium with dypnone. To an ethereal solution of phenyllithium prepared from 5.2 g. (0.6 g.-atom) of lithium, 47 g. (0.3 mole) of bromobenzene, and 300 ml. of dry ether was added a solution of 33 g. (0.15 mole) of dypnone in 150 ml. of dry ether. The mixture was heated under reflux for 4 hr. and decomposed with ice and hydrochloric acid. Upon drying and concentrating the organic extracts, an orange oil containing a suspended solid was obtained. Upon filtering, 16 g. of 1,1,3-triphenyl-1,3-butadiene, m.p. 164–167°, was isolated. Chromatographic purification of the filtrate produced an additional 4 g.; total yield 20 g. (46%). If the mixture was decomposed with ammonium chloride, the carbinol isolated was boiled at reflux for an hour with 25 ml. of acetic acid to effect dehydration of the alcohol. The resultant oil was then chromatographed on alumina. Upon distillation a viscous yellow oil was obtained, b.p. 160–165° (0.1 mm.); λ_{max} 231, 265; ϵ_{max} 29,600, 8,400. This mixture appears to contain both 1,1- and 1,3-diphenyl-3-methylindene.

Anal. Calcd. for $C_{22}H_{18}$: C, 93.58; H, 6.42. Found: C, 93.08; H, 6.30.

Further elution with a 4:1 petroleum ether–benzene mixture furnished approximately 0.1 g. of 2,2-diphenylbutyrophenone, identified by its infrared spectrum. Finally, continued elution with this mixture produced 5.2 g. (16%) of unchanged dypnone. Although a small amount of additional viscous oil could be eluted, identification was impossible.

Reaction of dypnone with ethylmagnesium bromide. A solution of 11 g. (0.05 mole) of dypnone in 50 ml. of dry ether was added slowly to 25 ml. of 3*M* ethereal ethylmagnesium bromide[10] in 100 ml. of dry ether. The mixture was stirred under reflux overnight and decomposed with cold hydrochloric acid. Distillation of the product produced two main fractions, b.p. 59–73° (0.07 mm.) and b.p. 96–104° (0.08 mm.). The first fraction was redistilled twice through a spinning band column to yield *2,4-diphenyl-2,4-hexadiene,* b.p. 149–150° (1 mm.), n_D^{20} 1.6028; yield 5.2 g. (44%).

Anal. Calcd. for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.17; H, 7.96.

The second fraction showed a strong carbonyl group at 1680 cm.$^{-1}$ in its infrared spectrum indicating it to be the known 2-methyl-2-phenylvalerophenone.[1] It formed a *2,4-dinitrophenylhydrazone,* m.p. 175–177°; yield 8.8 g. (44%).

Anal. Calcd. for $C_{24}H_{24}N_4O_4$: C, 66.65; H, 5.59. Found: C, 66.17; H, 4.89.

Reaction of dypnone with methylmagnesium bromide. In the same manner 33 g. (0.15 mole) of dypnone was treated with 100 ml. of 4*M* methylmagnesium bromide solution.[10] The reaction mixture was hydrolyzed with cold hydrochloric acid. The dried product was dissolved in petroleum ether and chromatographed on alumina. The first twenty 100-ml. fractions contained a colorless oil, b.p. 106–108° (0.02 mm.), n_D^{20} 1.6113; yield 12 g. (36%). It is assigned the structure of *2,4-diphenyl-1,3-pentadiene.*

Anal. Calcd. for $C_{17}H_{16}$: C, 92.68; H, 7.32. Found: C, 92.60; H, 7.71.

The next 2600 ml. (1:1 petroleum ether–benzene) contained a yellow oil which produced an orange dinitrophenylhydrazone, m.p. 243–247°. This derivative proved to be identical with acetophenone 2,4-dinitrophenylhydrazone.

Finally, elution with ether removed a viscous oil whose infrared spectrum indicated that it was the carbinol. It was dissolved in 50 ml. of acetic acid containing 1 ml. of sulfuric acid and heated under reflux for an hour. The resulting mixture was poured into water, extracted into ether, dried, and concentrated to give a colorless oil. Chromatography of this oil on alumina produced a water white oil, b.p. 105–106° (0.01 mm.), n_D^{20} 1.5969 (supercooled). It crystallized upon chilling in Dry Ice to give white needles, m.p. 50–52°; yielded 9.6 g. (30%).

Anal. Calcd. for $C_{17}H_{16}$: C, 92.68; H, 7.32. Found: C, 92.42; H, 7.41.

Its infrared spectrum had a band of medium intensity at 1623 cm.$^{-1}$ and one of strong intensity at 820 cm.$^{-1}$ attributable to a conjugated double bond and a lone hydrogen on a double bond, respectively. The ultraviolet spectrum had λ_{max} 220, 260; ϵ_{max} 27,000, 7200, similar in shape to that of 1,1-diphenyl-3-methylindene. The spectra of this material were identical to those of an authentic sample of *1-phenyl-1,3-dimethylindene.*

1-Phenyl-1,3-dimethylindene. To 25 ml. of a 4*M* solution of methylmagnesium bromide[10] in 100 ml. of dry ether was added slowly at ice-bath temperatures a solution of 11 g. (0.05 mole) of 3-phenyl-3-methyl-1-indanone[12] in 50 ml. of dry ether. The procedure for the preparation of 1,1-diphenyl-3-methylindene was followed exactly. The oil obtained was purified by distillation b.p. 118–120° (0.05 mm.). It crystallized upon cooling, m.p. 48–51°; yield 6.8 g. (62%).

Reaction of β-bromo-α-methylstyrene with magnesium. To 1.3 g. (0.05 g. atom) of magnesium turnings under 50 ml. of dry ether was added a solution of 9.8 g. (0.05 mole of β-bromo-α-methylstyrene[13] in 50 ml. of ether. This mixture was stirred under reflux for 24 hr. At the end of this period 6 g. (0.05 mole) of acetophenone was added and heating was continued for 3 hr. Distillation of the oily product led to the recovery of the acetophenone and isolation of 3.6 g. (31%) of a white hydrocarbon, m.p. 133–137°. Recrystallization from ligroin produced a pure sample, m.p. 136–138°, of *2,5-diphenyl-2,4-hexadiene.*

Anal. Calcd. for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.34; H, 7.66.

The ultraviolet spectrum of this material had the following characteristics; λ_{max} 320, ϵ_{max} 40,000. *trans,trans*-1,4-Diphenylbutadiene has λ_{max} 328, ϵ_{max} 41,000.

Preparation of 2,5-diphenyl-2,5-hexanediol. This diol has been prepared previously by the hydrogenation of the acetylenic diol produced by the action of acetylenedimagnesium

(11) C. F. Koelsch and C. D. LeClaire, *J. Org. Chem.*, 6, 516 (1939).

(12) C. F. Koelsch, H. Hochmann, and C. D. Le Claire, *J. Am. Chem. Soc.*, 65, 59 (1943).

(13) M. Tiffeneau, *Ann. chim.*, [8] 10, 168 (1907).

bromide on acetophenone.[14] It was found to be more conveniently prepared by the action of phenylmagnesium bromide on acetonylacetone.

The Grignard reagent was prepared in the usual way from 39 g. (0.25 mole) of bromobenzene, 6.1 g. (0.25 g.-atom) of magnesium, and 150 ml. of ether. A solution of 11.4 g. (0.1 mole) of acetonylacetone in 50 ml. of ether was added slowly at ice-bath temperatures. The resulting mixture was stirred at room temperature for 1 hr. and at reflux for 2 hr. Isolation was carried out in the usual manner and 17.8 g. (67%) of the desired diol, a mixture of the stereomers, was obtained.

Preparation of 2,5-diphenyl-2,4-hexadiene. Treatment of 2,5-diphenyl-2,5-hexanediol with 15% sulfuric acid produces only 2,5-diphenyl-2,5-dimethyltetrahydrofuran.[14] However, when 10.8 (0.04 mole) of the diol was heated with 10.2 g. (0.06 mole) of phosphorus oxychloride in 300 ml. of dry benzene, 4 g. (44%) of the desired diene, m.p. 135–138°, was obtained. It did not depress the melting point of the bromomethylstyrene magnesium product and their infrared spectra were identical.

Ultraviolet spectra.[15] The spectra were measured on a Beckmann DK-1 Spectrophotometer in 1-cm. cells in acetonitrile solution.

Acknowledgment. We are greatly indebted to Dr. Keith S. McCallum for helpful discussions of the infrared and ultraviolet spectra.

HUNTSVILLE, ALA.

(14) M. Tout and M. Guyard, *Bull. soc. chim. France*, 1087 (1947).

(15) These spectra were measured by Mr. R. Donald Strahm.

[CONTRIBUTION FROM THE TECHNICAL DEVELOPMENT DEPARTMENT OF HOFFMANN-LA ROCHE, INC.]

Synthesis of Pseudoionone Homologs and Related Compounds

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A series of ketones related to 6-methyl-5-hepten-2-one have been prepared in which substitutions have been effected at carbon atoms 3, 4, 5 and 6. These ketones were converted to the corresponding pseudoionones.

In addition to the pseudoionones, a number of compounds were prepared which may be of interest to the essential oil industry. These include (1) linalools (2) β-cyclopentenylethyl ketones, isomeric with the corresponding pseudoionones (3) α- and β-ionones and (4) geranyl acetones.

Recent investigations in these laboratories[1] have led to a practical total synthesis for pseudoionone, starting from acetone and acetylene. The method utilized 6-methyl-5-hepten-2-one (VIIa) as a key intermediate. The process for preparation of VIIa can be extended readily to permit substitutions at different positions in the molecule. Accordingly, five series of unsaturated ketones related to VIIa have been prepared. In the first series (A), the carbon chain was lengthened; *i.e.*, alterations were made at carbon atom 6. The next three series (B, C, D) involved substitution at carbon atoms 5, 4, and 3, respectively. The fifth series (E) utilized two of the above series (A and D) to produce, simultaneously, chain lengthening and substitution.

The substituted methylheptenones were converted to the corresponding pseudoionones, as previously described.[1] Since pseudoionone is a key intermediate in the production of Vitamin A[2] and β-carotene,[3] these pseudoionone homologs may be employed for the preparation of corresponding Vitamin A and β-carotene homologs. These should be valuable for study of the relationship between chemical structure and Vitamin A activity.

Also, we have converted the substituted pseudoionones, and certain of the intermediates used for their preparation, into products which may be of interest to the essential oil industry. These products include: (1) linalools (IX), obtained from the ethynylcarbinols (VIII) by selective reduction of the triple bond; (2) β-cyclopentenylethyl ketones (X), isomeric with the corresponding pseudoionones (XI) and produced as by-products of their synthesis[1]; (3) α- and β-ionones (XII and XIII), obtained by cyclization of XI; and (4) geranylacetones (XIV), formed when the linalools (IX) were treated with diketene and the resulting acetoacetates were pyrolyzed. Many of these compounds have interesting odor characteristics, which may make them attractive as flavoring and perfumery ingredients.

The complete flow sheet for preparation of the various products is shown in Table I.

Series A. In this series, $R^2 = R^3 = R^4 = H$. In the simplest case, $R' = CH_3$, and VII and XI are methylheptenone and pseudoionone, respectively. The starting material for those compounds was acetone (I; $R' = CH_3$).[1] For other members of this series, methyl ketones other than acetone were used, and R′ = alkyl or aryl. However, even cyclic ketones, such as cyclohexanone, were employed.

In a typical sequence, methyl ethyl ketone was ethynylated to give 3-methyl-1-pentyn-3-ol (IIb) which was hydrogenated selectively, in the presence

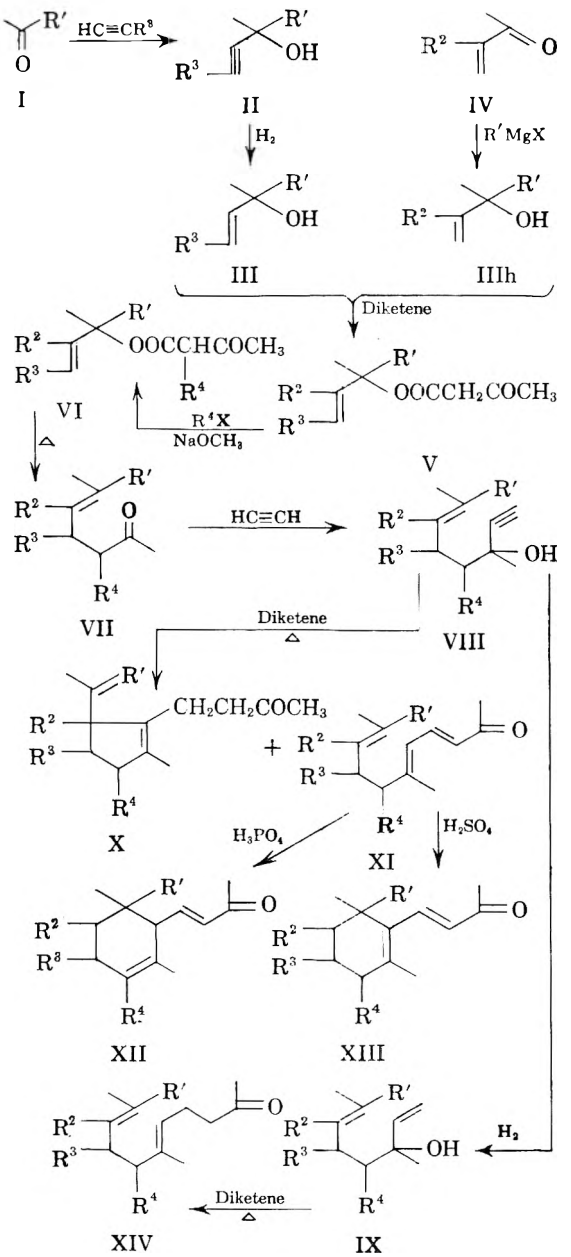
(1) W. Kimel, N. W. Sax, G. Eichmann, S. Kaiser, G. O. Chase, and A. Ofner; unpublished work.

(2) O. Isler, W. Huber, A. Ronco, and M. Kofler, *Helv. Chim. Acta*, **30**, 1911 (1947).

(3) O. Isler, H. Lindlar, M. Montavon, R. Ruegg, and P. Zeller, *Helv. Chim. Acta*, **39**, 249 (1956).

TABLE I

FLOW CHART OF REACTIONS



of Lindlar catalyst,[4] to yield 3-methyl-1-penten-3-ol (IIIb). This vinylcarbinol was treated with diketene to give the corresponding acetoacetate (Vb), which afforded 6-methyl-5-octen-2-one (VIIb) on pyrolysis. Ethynylation of the ketone VIIb gave 3,7-dimethyl-6-nonen-1-yn-3-ol (VIIIb). Treatment of the latter with diketene, and pyrolysis of the resultant acetoacetate, afforded a mixture of the pseudoionone homolog, 6,10-dimethyl-3,5,9-dodecatrien-2-one (XIb), and 4-[2-methyl-5-(1-methylpropenyl)cyclopenten-1-yl]-2-butanone (Xb).

The reaction scheme for Series A followed the sequence I → II → III → V → VII → VIII → XI in Table I.

(4) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

Series B. In this series, R′ = CH_3; R^3 = R^4 = H; R^2 = alkyl. The sequence starts with a substituted methyl vinyl ketone (IV). Thus, when R^2 = CH_3, methyl isopropenyl ketone was treated with methylmagnesium bromide to give 2,3-dimethyl-1-buten-3-ol (IIIh). This substituted allylic alcohol gave its corresponding acetoacetate on treatment with diketene. Pyrolysis of the ester afforded the methylheptenone homolog, 5,6-dimethyl-5-hepten-2-one (VIIh). Ethynylation of the latter gave the acetylenic alcohol, VIIIh. Condensation of VIIIh with diketene, followed by pyrolysis, afforded 6,9,-10-trimethyl-3,5,9-undecatrien-2-one (XIh), known commercially as pseudoirone. This is a precursor for the important perfume material α-irone (XIIh).

The reaction sequence for Series B followed the path IV → IIIh → V → VII → VIII → XI in Table I.

Series C. For this series, R′ = CH_3; R^2 = R^4 = H; R^3 = alkyl. The series is initiated by allowing acetone to react with the Grignard reagent of an alkyne, whereby an acetylenic carbinol (II) is obtained. Thus, for example, treatment of 1-butyne (obtained by reaction of ethyl bromide with sodium acetylide[5]) with ethylmagnesium bromide gave 1-butynemagnesium bromide. Then, addition of acetone caused formation of 2-methyl-3-hexyn-2-ol (IIf). This was reduced to the corresponding allylic alcohol, and the reaction sequence outlined for Series A was then followed; *i.e.*, I → II → III → V → VII → VIII → XI. In this case, the methylheptenone homolog was 4-ethyl-6-methyl-5-hepten-2-one (VIIf), and the pseudoionone homolog was 6,10-dimethyl-8-ethyl-3,5,9-undecatrien-2-one (XIf).

Series D. Alkylation of 2-methyl-3-buten-2-yl acetoacetate (Va) in the usual manner[6] gave α-substituted acetoacetates of type VI. Pyrolysis of these esters yielded methylheptenones substituted at carbon atom 3. Thus, for this series, R′ = CH_3; R^2 = R^3 = H; R^4 = alkyl. From Table I, the reaction sequence was I → II → III → V → VI → VII → VIII → XI.

Series E. By combining any two or more of the previously described series, it was possible to substitute the methylheptenone nucleus (and eventually the pseudoionone molecule) in several places. Series E involved substitution of methylheptenone at carbon atoms 3 and 7. Thus, in a typical sequence, methyl ethyl ketone was converted, as described previously under Series A, to 3-methyl-1-penten-3-yl acetoacetate (Vb). The latter was alkylated with ethyl bromide (as in Series D) to give the corresponding ethyl-substituted acetoacetate (VI). Pyrolysis of the ester afforded 3-ethyl-6-methyl-5-octen-2-one (VII l). The corresponding

(5) J. G. Aston, S. V. R. Mastrangelo, and G. W. Moessen, *J. Am. Chem. Soc.*, **72**, 5287 (1950).

(6) C. S. Marvel and F. D. Hager, *Org. Syntheses*, Coll. Vol. I, 248, (1941).

TABLE II

ACETYLENIC ALCOHOLS

Compound	R^1	R^3	B.P. °C.	B.P. Mm.	n_D^{25}	Yield, %
IIa[a,b]	CH_3	H	104	760	1.4182	90
IIb[b]	C_2H_5	H	121	760	1.4290	..
IIc[b]	$(CH_3)_2CHCH_2$	H	150	760	1.4333	..
IId[b,c]	$-(CH_2)_4-$	H	180	760	[d]	..
IIe[e]	C_6H_5	H	72–5	0.5	[f]	75
IIf[g]	CH_3	C_2H_5	46–7	7	1.4392	73
IIg[h]	CH_3	n-C_6H_{13}	99	10	1.4462	80

[a] J. F. Froning and G. F. Hennion, *J. Am. Chem. Soc.*, **62**, 653 (1940). [b] Obtained from Air Reduction Co. [c] This compound is 1-ethynylcyclohexanol. [d] m.p. 30°. [e] H. Rupe and L. Geisler, *Helv. Chim. Acta*, **11**, 656 (1925). [f] m.p. 51°. [g] Dupont, *Compt. rend.*, **148**, 1524 (1909). [h] Analysis: Calcd. for $C_{11}H_{20}O$: C, 78.50; H, 11.98. Found: C, 78.37; H, 12.21.

TABLE III

TERTIARY ALLYLIC ALCOHOLS

Compound	R^1	R^2	R^3	B.P. °C.	B.P. Mm.	n_D^{25}
IIIa[a]	CH_3	H	H	97–98	760	1.4141
IIIb[b]	C_2H_5	H	H	116	763	1.4263
IIIc[c]	$(CH_3)_2CHCH_2$	H	H	53	16	1.4310
IIId[d]	$-(CH_2)_4-$	H	H	72	16	1.4740
IIIe[e]	C_6H_5	H	H	60–62	0.6	1.5302
IIIf[f]	CH_3	H	C_2H_5	68–69	54	1.4330
IIIg[g]	CH_3	H	n-C_6H_{13}	94	10	1.4454
IIIh[h]	CH_3	CH_3	H	82–83	200	1.4296

[a] Reference (1). [b] H. Rupe and F. Vonaesche, *Ann.*, **442**, 81 (1925). [c] Commercial Solvents Corp., Brit. Patent **595,459**, Dec. 5, 1947. [d] P. S. Pinkney, G. A. Nesty, R. H. Wiley, and C. S. Marvel, *J. Am. Chem. Soc.*, **58**, 972 (1936). This compound is 1-vinylcyclohexanol. [e] A. I. Lebedeva, *J. Gen. Chem.* (*U. S. S. R.*), **20**, 431 (1950). [f] I. N. Nazarov and L. B. Fisher, *Bull. acad. sci. U. S. S. R.* 135 (1942). [g] F. S. Kipping and L. L. Lloyd, *J. Chem. Soc.*, **79**, 450 (1901). [h] Reference (8).

pseudoionone homolog was 7-ethyl-6,10-dimethyl-3,5,9-dodecatrien-2-one (XI l), obtained via the sequence VII → VIII → XI.

EXPERIMENTAL

The physical constants and yields obtained for all compounds are listed in Tables II to XI.[7]

Ethynylcarbinols (II; R^3 = H). Into a stirred solution of sodium (1.2 g.-atoms) in liquid ammonia (2 l.) was bubbled acetylene until conversion to sodium acetylide was complete (as indicated by a color change from blue to white). Into this solution was added, dropwise, a ketone I, (1.0 mole) in ether (300 ml.). The mixture was stirred for 8 hr., and then the ammonia was allowed to evaporate. The residue was poured, with ice cooling, onto 20% sulfuric acid. The layers were separated and the aqueous phase was extracted three times with ether (200 ml.). The ether layers were combined and washed with a 5% potassium carbonate solution (100 ml.) and with water until neutral. The organic portion was dried over calcium chloride and the product was isolated by distillation.

Acetylenic alcohols (II; R^3 = alkyl). Sodium (1.1 g.-atoms) was added, slowly, to liquid ammonia (2 l.) containing hydrated ferric nitrate (0.3 g.). Into the resultant suspension of sodamide was introduced acetylene, at a rapid rate, until a color change from grey to white to black occurred. An alkyl halide (1.0 mole) was added, dropwise, and the reaction mixture was stirred for 10 hr. The ammonia was allowed to evaporate and the alkyne was distilled from the residue. The alkyne was dissolved in ether (100 ml.) and the solution was added to a Grignard reagent prepared from magnesium (1.2 g.-atoms), ethyl bromide (1.25 moles), and ether (500 ml.). The resultant complex was stirred for 1 hr., acetone (1.25 moles) was introduced slowly, and the reaction mixture was stirred overnight. Saturated aqueous ammonium chloride was used to decompose the complex. The aqueous layer was separated, and was extracted with ether (300 ml.). The organic layers were combined, washed with water and dried. The product was purified by fractional distillation.

Allylic alcohols (III). An acetylenic alcohol (II, 1.0 mole) was dissolved in hexane (two volumes of solvent per weight of carbinol) to which was added 5% by weight of Lindlar catalyst.[4] The hydrogenation was performed at atmospheric pressure and was continued until one molar equivalent of hydrogen was consumed, at which time the rate of absorption had decreased markedly. The catalyst was removed by filtration and the product was isolated by distillation. Yields of 90–95% were obtained, in every instance.

2,3-Dimethyl-3-buten-2-ol (IIIh). This carbinol was prepared from methyl isopropenyl ketone (IV, R^2 = CH_3) according to the procedure of Ogloblin,[8] in yield of 70%.

Allylic acetoacetates (V). The appropriate allylic alcohol (III, 1.0 mole) was dissolved in an equal volume of hexane and to the solution was added 0.01 mole % of sodium methoxide. Diketene (1.1 moles) was then added, dropwise, maintaining the reaction temperature at 25–30°. After the addition was complete, the reaction was stirred at 25–30° for 10 hr. The solution was washed with saturated aqueous sodium bicarbonate and then with water. Removal of the solvent under diminished pressure afforded crude esters, V, in quantitative yield, of sufficient purity for use in succeeding steps.

(7) Melting points and boiling points are uncorrected.

(8) K. A. Ogloblin, *J. Gen. Chem.* (*U. S. S. R.*), **18**, 2153 (1948); *Chem. Abstr.* **43**, 3777 (1949).

TABLE IV

UNSATURATED KETONES (VII)

Compound	R¹	R²	R³	R⁴	B.P. °C.	B.P. Mm.	n_D^{25}	d_4^{25}	M_D Calcd.	M_D Found	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Yield, %
VIIa[a]	CH_3	H	H	H	58–59	10	1.4372								80
VIIb	C_2H_5	H	H	H	85–86	19	1.4406	0.8481	43.31	43.66	77.08	77.03	11.50	11.43	80
VIIc	$(CH_3)_2CHCH_2$	H	H	H	56–57	1.0	1.4430	0.8448	52.56	52.81	78.51	78.70	11.98	12.21	78
VIId[b]	—$(CH_2)_4$—	H	H	H	71–72	1.2	1.4763	0.9320	50.36	50.34	79.46	79.79	10.91	10.84	82
VIIe	C_6H_5	H	H	H	97–99	0.4	1.5389	0.9898	58.18	59.51	82.93	83.06	8.57	8.98	65
VIIf	CH_3	H	C_2H_5	H	71–75	12	1.4378	0.8391	47.91	48.25	77.93	78.05	11.76	11.91	43
VIIg	CH_3	H	n-C_6H_{13}	H	64–65	0.15	1.4452	0.8430	66.42	66.44	79.91	80.38	12.46	12.31	39
VIIh[c]	CH_3	CH_3	H	H	72–74	10	1.4483								74
VIIi	CH_3	H	H	C_2H_5	66–67	7.0	1.4396	0.8520	47.92	47.67	77.93	77.39	11.76	11.72	72
VIIj	CH_3	H	H	C_3H_5[d]	81–82	7.0	1.4550	0.8610	52.08	52.31	79.46	79.54	10.91	10.73	69
VIIk	CH_3	H	H	C_3H_3[e]	100–103	13	1.4639	0.9000	50.54	50.35	80.49	80.62	9.82	9.96	62
VIIl	C_2H_5	H	H	C_2H_5	104	22	1.4450	0.8480	52.54	52.80	78.57	78.14	11.98	11.78	62
VIIm	C_2H_5	H	H	C_3H_5[d]	114	18	1.4570	0.8677	56.71	56.58	79.94	79.65	11.18	10.90	54

[a] W. Kimel, U.S. Patent **2,638,484,** May 12, 1953. [b] This compound is 5-cyclohexylidene-2-pentanone. [c] W. Kimel, U.S. Patent **2,662,920,** December 15, 1953. [d] R^4 = allyl. [e] R^4 = propargyl.

TABLE V

ETHYNYLCARBINOLS (VIII)

Compound	R¹	R²	R³	R⁴	B.P. °C.	B.P. Mm.	n_D^{25}	d_4^{25}	M_D Calcd.	M_D Found	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
VIIIa[a]	CH_3	H	H	H	88–90	14	1.4608							
VIIIb	C_2H_5	H	H	H	52–53	1.2	1.4625	0.8728	52.05	52.28	79.46	78.96	10.91	10.86
VIIIc	$(CH_3)_2CHCH_2$	H	H	H	72–74	0.25	1.4599	0.8657	61.31	61.45	80.35	80.46	11.41	11.24
VIIId[b]	—$(CH_2)_4$—	H	H	H	88–90	1.8	1.4920	0.9384	59.11	59.44	81.19	81.47	10.48	10.56
VIIIe	C_6H_5	H	H	H	130–131	0.65	1.5495	0.9990	66.94	68.28	84.07	84.22	8.47	8.33
VIIIf	CH_3	H	C_2H_5	H	81–83	7	1.4560	0.8630	56.67	56.78	79.94	79.61	11.18	11.29
VIIIh[c]	CH_3	CH_3	H	H	94–96	9	1.4678							
VIIIi	CH_3	H	H	C_2H_5	66–67	0.9	1.4669	0.8847	56.67	56.53	79.94	80.02	11.18	11.12
VIIIj	CH_3	H	H	C_3H_5[d]	74–76	0.3–0.4	1.4771	0.8938	60.82	60.80	81.17	81.42	10.48	10.51
VIIIk	CH_3	H	H	C_3H_3[e]	83–86	0.7	1.4841	0.9202	59.31	59.16	82.05	82.15	9.53	9.47
VIIIl	C_2H_5	H	H	C_2H_5	82–84	1.4	1.4682	0.8806	61.29	61.36	80.35	80.21	11.41	11.22
VIIIm	C_2H_5	H	H	C_3H_5[d]	83–85	0.6	1.4780	0.8933	65.44	65.41	81.49	81.84	10.75	10.43

[a] L. Ruzicka and V. Fornasir, *Helv. Chim. Acta*, **2,** 182 (1919). [b] This compound is 6-cyclohexylidene-3-methyl-1-hexyn-3-ol. [c] H. Schinz, L. Ruzicka, C. F. Seidel, and Ch. Tavel, *Helv. Chim. Acta*, **30,** 1810 (1947). [d] R^4 = allyl. [e] R^4 = propargyl.

TABLE VI

VINYL CARBINOLS (IX)

Compound	R^1	R^2	R^3	R^4	B.P. °C.	B.P. Mm.	n_D^{25}	d_4^{25}	M_D Calcd.	M_D Found	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
IXa[a]	CH_3	H	H	H	86–88	14	1.4590							
IXb	C_2H_5	H	H	H	50	1.2	1.4606	0.8623	53.60	53.66	78.51	78.61	11.98	12.17
IXc	$(CH_3)_2CHCH_2$	H	H	H	77–78	1.0	1.4591	0.8580	62.83	62.56	79.53	79.54	12.32	12.09
IXd[b]	—$(CH_2)_4$—	H	H	H	80	0.3	1.4908	0.9228	60.63	60.96	80.35	80.85	11.41	11.08
IXe	C_6H_5	H	H	H	114–117	0.5	1.5420	0.9759	68.47	69.75	83.28	83.66	9.32	9.37
IXf	CH_3	H	C_2H_5	H	82–83	8	1.4543	0.8490	58.20	58.16	79.05	79.45	12.16	12.08
IXh[c]	CH_3	CH_3	H	H	50–52	0.6	1.4658							
IXl	C_2H_5	H	H	C_2H_5	66–68	0.3	1.4681	0.8709	62.82	62.67	79.53	79.62	12.32	12.62
IXm	C_2H_5	H	H	C_3H_5[d]	80–82	0.5	1.4779	0.8800	66.97	66.97	80.71	81.00	11.61	11.71

[a] J. L. Simonsen, *The Terpenes*, University Press, Cambridge, England, 1947, 2nd Ed., Vol. I, p. 57. [b] This compound is 6-cyclohexylidene-3-methyl-1-hexen-3-ol. [c] Y. R. Naves, A. V. Grampoloff, and P. Bachmann, *Helv. Chim. Acta*, **30**, 1599 (1947). [d] R^4 = allyl.

TABLE VII

PSEUDOIONONES (XI)

Compound	R^1	R^2	R^3	R^4	B.P. °C.	B.P. Mm.	n_D^{25}	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Yield, %
XIa[a]	CH_3	H	H	H	90–95	0.5	1.5297					55
XIb	C_2H_5	H	H	H	98–108	0.3–0.5	1.5260	81.50	81.50	10.75	10.48	53
XIc	$(CH_3)_2CHCH_2$	H	H	H	108–116	0.2	1.5175	81.99	81.64	11.19	10.94	54
XId[b]	—$(CH_2)_4$—	H	H	H	130–140	1.0–1.5	1.5430	82.70	82.45	10.41	10.45	43
XIf	CH_3	H	C_2H_5	H	121–125	1.0	1.5179	81.76	82.14	10.97	11.22	30
XIh[a]	CH_3	CH_3	H	H	105–110	0.5	1.5305					60
XIi	CH_3	H	H	C_2H_5	96–104	0.3–0.4	1.5230	81.76	82.12	10.97	10.97	41
XIj	CH_3	H	H	C_3H_5[c]	100–108	0.3	1.5313	82.70	82.77	10.41	10.18	40
XIk	CH_3	H	H	C_3H_5[d]	107–115	0.3–0.4	1.5412	83.42	83.09	9.63	9.68	34
XIl	C_2H_5	H	H	C_2H_5	110–120	0.1–0.3	1.5200	81.99	81.75	11.18	11.02	38
XIm	C_2H_5	H	H	C_3H_5[c]	110–118	0.15	1.5258	82.87	82.62	10.64	10.56	35

[a] W. Kimel and N. Sax, U.S. Patent **2,661,368**, December 1, 1953. [b] This compound is 9-cyclohexylidene-6-methyl-3,5-nonadien-2-one. [c] R^4 = allyl. [d] R^4 = propargyl.

TABLE VIII

CYCLOPENTENYLBUTANONES (X)

Compound	R^1	R^2	R^3	R^4	B.P. °C.	B.P. Mm.	n_D^{25}	Analyses: Carbon Calcd.	Analyses: Carbon Found	Analyses: Hydrogen Calcd.	Analyses: Hydrogen Found	Yield, %
Xa[a]	CH_2	H	H	H	59–61	0.3	1.4800					15
Xb	$CHCH_3$	H	H	H	88–89	0.6	1.4822	81.50	81.47	10.75	10.64	15
Xc	$CHCH(CH_3)_2$	H	H	H	96–99	0.3	1.4770	81.99	81.78	11.18	11.19	16
Xd[b]	$-(CH_2)_4CH-$	H	H	H	107	0.1	1.5030	82.70	82.41	10.41	10.13	21
Xf	CH_2	H	C_2H_5	H	85–90	0.5	1.4765	81.76	81.58	10.97	11.04	31
Xh	CH_2	CH_3	H	H	68–70	0.1	1.4839	81.50	81.27	10.75	10.59	10
Xi	CH_2	H	H	C_2H_5	90–92	0.4	1.4809	81.76	82.06	10.97	10.60	29
Xj	CH_2	H	H	C_3H_5[c]	90–92	0.3	1.4888	82.70	82.86	10.41	10.34	22
Xk	CH_2	H	H	C_3H_3[d]	101–103	0.4	1.4952	83.42	83.82	9.63	9.67	18
Xl	$CHCH_3$	H	H	C_2H_5	94–96	0.5	1.4818	81.99	81.67	11.18	11.16	25
Xm	$CHCH_3$	H	H	C_3H_5[c]	107–110	0.7	1.4902	82.87	83.22	10.64	10.89	27

[a] Reference (1). [b] This compound is 4-[5-(cyclohexen-1-yl)-2-methylcyclopenten-1-yl]-2-butanone. [c] R^4 = allyl. [d] R^4 = propargyl.

TABLE IX

α-IONONES (XII)

Compound	R^1	R^2	R^3	R^4	B.P. °C.	B.P. Mm.	n_D^{25}	Analyses: Carbon Calcd.	Analyses: Carbon Found	Analyses: Hydrogen Calcd.	Analyses: Hydrogen Found	Yield, %
XIIa[a]	CH_3	H	H	H	95–100	2	1.4978					80
XIIb	C_2H_5	H	H	H	79–81	0.15	1.5019	81.50	81.32	10.75	10.59	72
XIIc	$(CH_3)_2CHCH_2$	H	H	H	100–105	0.5	1.4970	81.99	82.23	11.18	11.40	80
XIId[b]	$-(CH_2)_4-$	H	H	H	111–116	0.35	1.5235	82.70	82.45	10.41	10.15	66
XIIf	CH_3	H	C_2H_5	H	106	0.8	1.5005	81.76	82.01	10.97	10.70	81
XIIh[c]	CH_3	CH_3	H	H	86–87	0.5	1.4987					77
XIIi	CH_3	H	H	C_2H_5	110	2	1.4968	81.76	81.77	10.97	11.26	83
XIIj	CH_3	H	H	C_3H_5[d]	117	2	1.5055	82.70	83.05	10.41	10.67	69
XIIl	C_2H_5	H	H	C_2H_5	126–128	0.3	1.5000	81.99	82.38	11.18	11.43	85
XIIm	C_2H_5	H	H	C_3H_5[d]	140–142	1.5	1.5090	82.87	82.89	10.64	10.40	66

[a] J. L. Simonsen, *The Terpenes*, University Press, Cambridge, England, 1947, 2nd Ed., Vol. I, p. 122. [b] This compound is 2-methyl-1-(3-oxo-1-buten-1-yl)-spiro[5,5]undec-2-ene. [c] H. Schinz, L. Ruzicka, C. F. Seidel, and Ch. Tavel, *Helv. Chim. Acta*, **30**, 1810 (1947). [d] R^4 = allyl.

TABLE X

β-IONONES (XIII)

Compound	R¹	R²	R³	R⁴	B.P. °C.	B.P. Mm.	n_D^{25}	Analyses: Carbon Calcd.	Analyses: Carbon Found	Analyses: Hydrogen Calcd.	Analyses: Hydrogen Found	Yield, %
XIIIa[a]	CH_3	H	H	H	94–97	0.8–1.0	1.5190					84
XIIIb	C_2H_5	H	H	H	98–100	0.6	1.5182	81.50	81.53	10.75	10.83	74
XIIIc	$(CH_3)_2CHCH_2$	H	H	H	116.5	0.35	1.5102	81.99	81.73	11.18	11.07	65
XIIId[b]	—$(CH_2)_4$—	H	H	H	102	0.05	1.5340	82.70	83.01	10.41	10.27	62
XIIIh[c]	CH_3	CH_3	H	H	100–102	1.1	1.5173					74

[a] J. L. Simonsen, *The Terpenes*, University Press, Cambridge, England, 1947, 2nd Ed., Vol. I, p. 122. [b] This compound is 2-methyl-1-(3-oxo-1-buten-1-yl)spiro[5,5]undec-1-ene. [c] H. Koster, *Ber.*, **80**, 248 (1947).

TABLE XI

GERANYL ACETONES (XIV)

Compound	R¹	R²	R³	R⁴	B.P. °C.	B.P. Mm.	n_D^{25}	d_4^{25}	M_D Calcd.	M_D Found	Analyses: Carbon Calcd.	Analyses: Carbon Found	Analyses: Hydrogen Calcd.	Analyses: Hydrogen Found	Yield, %
XIVa[a]	CH_3	H	H	H	83–85	0.7	1.4650								80
XIVb	C_2H_5	H	H	H	78–80	0.2	1.4661	0.8740	65.95	66.03	80.71	80.94	11.61	11.90	75
XIVc	$(CH_3)_2CHCH_2$	H	H	H	97–100	0.3–0.4	1.4646	0.8628	75.39	75.67	81.29	81.73	11.94	12.04	79
XIVd[b]	—$(CH_2)_4$—	H	H	H	108–110	0.15	1.4888	0.9246	72.99	73.13	81.99	82.21	11.18	11.19	78

[a] W. Kimel and A. C. Cope, *J. Am. Chem. Soc.* **65**, 1992 (1943). [b] This compound is 9-cyclohexylidene-6-methyl-5-nonen-2-one.

Allylic α-alkyl acetoacetates (VI). To a solution of sodium (1.05 g.-atoms) in ethanol (350 ml.) was added an allylic acetoacetate (V, 1.0 mole), and the mixture was stirred for 8 hr. An alkyl halide (1.05 moles) was added, dropwise, and stirring was continued for 48 hr. The sodium halide was removed by filtration and ethanol was removed under diminished pressure. To the residue was added water (2 l.) and petroleum ether (500 ml.), the layers were separated, and the aqueous phase was extracted twice with fresh petroleum ether (300 ml.). The organic portions were combined and were washed successively with ice-cold 1*N* sodium hydroxide (4 times 100 ml.), with ice water (2 times 100 ml.), with ice-cold 1*N* acetic acid (4 times 100 ml.) and finally with ice water (6 times 100 ml.). The solution was dried over calcium sulfate, the solvent was removed *in vacuo*, and the residue (VI) was used directly in the next step.

Unsaturated ketones (VII). The allylic acetoacetate (either V or VI, 1.0 mole) was heated with an aluminum alkoxide (3.0 g.) at a temperature sufficient to maintain a vigorous evolution of carbon dioxide (120–160°). Heating was continued until the gas evolution ceased, normally several hours. The product, VII, was then purified by fractional distillation.

Ethynylcarbinols (VIII). The unsaturated ketones (VII) were ethynylated by the same procedure as described for the ethynylcarbinols (II). In some cases, distillation afforded some unchanged ketone (VII) in addition to the desired ethynylcarbinol (VIII). However, based on reacted ketone, yields were in excess of 90% in every instance.

Vinylcarbinols (IX). These compounds were obtained by selective reduction of the ethynylcarbinols (VIII) in the same manner described earlier for the conversion of II to III. Yields were 90–95% in every instance.

Pseudoionones and cyclopentenylbutanynes (X and XI). Acetoacetates of the acetylenic alcohols (VIII) were obtained by the reaction of VIII with diketene in analogous fashion to the method described for the preparation of V. The requisite acetoacetate (1.0 mole), dissolved in an equal volume of decalin, was heated in the presence of acetic acid (3 g.) and aluminum isopropoxide (0.2 g.) to a temperature sufficient to maintain a vigorous evolution of carbon dioxide (150–200°). After termination of the reaction (cessation of gas evolution) the residual liquid was subjected to careful fractionation. Two main fractions were isolated; a lower-boiling ketone, X, and a higher-boiling product, XI.

α- and β-Ionones (XII and XIII). These ketones were obtained by cyclization of the corresponding pseudoionones (XI) according to the method of Royals.[9] The cyclization agent used for the α-isomers was phosphoric acid and for the β-isomers was a mixture of sulfuric and acetic acids.

Geranylacetones (XIV). These compounds were prepared from the corresponding vinylcarbinols (IX) by pyrolysis of the acetoacetates obtained by reaction of IX with diketene. The method employed was the same as described for the sequence III to V to VII.

Acknowledgment. We wish to thank Dr. Al Steyermark and his staff of the Roche Microchemical Laboratories for the carbon and hydrogen analyses.

NUTLEY 10, N. J.

(9) E. E. Royals, *Ind. Eng. Chem.*, **38**, 546 (1946).

[CONTRIBUTION FROM THE FRUIT AND VEGETABLE CHEMISTRY LABORATORY, WESTERN UTILIZATION RESEARCH AND DEVELOPMENT DIVISION, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

Spectral Studies on Flavonols—the Structure of Azalein

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Received May 27, 1957

Flavonols containing a free dihydroxyl grouping in the 3,4′- position are unstable in alcoholic sodium ethylate and can be distinguished spectrophotometrically by this instability. Sodium acetate produces a characteristic bathochromic shift of the short wave length band of flavonols containing a free 7-hydroxyl group. This shift provides a method for locating this hydroxyl group. The structure proposed for azalein, a flavonol glycoside discovered recently by Wada, has been confirmed by the application of these and other spectrophotometric procedures.

The use of spectrophotometric measurements in determining various structural features of flavonoid compounds is attractive because of its speed, simplicity, and economy of material. Spectral procedures are reported in this paper for the detection of the 3,4′-dihydroxyl and the 7-hydroxyl groups in flavonols. These methods, in combination with a previously reported procedure for detecting *ortho*-dihydroxyl groups,[2] make it possible to approach a virtually complete structural analysis for several widely occurring types of flavonols. The application of these methods in confirming the structure of azalein, a flavonol glycoside recently described by Wada,[3] will be discussed in detail.

Detection of the 3,4′-dihydroxyl group. It is generally considered that the decomposition of flavonols in alkali under ordinary conditions is not rapid, and that in the absence of other alkali-sensitive structures, *e.g.*, the pyrogallol grouping, they may be recovered from alkaline solutions by acidification without significant loss.[4] Dechene,[5] however, has shown that alkaline solutions of rutin, the 3-glycoside of quercetin, are more stable than those of quercetin. This indicates that the unprotected hydroxyl at C_3 in quercetin contributes to its instability. In this study an attempt has been made to define more closely the structural features necessary to produce instability in alkali. The spectra

(1) Collaborator employed by Diamond Walnut Growers, Inc.

(2) L. Jurd, *Arch. Biochem. and Biophys.*, **63**, 376 (1956).

(3) E. Wada, *J. Am. Chem. Soc.*, **78**, 4725 (1956).

(4) T. A. Geissman, in *Modern Methods of Plant Analysis*, K. Paech and M. V. Tracey, eds., Springer, Heidelberg, p. 451 (1955).

(5) E. B. Dechene, *J. Am. Pharm. Assoc.*, **40**, 495 (1951).

TABLE I

SPECTRA OF FLAVONOLS IN 0.002*M* SODIUM ETHYLATE

	EtOH		NaOEt–EtOH			
				Log ϵ		
	λ_{max}	Log ϵ	λ_{max}	0.1 Hr.	1.0 Hr.	$\Delta\lambda$[a]
3-Hydroxyflavone	343	4.22	407	4.20	4.13	64
	239	4.26	237		4.27	
3-Methoxyflavone	299	4.21	299	4.21	4.21	0
	246	4.25	246	4.25	4.25	
3,3′4′-Trihydroxyflavone	368	4.36	311	3.97		..
	250	4.26	234[b]	4.13		
Kaempferol	367.5	4.32	315	4.13		..
(3,4′,5,7-Tetrahydroxyflavone)	266	4.22				
Robinin	352	4.14	399	4.30	4.30	47
(Kaempferol 3-robinoside 7-rhamnoside)	268	4.18	272	4.15	4.15	
			248	4.12	4.12	
Kaempferol	357	4.35	389	4.25	4.24	32
4′,5-Dimethyl ether	259	4.24	275	4.37	4.37	
Quercetin	370	4.32	325	4.19		..
(3,3′,4′,5,7-pentahydroxyflavone)	257	4.31	242[b]	4.13		
Quercetin 3-methyl ether	360	4.31	412	4.33	4.30	52
	258	4.31	272	4.35	4.34	
Quercitrin (quercetin 3-rhamnoside)	350	4.18	402	4.30	4.30	52
	258	4.30	272	4.39	4.38	
Rutin (quercetin 3-rutinoside)	361	4.29	415	4.36	4.36	54
	258	4.37	273	4.35	4.35	
Rhamnetin (3,3′,4′,5-tetrahydroxy-7-	371	4.41	358	3.98		..
methoxyflavone)	256	4.40	294	4.11		
			238[b]	4.35		
Quercimeritrin (quercetin 7-glucoside)	372	4.33	361	4.00		..
	257	4.38	294	4.16		
Xanthorhamnin (Rhamnetin 3-rhamni-	362	4.22	411	4.38	4.37	49
noside)	258	4.33	270	4.35	4.34	
Quercetin 3′,4′,5,7-tetramethyl ether	360	4.31	403	4.23	4.23	43
	252	4.30	263	4.31	4.31	
Quercetin 3′,4′,5,7-tetrabenzyl ether	359	4.19	401	4.08		42
	252	4.22	264	4.08		
Quercetin 3,3′,4′,7-tetramethyl ether	352	4.34	372	4.00	4.00	20
	254	4.37	284	4.40	4.42	
Gossypin (3,3′,4′,5,7,8-hexahydroxy-	380	4.15	325	3.80		..
flavone 8-glucoside)	262	4.12				

[a] $\Delta\lambda$ = λ_{max} of the long wave length band (390–420 mμ) in NaOEt minus λ_{max} of long wave length band (340–380 mμ) in EtOH. Compounds with a positive $\Delta\lambda$ are stable. [b] Inflection.

of a variety of flavonols containing a selected combination of free and protected hydroxyl groups were measured in neutral and in alkaline (0.002*M* NaOEt) solutions at definite time intervals. The results thus obtained are summarized in Table I. Those compounds listed as stable showed the normal spectral shifts to be expected from the ionization of phenolic hydroxyl groups in alkaline solution,[6] *i.e.* the long wave length band shifted from 340–380 mμ in ethanol to about 380–420 mμ in sodium ethylate.[7] The flavonols listed as unstable, however, decomposed within a few minutes after adding the sodium ethylate and the long wave length band disappeared. It is apparent that all of the compounds in which the hydroxyl at C_3 is protected by methylation or glycosidation are stable in the alkaline medium, and that this stability is not appreciably influenced by the number and location of other hydroxyl groups in the molecule (Fig. 1). It is also apparent that of the compounds examined only those which contain a free 4′-hydroxyl in addition to a free 3-hydroxyl are unstable. A free hydroxyl at C_7 does not produce instability. Thus

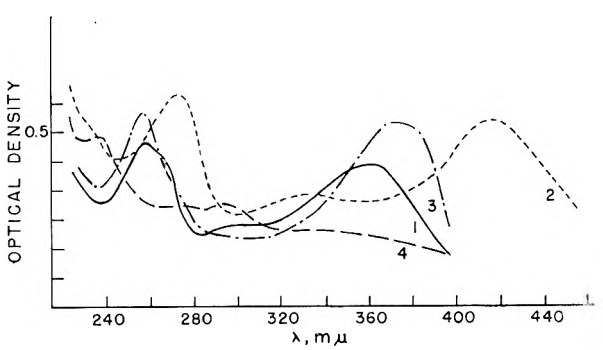
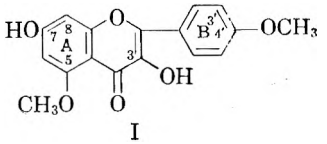


FIG. 1. (1) RUTIN IN ETHANOL, (2) RUTIN IN 0.002 *M* SODIUM ETHYLATE, (3) QUERCIMERITRIN IN ETHANOL, AND (4) QUERCIMERITRIN IN 0.002 *M* SODIUM ETHYLATE.

(6) G. H. Mansfield, T. Swain, and C. G. Nordström, *Nature*, **172**, 23 (1953).

(7) The log ϵ value of the long wave length band slowly decreases on long standing, but the position of the band is unaltered.

kaempferol rapidly decomposes in sodium ethylate, whereas kaempferol 4′,5-dimethyl ether (I) is stable (Fig. 2).



I

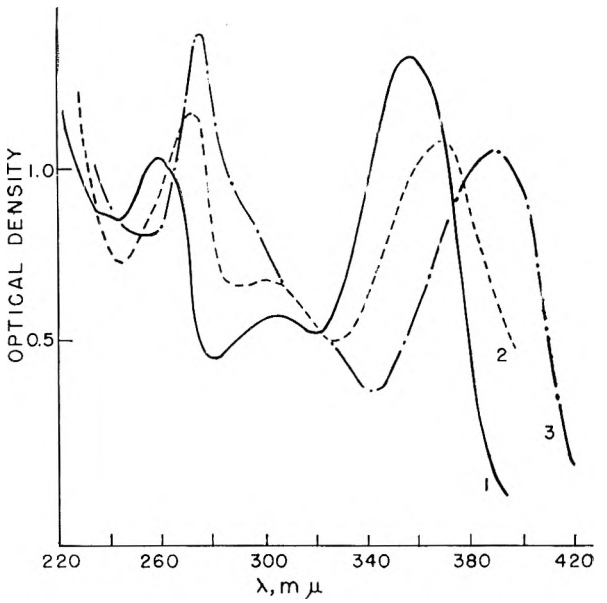


FIG. 2. KAEMPFEROL 4′,5-DIMETHYL ETHER (1) ethanol, (2) ethanolic sodium acetate, and (3) 0.002*M* sodium ethylate.

Detection of the 7-hydroxyl group. Sodium ethylate ionizes all phenolic hydroxyl groups except those which are sterically hindered. Sodium acetate, on the other hand, is capable of ionizing only those groups which are rather strongly acidic. It has been employed in related studies on phenolic acids[8] and on certain flavones.[9] Since theoretical and experimental evidence[10] indicates that the 7-hydroxyl group of flavones and flavonols is probably more acidic than the other hydroxyls, the possibility of using sodium acetate to differentiate this group was studied. It has now been found that in the case of those compounds having a free 7-hydroxyl group (Table II; compounds 2, 3, 5, 6, 8, 9, 14) the short-wave length band which usually occurs at 250–270 mμ in neutral solution is shifted 8–19 mμ toward longer wave lengths on the addition of sodium acetate. Those compounds in which a 7-hydroxyl is not present (Table II; compound 1) or, if present, is protected by alkylation (Table II; compounds 7, 11, 12, 13) or glycosidation (Table II; compounds 4, 10, 15) exhibit no significant change in the position of the short-wave length band on the addition of sodium acetate. Thus, rhamnetin (3,5,-3′,4′-tetrahydroxy-7-methoxyflavone) (II) does not give a shift of this band when sodium acetate is added (Fig. 3). However, shifts are observed with

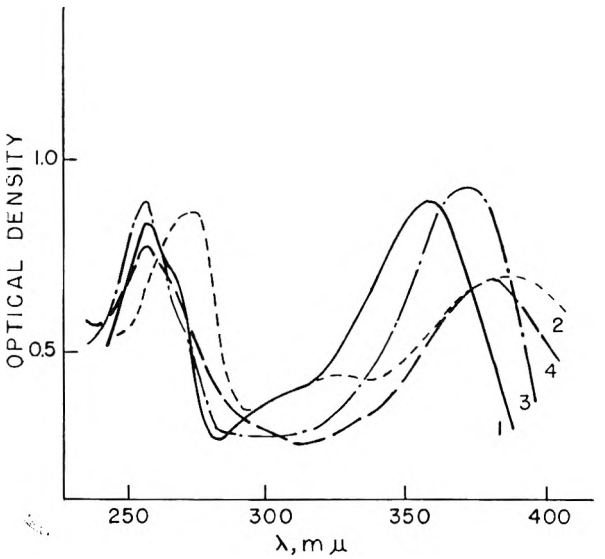
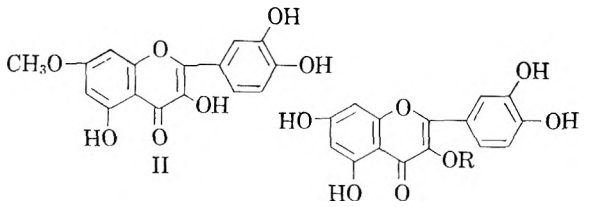


FIG. 3. (1) QUERCETIN 3-METHYL ETHER IN ETHANOL, (2) QUERCETIN 3-METHYL ETHER IN ETHANOLIC SODIUM ACETATE, (3) RHAMNETIN IN ETHANOL, AND (4) RHAMNETIN IN ETHANOLIC SODIUM ACETATE.

quercetin (3,5,7,3′,4′-pentahydroxyflavone) (III) and quercetin 3-methyl ether (IV) where the 7-methoxyl of rhamnetin has been replaced with a 7-hydroxyl. Furthermore gossypitrin, the 7-glucoside of gossypetin (3,5,7,8,3′,4′-hexahydroxyflavone), fails to give a shift, whereas gossypin, the 8-glucoside of gossypetin, does give a shift. The data in Table II show clearly that hydroxyls at positions 3,5,8,3′, and 4′ do not interfere with the test for a free 7-hydroxyl group. The conclusion may be drawn that the 250–270 mμ band in flavonol spectra is associated mainly with absorption in the A-ring and heterocyclic ring of the flavonol, and that a bathochromic shift of this band in the presence of sodium acetate is caused by the ionization of the 7-hydroxyl group. A 5-hydroxyl group is chelated with the carbonyl group at C_4 and is not sufficiently acidic to react with sodium acetate. It can be ionized readily with sodium ethylate, however, and when this occurs, the change in the spectrum is similar to that taking place through ionization of the 7-hydroxyl grouping. For example, the λ_{max} for quercetin 3,3′,4′,7-tetramethyl ether (Table II; compound 13) changes from 254 mμ to 284 mμ in the presence of sodium ethylate. It is noteworthy that in almost all cases a bathochromic shift of the long wave length band (340–380 mμ) occurs upon addition of sodium acetate. This shift is probably due mainly to a partial ionization of the 4′-, 3′-, and 3-hydroxyl groups.

(8) L. Jurd, *Arch. Biochem. and Biophys.*, 66, 284 (1957).
(9) L. Jurd, T. A. Geissman, and M. K. Seikel, *Arch. Biochem. and Biophys.*, 67, 284 (1957).
(10) T. H. Simpson and J. L. Beton, *J. Chem. Soc.*, 4065 (1954).



III, R = H
IV, R = CH_3

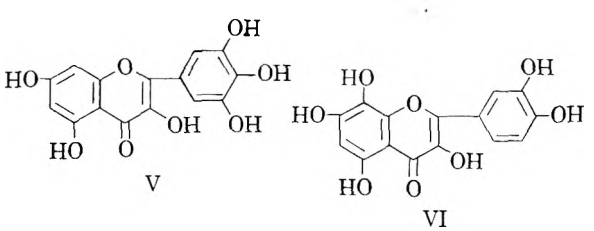
TABLE II

SPECTRA OF FLAVONOLS IN SODIUM ACETATE SOLUTION

Flavonols	EtOH λ_{max}	EtOH–NaOAc λ_{max}	$\Delta\lambda$[a]
(1) 3,3′,4′-Trihydroxyflavone	250	249	−1
(2) Kaempferol	267	275	8
(3) Kaempferol 4′,5-dimethyl ether	259	273	14
(4) Robinin	268	267	−1
(5) Quercetin	256	268	12
(6) Quercetin 3-methyl ether	258	274	16
(7) Rhamnetin	257	257	0
(8) Quercitrin	258	272	16
(9) Rutin	258	270	12
(10) Quercimeritrin	257	258	1
(11) Xanthorhamnin	258	260	2
(12) Quercetin 3′,4′,5,7-tetramethyl ether	252	252	0
(13) Quercetin 3,3′,4′,7-tetramethyl ether	254	253	−1
(14) Gossypin	262	281	19
(15) Gossypitrin (3,3′,4′,5,7,8-hexadroxyflavone 7-glucoside)	262	262	0

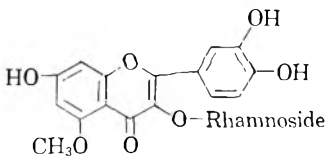
[a] $\Delta\lambda = \lambda_{max}$ (NaOAc) − λ_{max} (EtOH).

Instability of flavonols in sodium ethylate solution may thus be taken to indicate the presence of an unprotected 3,4′-dihydroxyl grouping, while a bathochromic shift of the short-wave length band in the presence of sodium acetate indicates a free 7-hydroxyl group. These conclusions may be applied to the structural analysis of most of the commonly occurring types of flavonols with but few exceptions. The exceptions are those compounds which contain a pyrogallol, *e.g.* myricetin (V), or hydroquinone, *e.g.*, gossypetin (VI), system of unprotected hydroxyl groups. These are highly sensitive to alkali and decompose in sodium ethylate independently of whether the hydroxyl at C_3 is protected. Some of these compounds are unstable even



in the faintly alkaline sodium acetate solution, but it is usually possible to observe whether a bathochromic shift of the short wave length band has occurred if the spectrum is determined immediately upon mixing the reagents.

The structure of azalein. Azalein was isolated by Wada[3] from *Rhododendron mucronatum* and was assigned the structure 3,7,3′,4′-tetrahydroxy-5-methoxyflavone 3-rhamnoside (VII). Since a direct comparison of the aglycone of this compound with an authentic sample of quercetin 5-methyl ether was



VII

not reported, it was considered desirable to confirm the position assigned to the methoxyl and rhamnosido substituents by the spectrophotometric procedures described here.

The spectral data for azalein are given in Table III and Fig. 4 and 5. The presence of a free 7-hy-

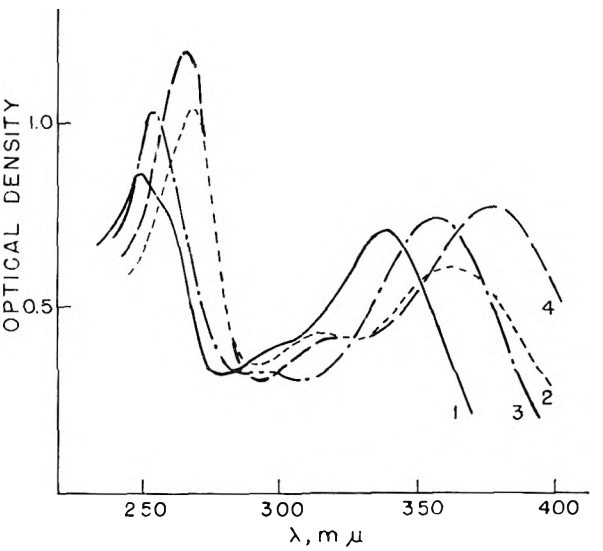


FIG. 4. AZALEIN (1) ethanol, (2) ethanolic sodium acetate, (3) ethanolic boric acid-sodium acetate, and (4) 0.002 *M* sodium ethylate.

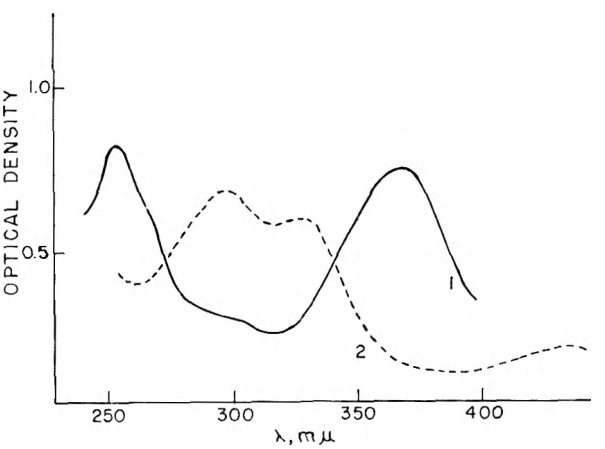


FIG. 5. AZALEATIN (1) ethanol, and (2) 0.002 *M* sodium ethylate.

droxyl group is shown by the 19 mμ shift of the low wave length band in alcoholic sodium acetate. A free *ortho*-dihydroxyl group is indicated by the 18 mμ shift of the long wave length band in the presence of boric acid and sodium acetate.[2] Since azalein is a derivative of quercetin the *ortho*-dihydroxyl group must be in the 3′,4′-position. This leaves positions 3 and 5 as the only remaining sites for the methoxyl and glycosidoxy functions. The glycoside is stable in 0.002*M* sodium ethylate solution, whereas azaleatin, the aglycone produced on acid hydrolysis of azalein, decomposes at once in alkali. From this result it is clear that the rhamnosido linkage is located at position 3 and the methoxyl, therefore, at position 5. Wada's structure for azalein is thus confirmed by a few spectrophotometric measurements requiring less than 1 mg. of material.[11] It should be noted that this determination of structure would not have been possible without prior knowledge that azalein was a mono-methyl ether of a quercetin glycoside. This information was obtained by Wada by classical procedures of isolation, analysis, and degradation. In many favorable cases, where only small amounts of material are available, it should be possible to obtain much of this information by inference from various color tests, wave length of the absorption bands, R_f values, etc. Indeed, unpublished work[12] in this laboratory on a small quantity of a new citrus flavonol has fully confirmed the usefulness of these spectrophotometric procedures in the elucidation of structures.

TABLE III

SPECTRAL DATA FOR AZALEIN AND AZALEATIN

	λ_{max} (Log ϵ)	
Azalein		
EtOH	251 (4.32)	339 (4.23)
NaOAc	270 (4.40)	363 (4.15)
NaOAc-H_3BO_3	255 (4.40)	358 (4.25)
0.002*M* NaOEt	268 (4.46)	379 (4.26)
NaOEt soln. acidified after 30 min.	251 (4.32)	338 (4.17)
Azaleatin		
EtOH	254 (4.30)	369 (4.25)
0.002*M* NaOEt	300 (4.21)	330 (4.16); ~438(3.68)
NaOEt soln. acidified after 30 min.	267 (4.09)	298 (4.03)

EXPERIMENTAL

Spectra in absolute ethanol. A 0.0001*M* solution of each of the flavonols in absolute ethanol was prepared and used as a stock solution. For the determination of the spectra in absolute ethanol, 2.0 ml. of the 0.0001*M* solution was diluted to 10.0 ml. with absolute ethanol to give a concentration C, 0.00002*M*.

Spectra in 0.002M sodium ethylate. To 2.0 ml. of the 0.0001*M* solution of the flavonol, 2.0 ml. of 0.01*M* sodium ethylate was added. The solution was diluted to 10.0 ml. and the spectrum was determined after 5 min., 1 hr., and, in some cases, after 18 hr.

Spectra in alcoholic sodium acetate. After determining the spectrum in absolute alcohol, excess of anhydrous *fused* sodium acetate was added to the sample cell and to the blank solution. The spectrum was measured after 5–10 min.[13]

Azalein. One mg. of azalein (m.p. 183–186°) was dissolved in 10.0 ml. of absolute ethanol. Two ml. portions of this stock solution were then treated with ethanol, sodium acetate, and sodium ethylate exactly as described above. The boric acid–sodium acetate spectrum was determined by the previously reported method.[2]

Azaleatin. One ml. of the stock solution of azalein was treated with one drop of concd. hydrochloric acid and heated on the steam bath for 70 min. The solution was evaporated to dryness *in vacuo* and the residue was diluted to 5.0 ml. with the appropriate reagent.

All spectra were determined at room temperature on a Cary Recording Spectrophotometer or on a Beckman Model DU Spectrophotometer with 1 cm. silica cells.

Acknowledgments. The authors are greatly indebted to Dr. T. A. Geissman for his gift of a specimen of azalein and to Mr. L. Rolle for determining many of the spectra in sodium ethylate solution.

PASADENA, CALIF.

(11) Additional confirmatory evidence is provided by the fluorescence in ultraviolet light of the glycoside and aglycone. When examined on filter paper or in acetic anhydride, the glycoside fluoresces blue and the aglycone yellow. The results of Kuhn and Löw[14] as well as experience in this laboratory indicate that a 5,3-dialkoxy group gives a blue or blue-white, while a 5-alkoxy-3-hydroxyl group gives a yellow color. A free 5-hydroxyl abolishes or greatly diminishes the fluorescence.

(12) R. M. Horowitz, data presented at the 131st meeting of the AMERICAN CHEMICAL SOCIETY, Miami, Fla., April, 1957.

(13) The spectrum of gossypitrin in alcoholic sodium acetate must be determined immediately after the reagents are mixed.

(14) R. Kuhn and I. Löw, *Ber.*, 77, 211 (1944).

[CONTRIBUTION FROM THE LABORATORIES OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Alkylation of Fluorene with Alcohols and Their Alkoxides. III. Polyhydroxy Compounds

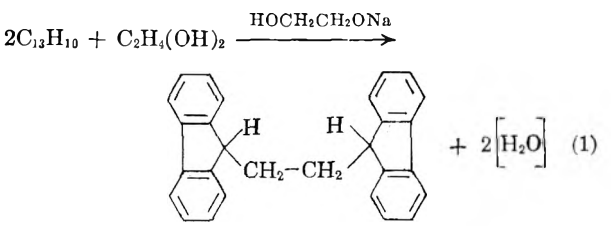
ISAAC D. RUBIN[1] AND ERNEST I. BECKER[2]

Received May 23, 1957

Ethylene glycol, 1,2-propylene glycol, tetramethylene glycol, and pentamethylene glycol with catalytic quantities of their sodium derivatives react with fluorene at 180° to 220° to give 1,2-bis(9-fluorenyl)ethane, 1,2-bis(9-fluorenyl)propane, 1,4-bis(9-fluorenyl)butane and 1,5-bis(9-fluorenyl)pentane, respectively. Trimethylene glycol gave no isolable product. Glycerol gave the same product that ethylene glycol did, but in very poor yield. 2,2-Dimethylpropan-1,3-diol gave 59% of 9-isobutylfluorene.

Previous reports have shown that the pentagonal ring in 1,2,3,4-tetraphenylcyclopentadiene,[3] and in fluorene[4,5] can be alkylated with alcohols and their alkoxides. The first two reports showed that primary alcohols will undergo the reaction while the third showed that secondary alcohols may be used.[6] Abramoff and Sprinzak[7] have quite recently reported a related alkylation of 2-picoline with benzyl alcohol to give 2-phenethylpyridine. The previous articles review the prior literature. The purpose of this investigation was to determine the feasibility of employing polyfunctional alcohols in this novel alkylation reaction.

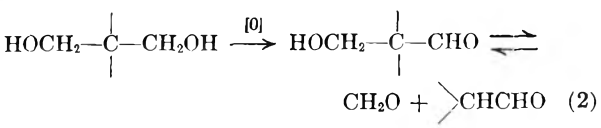
It has now been found that ethylene glycol, 1,2-propylene glycol, tetramethylene glycol and pentamethylene glycol give the corresponding bis-fluorenyl alkanes. Equation 1 illustrates this using ethylene glycol as an example. The products were identified by their molecular weights, ultimate analysis, the presence only of hydrocarbon bands in their infrared spectra, and their insolubility in cold, concentrated sulfuric acid. In the case of 1,2-bis(9-fluorenyl)ethane the melting point agreed with the literature value.



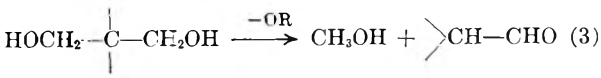
Trimethylene glycol, in contrast to its isomer, 1,2-propylene glycol, did not give an isolable product. Glycerol afforded a mixture from which only 1,2-bis(9-fluorenyl)ethane was isolated together with unreacted fluorene. This unexpected product was characterized by the melting point, mixture melting point, and identity of its infrared spectrum with that of the product prepared from ethylene glycol.

With 2,2-dimethylpropan-1,3-diol, again the loss of one carbon atom was observed and the product, 9-isobutylfluorene, was obtained in 59% yield. It was characterized by ultimate analysis, molecular weight, and a mixture melting point determination with a sample synthesized independently according to a known procedure.[5]

The loss of a carbon atom in the two preceding cases can be ascribed reasonably to degradation of the glycol prior to condensation with fluorene.[4] It is reasonable that the 1,3-glycol is oxidized to a β-hydroxyaldehyde, which could then undergo a reverse aldol condensation, eliminating formaldehyde and giving an aldehyde (Equation 2). The aldehyde could then enter into the reaction scheme



proposed for the alkylation.[4] An alternative and possibly more feasible route is that patterned after Searles and Ives.[8] According to this scheme formaldehyde would be eliminated directly giving an alcohol which would then enter the alkylation. Finally, methanol might be lost directly giving an aldehyde which could enter the alkylation (Equation 3).[9]



(1) From the thesis submitted by Isaac D. Rubin to the Graduate Faculty of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Master of Science, 1957.

(2) To whom inquiries should be directed.

(3) S. M. Linder, E. I. Becker, and P. E. Spoerri, *J. Am. Chem. Soc.*, **75**, 5972 (1953).

(4) K. L. Schoen and E. I. Becker, *J. Am. Chem. Soc.*, **77**, 6030 (1955).

(5) D. N. Matthews and E. I. Becker, *J. Org. Chem.*, **21**, 1317 (1956).

(6) M. F. Carroll, *J. Chem. Soc.*, 507 (1941), also used a secondary alcohol, methyl phenyl carbinol, in the alkylation of ethyl acetoacetate in the α-position, a similar reaction.

(7) M. Abramoff and Y. Sprinzak, *J. Am. Chem. Soc.*, **78**, 4090 (1956).

(8) S. Searles, Jr., and K. E. Ives, 127th Meeting of the American Chemical Society, Cincinnati, Ohio, March 29 to April 7, 1955, Abstracts, p. 24N.

(9) R. W. Brown and G. Dougherty, *J. Org. Chem.*, **13**, 173 (1948).

TABLE I

9-FLUORENYLALKANES

Compound[a]	Method	Yield %	Yield M°C.P.,	M.P. of Pure Product, °C.	Analyses Carbon Caled.	Carbon Found	Hydrogen Caled.	Hydrogen Found	Molecular Weight[b] Caled.	Molecular Weight[b] Found
F—CH_2—CH_2—F	A	56	222–226	227.5–228.3[c-e]	93.80	94.11	6.20	6.05	358	341
	B	48.5	220–224.5							
F—$(CH_2)_4$—F	A	63	155–158	158–158.5	93.21	93.40	6.79	6.87	387	361
	B	54	154–157							
F—$(CH_2)_5$—F	B	35	77–81	81–82	92.94	93.14	7.06	7.15	400	385
F—$CH_2CH(CH_3)_2$	A	59	42–45	45.6–46.6	91.83	92.17	8.17	8.00	222	266, 238
F—CH_2—$\underset{\displaystyle F}{\underset{\vert}{CH}}$—$CH_3$	B	21.5	157–160	161.5–162.5	93.49	93.74	6.51	6.27	372	356

[a] F = 9-fluorenyl. [b] Ebullioscopic in benzene. [c] E. Bergmann, H. Hoffmann, and D. Winter, report m.p. 218–219° [*Ber.*, **66**, 46 (1933)]. [d] M. Wieland and O. Probst [*Ann.*, **530**, 274 (1937)] report m.p. 224–225°. [e] W. Wislicenus reported m.p. 224–225° (uncor.) [*Ber.*, **48**, 617 (1915)].

In the course of the synthesis of 9-isobutylfluorene from isobutyl alcohol and fluorene it was possible to contribute to an understanding of the reaction. It is first necessary to consider the alkylation of certain amines, a related reaction. Pratt and Frazza,[10] Rice and Kohn,[11] Carson and Dressler,[12] and Ainsworth[13] have shown that the alkylation of amines is catalyzed by the use of active nickel catalysts. In particular Rice and Kohn showed that alkylation did not take place until conditions were such that the alcohol used was converted to the corresponding aldehyde. The only base present was the amine being alkylated. Pratt and Frazza used the alkoxide along with the amine without demonstrating the effect of the alkoxide. Likewise in the alkylation of hydrocarbons in this laboratory the catalytic effect of nickel had been shown, but the necessity for a base had not been shown. In the alkylation of fluorene with isobutyl alcohol in the presence of Raney nickel no alkylation took place during 18 hours' reflux, although under the same conditions in a separate reaction, isobutyraldehyde was formed as was demonstrated by the isolation of its 2,4-dinitrophenyl-hydrazone. Using Raney nickel and potassium isobutylate at the same temperature, fluorene was alkylated. Thus, for the alkylation of hydrocarbons not only conditions which give the aldehyde, but also a base is required.

EXPERIMENTAL[14]

Starting materials. The polyhydric alcohols were commercially available materials and before use were distilled, if liquid, or recrystallized, if solid. Their constants agreed with those in the literature.[15] Fluorene was 98% material from Reilly Tar and Chemical Co., recrystallized from alcohol.

Alkylation reactions. Method A. Two grams (0.087 atom) of sodium were added in small chips to 30 g. of the glycol (20 g. in the case of 2,2-dimethylpropan-1,3-diol) in a Carius tube temporarily fitted with a reflux condenser. With the solid 2,2-dimethylpropan-1,3-diol an oil bath was used to melt it before addition of the sodium. Heating was used in all cases to hasten the reaction of the sodium. Fluorene (10 g., 0.060 mole) was then added, and the tube was sealed, heated to 215–220° and maintained at this temperature for 24 hr. After cooling, the tube was opened and the contents were neutralized with 10% hydrochloric acid and transferred to a beaker. After adding 200 ml. of water, the mixture was allowed to stand in the refrigerator overnight whereupon the pasty reaction mass became more tractable. Approximately 11–12 g. of crude product was collected. Two recrystallizations, once from ethanol and once from acetic acid, gave the yields and accompanying melting points shown in Table I. After two further crystallizations

(10) E. F. Pratt and E. J. Frazza, *J. Am. Chem. Soc.*, **76**, 6174 (1954).

(11) R. G. Rice and E. J. Kohn, *J. Am. Chem. Soc.*, **77**, 4052 (1955).

(12) B. B. Carson and H. Dressler, *J. Org. Chem.*, **21**, 474 (1956).

(13) C. Ainsworth, *J. Am. Chem. Soc.*, **78**, 1635 (1956).

(14) All melting points are corrected. Analyses were carried out by Dr. F. Schwartzkopf, 56-19 37th Avenue, Woodside 77, N. Y.

(15) We are grateful for a generous sample of 2,2-dimethylpropan-1,3-diol from Texas Eastman Co.

the product was stirred with cold, concentrated sulfuric acid until no further color developed. Separation of the hydrocarbon was followed by washing with water, drying and recrystallizing from ethanol and then acetic acid to give the analytical samples as indicated in Table I.

Method B. The same quantities of starting materials were used as in Method A. The sodium was added to the glycol and the mixture was heated under reflux until it had all reacted. The fluorene was added and the flask was heated under reflux until it had all reacted. The fluorene was added and the flask was heated by means of an oil bath to reflux or to 215–220°, whichever temperature was reached earlier. After cooling, the same procedure for isolation as in Method A was followed.

Reaction of fluorene with trimethylene glycol. This reaction was carried out using both Methods A and B. Upon recrystallization from acetic acid a yellow solid, m.p. 125–180°, was obtained. No pure compound was isolated from this product using fractional crystallization, vacuum distillation, chromatography on alumina, and sublimation.

Reaction of fluorene with glycerin. Sodium (2 g., 0.087 atom) was added under nitrogen with great caution to 30 ml. (0.41 mole) of glycerine in a 125-ml. flask. The metal was added in small amounts. The flask was heated gently in an oil bath, but at no time was the temperature in the flask allowed to rise above 65°. In a few cases without these precautions the reaction mixture caught fire. Fluorene (10 g., 0.060 mole) was added, the nitrogen tube removed and the mixture was heated at 200–210° for 24 hr. After cooling, it was extracted with successive portions of water and benzene and neutralized with 10% hydrochloric acid. The benzene layer was washed several times with water and dried over potassium carbonate. Distillation of the benzene afforded 9.6 g. of yellowish residue. By means of difference in solubility in glacial acetic acid, two substances, A and B, were isolated. Substance A (8.5 g.), the more soluble one, melted at 113–114.5°, and showed no melting point depression when mixed with a sample of pure fluorene. Substance B (0.3 g.) melted at 227–228.4°. An infrared spectrum of this compound was identical with that of 1,2-bis(9-fluorenyl)ethane prepared by treating fluorene with ethylene glycol. A mixture melting point determination with 1,2-bis(9-fluorenyl)ethane showed no depression.

Identical results were obtained carrying out the reaction in a Carius tube at 220° for 24 hr.

Unsuccessful attempt to alkylate fluorene with 2,2-dimethylpropan-1,3-diol. 2,2-Dimethylpropan-1,3-diol (10.4 g., 0.10 mole) was dissolved in 200 ml. of xylene heating to bring all the glycol into solution. Sodium (0.46 g., 0.020 mole) was then added and after the reaction was complete, 10 g. (0.05 mole) of fluorene was added together with 2 g. of Davison nickel catalyst. The mixture was refluxed under a Dean-Stark trap for 24 hr. The hot liquid was then filtered, washed repeatedly with water, and distilled, leaving 9.2 g. of a light solid, m.p. 108–112°. A mixture melting point determination with fluorene showed no depression.

9-Isobutylfluorene. The alkylation Reaction Method II of Matthews and Becker[5] was followed. Potassium (10 g., 0.026 atom) was added in portions to a solution of 13.5 g. (0.18 mole) of isobutyl alcohol in 50 ml. of xylene. Then a slurry of 18 g. (0.11 mole) of fluorene in 200 ml. of xylene was added together with 4 g. of Davison nickel catalyst which had previously been washed with methanol and three times with isobutyl alcohol. The mixture was refluxed under a Dean-Stark trap for 18 hr. and then filtered hot. After washing with three 100-ml. portions of water, it was distilled leaving a residue which was recrystallized from methanol to give 14 g. of colorless product, m.p. 31–36°. A number of recrystallizations alternately from ethanol and from acetic acid gave the analytical sample, m.p. 45–46°. A mixture melting point with the product of the reaction between 2,2-dimethylpropan-1,3-diol was not depressed.

Unsuccessful attempt to prepare 9-isobutylfluorene. I. Xylene (200 ml.) and Davison nickel catalyst (4 g.), which had been previously washed as described above, were refluxed under a Dean-Stark Trap for 15 min. until no more water was accumulated in the trap. Isobutyl alcohol (13.5 g., 0.18 mole) and fluorene (18 g., 0.11 mole) were added and the mixture was refluxed for 18 hr. No water layer was formed in the trap during refluxing. The mixture was filtered while hot, washed with three 100-ml. portions of water and distilled. The residue consisted of 17.5 g. of unreacted fluorene, m.p. 112–113°.

Unsuccessful attempt to prepare 9-isobutylfluorene. II. Isobutyl alcohol (100 g., 1.33 moles) was refluxed together with 30 g. of washed Davison nickel catalyst and 10 g. (0.06 mole) of fluorene for 24 hr. over a Soxhlet extractor, the thimble of which contained calcium hydride. The solution was then filtered while hot, and the alcohol distilled. The residue consisted of 9.3 g. of unreacted fluorene, m.p. 113–115°. No alkylation product was observed.

Formation of isobutyraldehyde in presence of Raney nickel. Isobutyl alcohol (20 g., 0.266 mole) was refluxed with 6 g. washed Davison nickel catalyst and the vapors formed in the reaction were collected in a test tube. The condensate was treated with 2,4-dinitrophenylhydrazone reagent and gave an orange precipitate. Two recrystallizations from alcohol gave an orange product, m.p. 179–181° (reported for 2,4-dinitrophenylhydrazone of isobutyraldehyde, 182°). A mixture melting point determination with the 2,4-dinitrophenylhydrazone prepared from isobutyraldehyde showed no depression.

BROOKLYN 1, N. Y.

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, THE INSTITUTE OF SCIENCE]

Formylation of Benzopyrones. I. Formylation of Hydroxycoumarins with Hexamethylenetetramine[1]

R. M. NAIK AND V. M. THAKOR[2]

Received May 22, 1957

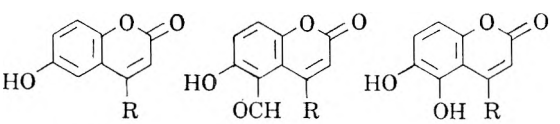
The applicability of hexamethylenetetramine as a formylating agent to some typical hydroxycoumarins has been systematically investigated. The successful Dakin oxidation of the formylcoumarins has offered a method of introduction of a hydroxyl group in the *ortho* position, thus constituting a method for the synthesis of polyhydroxycoumarins. It is significant that 5-hydroxy-4-methylcoumarin and 5-hydroxy-4,7-dimethylcoumarin yielded diformyl derivatives. The hitherto unknown 4-methyl-5,6,7,8-tetrahydroxycoumarin and its partially and completely methylated derivatives have been synthesized.

In connection with the work on the synthesis of some naturally occurring furanocoumarins we were interested in the preparation of hydroxyformylcoumarins, being the intermediates for the synthesis of these compounds. A perusal of literature revealed that no systematic work has been done in this direction.[3] The formylcoumarins would also be important starting materials for the synthesis of a number of heterocyclic compounds and polyhydroxycoumarins, and therefore it was thought of interest to investigate the application of various methods of formylation to the coumarin series.

Attempts were first made to formylate 7-hydroxy-4-methylcoumarin by the Gattermann reaction with zinc cyanide and hydrogen chloride. However, all the attempts—in ether at 0°, in nitrobenzene at room temperature (*ca.* 30°) or applying the modifications of Adams,[4] Hinkel[5] and their co-workers using anhydrous aluminum chloride in *o*-dichlorobenzene at 80°—were unsuccessful.

However, earlier Späth and Pailer[6] and later Rangaswami and Seshadri[7] had employed the Duff and Bills method[8] using hexamethylenetetramine in the formylation of 7-hydroxycoumarin and its 4-methyl derivative, respectively. In the present communication, the application of this method to some typical hydroxycoumarins is described. The *ortho*-hydroxyformylcoumarins obtained smoothly underwent Dakin oxidation to the corresponding *ortho*-dihydroxycoumarins.

6-Hydroxy-4-methylcoumarin (I, R = CH_3), on formylation with hexamethylenetetramine, furnished an aldehyde, m.p. 191°, in poor yield. The reaction was found to proceed with difficulty and even after prolonged heating (36 hours) on a steam bath, a considerable amount of the original coumarin was recovered. The Dakin oxidation of the aldehyde afforded the known[9] 5,6-dihydroxy-4-methylcoumarin (III, R = CH_3). Hence the structure of 5-formyl-6-hydroxy-4-methylcoumarin (II, R = CH_3) has been assigned to the aldehyde. 6-Hydroxycoumarin (I, R = CH_3) on similar formylation, gave a monoformyl derivative, m.p. 189°, in fairly good yield, and the unreacted coumarin



I II III

could not be isolated. The aldehyde, on oxidation with hydrogen peroxide, furnished a dihydroxycoumarin, m.p. 269°, which considerably depressed the m.p. of 6,7-dihydroxycoumarin (m.p. 268°). The dimethyl ether of the dihydroxycoumarin obtained in the present case melted at 111°, whereas the melting point of 6,7-dimethoxycoumarin has been reported[10] to be 146°. Hence the structures of 5-formyl-6-hydroxycoumarin (II, R = H) and 5,6-dihydroxycoumarin (III, R = H) have been respectively assigned to the aldehyde and its oxidation product. This is also confirmed by the behavior of 6-hydroxy-4-methylcoumarin observed earlier.

When the whole work was complete, a paper by Sastri and co-workers[11] appeared in which they reported the formylation of the above two coumarins by the same method. However, the melting points of the substances reported by them are different

(1) This paper comprises a portion of the thesis presented by R. M. Naik towards the requirement of the degree of Doctor of Philosophy of the University of Bombay, and the work was carried out during the tenure of the Government of India research scholarship.

(2) Present address: Department of Chemistry, Gujarat College, Ahmedabad.

(3) R. M. Naik and V. M. Thakor, *Current Sci. (India)*, **21**, 349 (1952).

(4) R. Adams and E. Montgomery, *J. Am. Chem. Soc.*, **46**, 1518 (1924).

(5) L. E. Hinkel, E. E. Ayling, and J. H. Beynon, *J. Chem. Soc.*, 339 (1936).

(6) E. Späth and M. Pailer, *Ber.*, **68**, 940 (1935).

(7) S. Rangaswami and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **6A**, 112 (1937).

(8) J. C. Duff and E. J. Bills, *J. Chem. Soc.*, 1987 (1932); 1305 (1934).

(9) V. J. Dalvi, R. B. Desai, and S. Sethna, *J. Indian Chem. Soc.*, **28**, 366 (1951).

(10) H. Simada, *J. Pharm. Soc.*, **57**, 618 (1937).

(11) V. D. Nageswara Sastri and Co-workers, *Proc. Indian Acad. Sci.*, **37A**, 681 (1953).

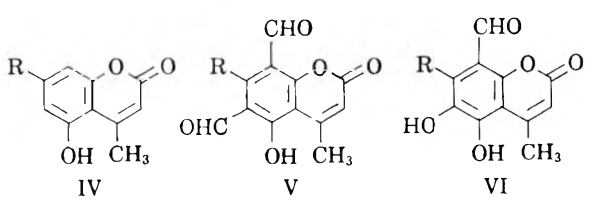
from those observed by us. Table I is given for comparison of the melting points.

TABLE I

Substance	M.P., °C. Observed	Reported[11]
5-Formyl-6-hydroxy-4-methylcoumarin	191	202–203
5-Formyl-6-hydroxycoumarin	189	212–213
5,6-Dihydroxycoumarin	269	256–258
5,6-Dimethoxycoumarin	111	132–133

The melting points of the aldehydes obtained in the present case could not be raised even after several crystallizations. The aldehydes, on treatment with 10% sodium hydroxide, yielded the corresponding deep yellow insoluble sodium salts, whereas the original coumarins remained in solution under the same conditions. The sodium salts were isolated but could not be crystallized. On acidification with hydrochloric acid the aldehydes of unchanged melting points were obtained. On repetition of the reaction with 6-hydroxy-4-methylcoumarin under the conditions (heating for 8 hours on a steambath) described by Sastri and coworkers,[11] mostly the unreacted coumarin was recovered along with only traces of the aldehyde, m.p. 191°.

5-Hydroxy-4-methylcoumarin (IV, R = H) afforded a diformyl derivative (as shown by analysis) on reaction with hexamethylenetetramine. The structure of 6,8-diformyl-5-hydroxy-4-methylcoumarin (V, R = H) has been assigned to this product, as only two positions, *viz.*, 6 and 8 being *ortho* and *para* to the hydroxyl group in 5 position, would be the most reactive. Moreover, the diformyl derivative on oxidation with hydrogen peroxide furnished a dihydroxycoumarin which gave green coloration with alcoholic ferric chloride and also afforded a 2,4-dinitrophenylhydrazone. The structure of 5,6-dihydroxy-8-formyl 4-methylcoumarin (VI, R = H) has been assigned to the oxidation product as (*i*) with ferric chloride it gave a green coloration characteristic of *o*-dihydroxy compound, and (*ii*) during this reaction, the *ortho*-carbonyl group is more easily oxidized than the *para*-carbonyl one.

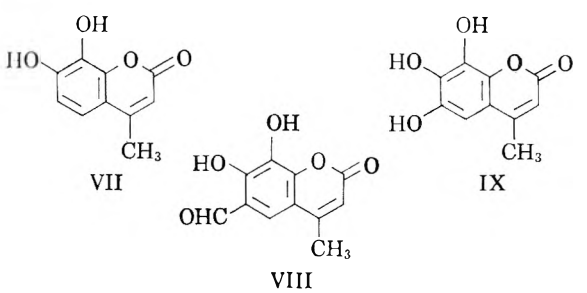


IV V VI

The formylation of 5-hydroxy-4,7-dimethylcoumarin (IV, R = CH_3) similarly furnished 6,8-diformyl-4,7-dimethyl-5-hydroxycoumarin (V, R = CH_3) which gave 5,6-dihydroxy-4,7-dimethyl-8-formylcoumarin (VI, R = CH_3) on oxidation with hydrogen peroxide. It is significant to note that both of the above 5-hydroxycoumarins yielded the diformyl derivatives on reaction with hexamethylenetetramine. The simultaneous introduction of two formyl groups has been observed by Duff[12] in case of *o*-cresol and 6-chloro-*m*-cresol.

Both these 5-hydroxycoumarins also gave rise to insoluble orange red complex products along with the diformylcoumarins. This tendency to form red, insoluble, complex products appeared to be general with 5-hydroxycoumarin derivatives. Thus, attempts to formylate 5,7-dihydroxy-4-methylcoumarin and 5,6,7-trihydroxy-4-methylcoumarin met with failure and only complex products were quantitatively formed.

The interaction of 7,8-dihydroxy-4-methylcoumarin (VII) with hexamethylenetetramine afforded a fairly good yield of the formyl derivative which underwent hydrogen peroxide oxidation to furnish 4-methyl-6,7,8-trihydroxycoumarin (IX) identified by direct comparison with the specimen prepared according to Parikh and Sethna.[13] Hence the structure of 7,8-dihydroxy-6-formyl-4-methylcoumarin (VIII) has been assigned to the formyl derivative. This provided another convenient method for the preparation of 4-methyl-6,7,8-trihydroxycoumarin (IX). Similar formylation of 7,8-dihydroxy-5-methoxy-4-methylcoumarin met with failure, the resultant product being a crimson red complex product. This observation is in accordance with the behavior of 5-hydroxycoumarin derivatives. The formylation of 7,8-dimethoxy-6-hydroxy-4-methylcoumarin (X) afforded an aldehyde, m.p. 156°, in fairly good yield and the original coumarin was not recovered, in contrast to the behavior of 6-



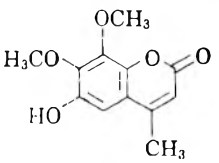
VII VIII IX

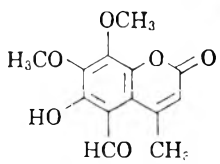
hydroxy-4-methylcoumarin. The structure of 5-formyl-7,8-dimethoxy-6-hydroxy-4-methylcoumarin (XI) has been assigned to the formyl derivative as it gave a red coloration with alcoholic ferric chloride and only one position, *viz.* 5, is vacant for the formyl group to enter. This aldehyde (XI) underwent Dakin oxidation to furnish 5,6-dihydroxy-7,8-dimethoxy-4-methylcoumarin (XII) which gave a characteristic bottle-green coloration with alcoholic ferric chloride. This was fully methylated with dimethyl sulfate to give 4-methyl-5,6,7,8-tetramethoxycoumarin (XIII). On account of the

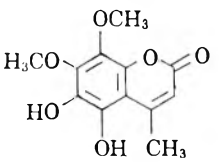
(12) J. C. Duff, *J. Chem. Soc.*, 547 (1941).

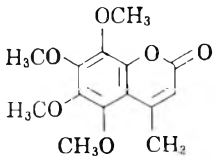
(13) R. J. Parikh and S. Sethna, *J. Indian Chem. Soc.*, **27**, 369 (1950).

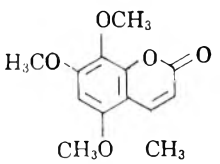
low yield of XII during Dakin oxidation, the demethylation was not carried out. On the other hand, the Elbs persulfate oxidation of 4-methyl-5,7,8-trimethoxycoumarin (XIV) furnished a fairly good yield of 6-hydroxy-5,7,8-trimethoxy-4-methylcoumarin (XV). The methylation of this product (XV) furnished the above described 4-methyl-5,6,7,8-tetramethoxycoumarin (XIII), while the demethylation of XV with hydriodic acid in acetic anhydride gave 4-methyl-5,6,7,8-tetrahydroxycoumarin (XVI) which gave with alcoholic ferric chloride, a crimson-red coloration which rapidly changed to purple-violet and then to pale green. The color disappeared completely on keeping. It dissolved in

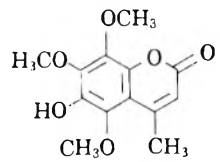

X

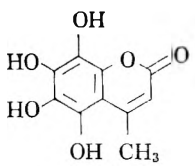

XI


XII


XIII


XIV


XV


XVI

alkali but soon blue particles separated indicating the great susceptibility to oxidation.

EXPERIMENTAL[14]

5-Formyl-6-hydroxy-4-methylcoumarin (II, R = CH_3). To a solution of 5.0 g. of 6-hydroxy-4-methylcoumarin in 100 cc. of hot acetic acid, 10.0 g. of hexamethylenetetramine was added and the reaction mixture was gently refluxed for 10 hr. A hot mixture of 75 cc. of concentrated hydrochloric acid and 75 cc. of water was added to the hot reaction mixture and the contents were further heated on a steam bath for 2 hr., cooled, and extracted with ether. The products obtained on removal of ether and residual acetic acid were found to consist of the formyl derivative and the original coumarin. The mixture was triturated with alcohol and filtered. The undissolved part melting over the range 205–230° was found to contain mostly the unreacted coumarin with traces of the formyl derivative. The filtrate on cooling gave the formylcoumarin. It was crystallized from alcohol in clusters of shining yellow needles, m.p. 190–191°, yield 1.1 g. A sample of this was twice recrystallized from alcohol, m.p. 191°.

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.7; H, 3.9. Found: C, 64.9; H, 4.2.

Since Sastri and co-workers[11] gave m.p. 202–203°, the product was treated with 10% sodium hydroxide. The sodium salt of the formyl coumarin separated. The salt was isolated but could not be crystallized. On acidification it gave the aldehyde which was crystallized from alcohol, m.p. 191°. It gives deep red coloration with alcoholic ferric chloride.

It was characterized by the preparation of the 2,4-dinitrophenylhydrazone, crystallized from acetic acid in orange yellow needles, m.p. 312° (dec.).

Anal. Calcd. for $C_{17}H_{12}O_7N_4$: N, 14.6. Found: N, 14.8.

5,6-Dihydroxy-4-methylcoumarin (III, R = CH_3). To a solution of 0.2 g. of 5-formyl-6-hydroxy-4-methylcoumarin in 5 cc. of 2% sodium hydroxide and 5 cc. of water at 0°, 1.5 cc. of 6% hydrogen peroxide was added dropwise. The reaction mixture was kept at 0° for an hour with occasional stirring when some product separated out. The reaction mixture was acidified and the product which separated was crystallized from alcohol (charcoal) in thin shining yellow needles, m.p. 248° alone and when mixed with 5,6-dihydroxy-4-methylcoumarin prepared according to Dalvi, Desai, and Sethna.[9]

5-Formyl-6-hydroxycoumarin (II, R = H). Five grams of 6-hydroxycoumarin, 10 g. of hexamethylenetetramine and 100 cc. of glacial acetic acid were heated on a steam bath for 8 hr., and 75 cc. each of concentrated hydrochloric acid and hot water were added. After the usual treatment the ether extract gave a deep yellow product which crystallized from alcohol in clusters of yellow needles, m.p. 189°, yield 2.2 g. A sample was twice recrystallized from alcohol, m.p. 189°.

Anal. Calcd. for $C_{11}H_8O_5$: C, 60.0; H, 3.6. Found: C, 60.3; H, 3.7.

Since Sastri and co-workers[11] give m.p. 212–213°, an attempt was made to purify it by preparation of its sodium salt and acidification. The product even after repeated crystallization from alcohol and acetic acid melted at 189°. It gave deep red coloration with alcoholic ferric chloride.

Its *2,4-dinitrophenylhydrazone* was crystallized from acetic acid in orange yellow plates, m.p. >315°.

Anal. Calcd. for $C_{16}H_{10}N_4O_7$: N, 15.1. Found: N, 15.4.

5,6-Dihydroxycoumarin (III, R = H). To 0.4 g. of 5-formyl-6-hydroxycoumarin in 4 cc. of 2% sodium hydroxide solution at 0°, 2 cc. of 6% hydrogen peroxide was dropwise added with stirring. The sodium salt of the aldehyde which separated slowly reacted and the color of the reaction mixture gradually changed from orange-red to light yellow. It was kept at 0° for 0.5 hr. with occasional shaking. It was worked up as usual and the product crystallized twice from alcohol to yield 0.2 g. of thin golden yellow prisms, m.p. 269°. It gives a deep green coloration with alcoholic ferric chloride and depresses the melting point of 6,7-dihydroxycoumarin (m.p. 268°). Sastri and co-workers give m.p. 256–258°.

Anal. Calcd. for $C_9H_6O_4$: C, 60.7; H, 3.4. Found: C, 60.9; H, 3.5.

5,6-Dimethoxycoumarin obtained by methylation of III (R = H) was crystallized from alcohol in shining yellow needles, m.p. 111°. Sastri and co-workers give m.p. 132–133°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.1; H, 4.9. Found: C, 64.4; H, 4.9.

6,8-Diformyl-5-hydroxy-4-methylcoumarin (V, R = H). A mixture of 2 g. of 5-hydroxy-4-methylcoumarin, 4.0 g. of hexamethylenetetramine and 50 cc. of acetic acid was heated on a steam bath for 5 hr. The solution turned red and an orange-yellow complex product separated. Hot concentrated hydrochloric acid (20 ml.) and water were then added and the contents heated for 2 hr. The complex which went into solution reseparated on cooling. Exhaustive ether

(14) Melting points are uncorrected and were taken in open capillary tubes.

extraction of the contents afforded a yellow product which crystallized from acetic acid in thin light yellow needles, m.p. 242°, yield 1.1 g. A sample of it was twice recrystallized, m.p. 242°.

Anal. Calcd. for $C_{12}H_8O_5$ (based on 2-formyl groups): C, 62.1; H, 3.5. Found: C, 62.1; H, 3.6.

It gives a deep blood-red coloration with alcoholic ferric chloride and forms a crimson red *2,4-dinitrophenylhydrazone*, almost insoluble in boiling acetic acid, m.p. >315°.

Anal. Calcd. for $C_{18}H_{12}N_4O_8$ (monohydrazone): N, 13.6. Found: N, 14.1.

The complex product which remained in the aqueous layer was collected. It is insoluble in ether, ethanol, acetic acid and could not be crystallized. It contains nitrogen but is insoluble in hydrochloric acid. It dissolves in alkali and reprecipitates on acidification. It was recovered unchanged after keeping with cold concentrated sulfuric acid or boiling with hydrochloric acid alone or in acetic acid. It does not melt but chars and leaves a residue.

5,6-Dihydroxy-8-formyl-4-methylcoumarin (VI, R = H). A solution of 0.2 g. of 6,8-diformyl-5-hydroxy-4-methylcoumarin in 3.0 cc. of 2% sodium hydroxide at 0° was treated with 2.0 cc. of 6% hydrogen peroxide as usual. The product crystallized from glacial acetic acid (charcoal) as light yellow plates, m.p. 295° (dec.).

Anal. Calcd. for $C_{11}H_8O_5$: C, 60.0; H, 3.6. Found: C, 60.4; H, 3.9.

It gives a deep green coloration with alcoholic ferric chloride and forms a *2,4-dinitrophenylhydrazone* almost insoluble in boiling acetic acid, m.p. >315°.

Anal. Calcd. for $C_{17}H_{12}N_4O_8$: N, 14.0. Found: N, 14.3.

6,8-Diformyl-4,7-dimethyl-5-hydroxycoumarin (V, R = CH_3). Two grams of 4,7-dimethyl-5-hydroxycoumarin, 4 g. of hexamethylenetetramine, and 50 cc. of glacial acetic acid were heated on a steam bath for 5 hr. The reaction mixture was worked up as in the previous case. The ether extract afforded the product which crystallized from acetic acid as light yellow needles, m.p. 196°, yield 0.7 g.

Anal. Calcd. for $C_{13}H_{10}O_5$ (based on 2-formyl groups): C, 63.4; H, 4.1. Found: C, 63.6; H, 4.3.

It gives a blood-red coloration with alcoholic ferric chloride and forms a crimson red *2,4-dinitrophenylhydrazone* almost insoluble in boiling acetic acid, m.p. >315°.

Anal. Calcd. for $C_{19}H_{14}N_4O_8$ (monohydrazone): N, 13.1. Found: N, 12.6.

The orange-red complex product obtained from the aqueous layer showed behavior similar to the product obtained in the previous case.

5,6-Dihydroxy-4,7-dimethyl-8-formylcoumarin (VI, R = CH_3). The Dakin oxidation of V (R = CH_3) was carried out under the same conditions as in the case of 6,8-diformyl-5-hydroxy-4-methylcoumarin (V, R = H). The product obtained was crystallized from acetic acid (charcoal), in thin light yellow plates, m.p. 282–283° (dec.).

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.5; H, 4.2. Found: C, 61.6; H, 4.3.

It gives a deep green coloration with alcoholic ferric chloride and forms a *2,4-dinitrophenylhydrazone* crystallized from acetic acid in thin crimson red needles, m.p. 298–299° (dec.).

Anal. Calcd. for $C_{18}H_{14}N_4O_8$: N, 13.5. Found: N, 13.1.

7,8-Dihydroxy-6-formyl-4-methylcoumarin (VIII). A mixture of 5 g. of 7,8-dihydroxy-4-methylcoumarin, 5 g. of hexamethylenetetramine and 60 cc. of acetic acid was heated on a steam bath for 5 hr. It was then further heated with dilute hydrochloric acid for an hour, cooled, and extracted with ether. Ether and residual acetic acid were evaporated and the greenish yellow product which separated was crystallized from acetic acid in thin light yellow needles, m.p. 268°, yield 2.1 g. It gives a deep bottle-green coloration with alcoholic ferric chloride.

Anal. Calcd. for $C_{11}H_8O_5$: C, 60.0; H, 3.6. Found: C, 60.3; H, 3.7.

4-Methyl-6,7,8-trihydroxycoumarin (IX). Two ml. of 6% hydrogen peroxide were dropwise added with stirring to a solution of 0.4 g. of 7,8-dihydroxy-6-formyl-4-methylcoumarin in 10 cc. of 2% sodium hydroxide at 0°. After keeping for an hour at 0°, it was acidified. The product obtained was crystallized from alcohol, m.p. 274–275° alone and when mixed with an authentic specimen prepared according to Parikh and Sethna.[13]

7,8-Dimethoxy-6-hydroxy-5-formyl-4-methylcoumarin (XI). A mixture of 3 g. of 7,8-dimethoxy-6-hydroxy-4-methylcoumarin, 6 g. of hexamethylenetetramine, and 20 cc. of acetic acid was heated on a steam bath for 5 hr. On working up as in the previous case, a deep yellow pasty product was obtained, which solidified on keeping overnight in a desiccator. It was crystallized from alcohol, in shining needles, m.p. 156°, yield 0.8 g. It gives a deep red coloration with alcoholic ferric chloride and dissolves in alkali giving an orange solution.

Anal. Calcd. for $C_{13}H_{12}O_6$: C, 59.1; H, 4.5. Found: C, 58.9; H, 4.4.

5,6-Dihydroxy-7,8-dimethoxy-4-methylcoumarin (XII). A solution of 0.3 g. of 7,8-dimethoxy-6-hydroxy-5-formyl-4-methylcoumarin in 1.5 cc. of 2% sodium hydroxide and 3 cc. of water at 0° was as usual treated with 1 cc. of 6% hydrogen peroxide and then worked up. The substance which separated after acidification was collected and crystallized from dilute alcohol to yield 0.1 g. of thin light pink flakes, m.p. 190°.

Anal. Calcd. for $C_{12}H_{12}O_6$: C, 57.2; H, 4.7. Found: C, 57.0; H, 4.3.

4-Methyl-5,6,7,8-tetramethoxycoumarin (XIII). It was prepared by methylation of 5,6-dihydroxy-7,8-dimethoxy-4-methylcoumarin and crystallized from methyl alcohol in white needles, m.p. 65–66°. It is insoluble in alkali and does not give any coloration with ferric chloride.

Anal. Calcd. for $C_{14}H_{16}O_6$: C, 60.0; H, 5.7. Found: C, 60.1; H, 5.7.

6-Hydroxy-5,7,8-trimethoxy-4-methylcoumarin (XV). To a well stirred solution of 2.5 g. of 4-methyl-5,7,8-trimethoxycoumarin in 20 cc. of 10% sodium hydroxide obtained by warming on a steam bath was dropwise added at 0°, a solution of 2.7 g. of potassium persulfate in 55 cc. of water during the course of 2 hr. The reaction mixture was kept overnight and then just acidified. The original substance which separated was removed and the filtrate was heated with excess of hydrochloric acid when a brown product separated. It crystallized from methanol (charcoal) as 0.1 g. of thin long shining yellow needles, m.p. 212°. It does not give any coloration with alcoholic ferric chloride.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.6; H, 5.3. Found: C, 58.4; H, 5.3.

The product was methylated to furnish the same 4-methyl-5,6,7,8-tetramethoxycoumarin, m.p. 65–66° as described above.

4-Methyl-5,6,7,8-tetrahydroxycoumarin (XVI). A mixture of 0.2 g. of 6-hydroxy-5,7,8-trimethoxy-4-methylcoumarin, 5 cc. of acetic anhydride and 5 cc. of hydriodic acid was refluxed for 3 hr. in an oil bath at 135–140°. It was then poured into sodium bisulfite solution and the bright yellow substance which separated was crystallized from alcohol in grey-colored prisms, m.p. 278–279°, yield 80 mg. It dissolved in alkali giving an orange-yellow solution, but soon blue particles separated. With alcoholic ferric chloride, it gives a crimson red coloration which rapidly changes to purple-violet and then to pale green. The color disappears completely on keeping.

Anal. Calcd. for $C_{10}H_8O_6$: C, 53.6; H, 3.6. Found: C, 53.3; H, 3.4.

Acknowledgment. The authors thank Dr. R. C. Shah, National Chemical Laboratory, Poona for his keen interest in the work.

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[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, THE INSTITUTE OF SCIENCE]

Formylation of Benzopyrones. II. Formylation of Hydroxycoumarins with *N*-Methylformanilide[1]

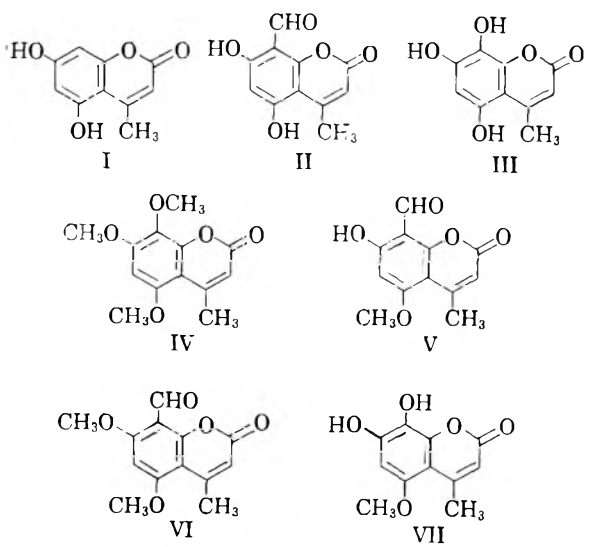
R. M. NAIK AND V. M. THAKOR[2]

Received May 22, 1957

The formylation of 5,7-dihydroxy-4-methyl-, 5-hydroxy-4-methyl-, and 4,7-dimethyl-5-hydroxycoumarins with *N*-methylformanilide has been investigated for the first time and the resulting formylcoumarins have been subjected to Dakin oxidation to furnish the corresponding *o*-dihydroxycoumarin derivatives. The formylation of 4-methyl-5,6,7-trihydroxycoumarin met with a failure although 4-methyl-5,6,7-trimethoxy-4-methylcoumarin could be formylated to furnish the 8-formyl derivative in poor yield. The applicability of *N*-methylformanilide as a formylating agent to the coumarin series appears to be limited. With almost all coumarins a good amount of the unreacted substance was recovered.

In an earlier publication[3] it was pointed out that the formylation of 5,7-dihydroxy- and 5,6,7-trihydroxy-4-methylcoumarins with hexamethylenetetramine met with failures. To find a suitable method of formylation, which could also be applicable to 5,7-dihydroxy- and 5,6,7-trihydroxy-coumarins, *N*-methylformanilide has been tried for the first time in the coumarin series and the findings are described in this communication.

The formylation of 5,7-dihydroxy-4-methylcoumarin (I) with *N*-methyl-formanilide in the presence of phosphorus oxychloride furnished a monoformyl derivative m.p. >315°, in a fairly good yield. This aldehyde smoothly underwent Dakin oxidation to give the known[4] 4-methyl-5,7,8-trihydroxycoumarin (III) which was methylated to 4-methyl-5,7,8-trimethoxycoumarin (IV). Hence

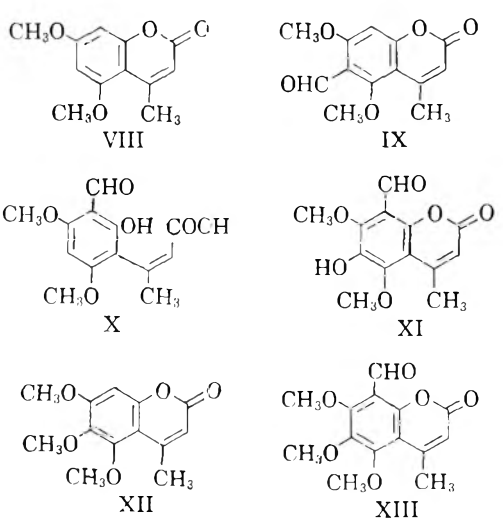


I II III

IV V

VI VII

the structure of 5,7-dihydroxy-8-formyl-4-methylcoumarin (II) has been assigned to the monoformyl derivative. The 6-formyl isomer does not appear to have been formed. The methylation of 5,7-dihydroxy-8-formyl-4-methylcoumarin (II) furnished 8-formyl-7-hydroxy-5-methoxy-4-methylcoumarin (V) and 5,7-dimethoxy-8-formyl-4-methylcoumarin (VI), the former (V) of which afforded 7,8-dihydroxy-5-methoxy-4-methylcoumarin (VII) on Dakin oxidation. The reaction of *N*-methylformanilide with 5,7-dimethoxy-4-methylcoumarin (VIII) yielded two monoformyl derivatives, melting point 267° and 284°. The aldehyde, m.p. 267°, was identical with the above described 5,7-dimethoxy-8-formyl-4-methylcoumarin (VI) and hence the only other possible structure of 5,7-dimethoxy-6-formyl-4-methylcoumarin (IX) has been assigned to the other isomer, m.p. 284°. On warming with 10% sodium hydroxide on a steam bath, both the isomers (VI and IX) went into solution, but on gentle acidification the 8-formyl derivative (VI) furnished presumably 4,6-dimethoxy-3-formyl-β-methylcoumarinic acid (X), whereas the 6-formyl isomer (IX) was recovered. The Elbs persulphate oxidation of 5,7-dimethoxy-8-formyl-4-methylcoumarin (VI) afforded 5,7-dimethoxy 6-hydroxy-8-formyl-4-methylcoumarin (XI) in poor yield. The formylation of



VIII IX

X XI

XII XIII

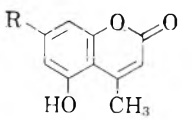
(1) This paper comprises a portion of the thesis presented by R. M. Naik towards the requirement for the degree of Doctor of Philosophy of the University of Bombay and the work was carried out during the tenure of the Government of India Scholarship.

(2) Present address: Department of Chemistry, Gujarat College, Ahmedabad.

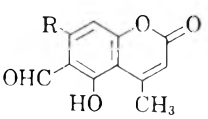
(3) R. M. Naik and V. M. Thakor, *J. Org. Chem.*, **22**, 1626 (1957).

(4) V. D. Nageswara Sastri and Co-workers, *Proc. Ind. Acad. Sci.*, **37A**, 681 (1953).

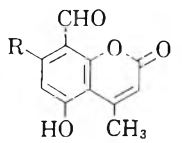
4-methyl-5,6,7-trihydroxycoumarin with *N*-methylformanilide did not succeed and the substance was either recovered almost quantitatively or destroyed under drastic conditions. However, the formylation of 4-methyl-5,6,7-trimethoxycoumarin (XII) succeeded partially to give the 8-formyl derivative (XIII) as a light yellow oil. It was characterized by the preparation of a 2,4-dinitrophenylhydrazone which was found to be identical with that of the methyl ether of 5,7-dimethoxy-6-hydroxy-8-formyl-4-methylcoumarin (XI).



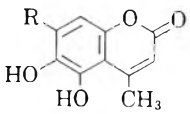
XIV



XV



XVI



XVII

The *N*-methylformanilide reaction with 5-hydroxy-4-methylcoumarin (XIV, R = H) furnished a monoformyl derivative, m.p. 220°, in poor yield and most of the unreacted coumarin was recovered. The structure of 6-formyl-5-hydroxy-4-methylcoumarin (XV, R = H) has been assigned to the aldehyde as it furnished the known[5] 5,6-dihydroxy-4-methylcoumarin (XVII, R = H) on Dakin oxidation. The 8-formyl isomer could not be traced. The formylation of 4,7-dimethyl-5-hydroxycoumarin (XIV, R = CH_3) with *N*-methylformanilide afforded two monoformyl isomers, m.p. >315° and m.p. 218°, both in poor yield, whereas most of the original coumarin was recovered. The product, m.p. >315° was practically insoluble in boiling alcohol and hence it could be conveniently separated. However, the separation of the original coumarin and the product, m.p. 218°, offered difficulty. The structure of 4,7-dimethyl-6-formyl-5-hydroxycoumarin (XV, R = CH_3) has been assigned to the product m.p. 218°, since it gave a red coloration with alcoholic ferric chloride and underwent Dakin oxidation to furnish the known[6] 5,6-dihydroxy-4,7-dimethylcoumarin (XVII, R = CH_3). The product, m.p. >315° did not give any coloration with alcoholic ferric chloride and has been assigned the structure 4,7-dimethyl-8-formyl-5-hydroxycoumarin (XVI, R = CH_3).

The *N*-methylformanilide method met with failure in the case of 7-hydroxy-4-methylcoumarin and its methyl ether, the unreacted substances being recovered almost quantitatively.

The present study shows that the applicability of *N*-methylformanilide as a formylating agent to the coumarin series is apparently very limited, 5,7-dihydroxy-4-methylcoumarin being the only one which gave the aldehyde in a fairly good yield. The rest of the coumarins could be formylated only partially giving poor yields of the aldehydes or could not be formylated at all. The separation of the unreacted substances and the formyl derivatives or sometimes the mono-formyl isomers, eventually turned out to be difficult.

(5) V. J. Dalvi, R. B. Desai, and S. Sethna, *J. Ind. Chem. Soc.*, **28**, 366 (1951).

(6) R. J. Parikh and S. Sethna, *J. Ind. Chem. Soc.*, **27**, 369 (1950).

EXPERIMENTAL[7]

5,7-Dihydroxy-8-formyl-4-methylcoumarin (II). To a mixture of 5.7 g. of 5,7-dihydroxy-4-methylcoumarin and 5.0 g. of *N*-methylformanilide in 15 cc. of distilled, dry *o*-dichlorobenzene, 5 cc. of phosphorus oxychloride was added and the reaction mixture, fitted with a condenser and guarded from moisture, was heated on a steam bath for 0.5 hr. with intermittent shaking. Vigorous fumes evolved for about 15 min. and then subsided. On adding about 100 cc. of saturated sodium acetate solution and removing *o*-dichlorobenzene by steam distillation, a pinkish brown amorphous product separated. It was filtered hot and the amorphous product (3.5 g.) obtained was found to be very sparingly soluble in boiling alcohol, acetic acid, benzene, chloroform, or acetone. A sample of this product was twice crystallized from acetone in thin white flocculent needles, m.p. >315°. It gives a blood red coloration with alcoholic ferric chloride and dissolves in alkali giving light yellow solution.

Anal. Calcd. for $C_{11}H_8O_5$: C, 60.0; H, 3.6. Found: C, 60.3; H, 3.8.

The methylation of II afforded a mixture of 8-formyl-7-hydroxy-5-methoxy-4-methylcoumarin (V) and 5,7-dimethoxy-8-formyl-4-methylcoumarin (VI). It was separated by treatment with dilute alkali. The filtrate on acidification yielded 8-formyl-7-hydroxy-5-methoxy-4-methylcoumarin (V) which crystallized from acetic acid (charcoal) as 1.8 g. of thin white needles, m.p. 224°. It gives a red coloration with alcoholic ferric chloride and forms a yellow insoluble sodium salt on treatment with alkali.

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.6; H, 4.3. Found: C, 61.5; H, 4.3.

The alkali-insoluble 5,7-dimethoxy-8-formyl-4-methylcoumarin (VI) was crystallized from acetic acid (charcoal) as 0.8 g. of thin shining light yellow needles, m.p. 267°.

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.8; H, 4.8. Found: C, 62.7; H, 4.6.

4-Methyl-5,7,8-trihydroxycoumarin (III). Six ml. of 6% hydrogen peroxide was added dropwise with stirring to a cooled solution (0°) of 0.5 g. of 5,7-dihydroxy-8-formyl-4-methylcoumarin in 10 cc. of 1% sodium hydroxide, and the reaction mixture was kept at 0° for 1 hr. The product obtained on acidification was taken up in ether and the ether treated with activated charcoal and filtered. A bright yellow substance was obtained on evaporation of ether. It was crystallized with difficulty from ethyl acetate as 0.3 g. of thin pale yellow plates, m.p. 273°. With alcoholic ferric chloride it gives a light greenish yellow coloration which soon turns brown. It is very soluble in methyl alcohol, ethyl alcohol, acetic acid, acetone, etc. Sastri and co-workers[4] give m.p. 273–275°.

4-Methyl-5,7,8-trimethoxycoumarin (IV) was obtained by methylation of III and crystallized from methyl alcohol (charcoal) in thin light yellow flakes, m.p. 174°. Sastri and co-workers[4] give m.p. 173–174°.

7,8-Dihydroxy-5-methoxy-4-methylcoumarin (VII). Three ml. of 6% hydrogen peroxide was added dropwise at 0°

(7) Melting points are uncorrected and were taken in open capillary tubes.

with stirring, to a mixture of 0.2 g. of 8-formyl-7-hydroxy-5-methoxy-4-methylcoumarin, 4 cc. of 2% sodium hydroxide, and 10 cc. of water, and the reaction mixture was kept at 0° for 2 hr., when the sodium salt, which separated in small quantity, slowly reacted. The product obtained on acidification was crystallized from methyl alcohol to yield 0.1 g. of thin light yellow needles, m.p. 231°. It gives a light green coloration with alcoholic ferric chloride and dissolves in alkali giving an orange yellow solution.

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 59.5; H, 4.5. Found: C, 59.4; H, 4.5.

This product also furnished 4-methyl-5,7,8-trimethoxycoumarin on methylation with dimethyl sulphate by the acetone–potassium carbonate method, m.p. and mixed m.p. 174°.

5,7-Dimethoxy-8-formyl-4-methylcoumarin (VI) *and 5,7-dimethoxy-6-formyl-4-methylcoumarin* (IX). To a mixture of 2.2 g. of 5,7-dimethoxy-4-methylcoumarin and 1.6 g. of *N*-methylformanilide in 15 cc. *o*-dichlorobenzene, 1.5 cc. of phosphorus oxychloride was added and the reaction mixture was heated on a steam bath for 2 hr. with intermittent shaking. On adding 100 cc. of sodium acetate solution and removing *o*-dichlorobenzene by steam distillation, the product separated in the form of dark globules. It was refluxed with excess of acetic acid and filtered. The filtrate gave 5,7-dimethoxy-8-formyl-4-methylcoumarin on cooling. It was purified by crystallization from acetic acid (charcoal), m.p. and mixed m.p. with the product obtained earlier, 267°. The light green product obtained as insoluble in boiling acetic acid, was crystallized from nitrobenzene to yield 0.8 g. of thin pale yellow needles of 5,7-dimethoxy-6-formyl-4-methylcoumarin, m.p. 284–285°. It is insoluble in almost all of the usual organic solvents.

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.8; H, 4.8. Found: C, 62.4; H, 4.8.

An attempt to demethylate both the 8-formyl and the 6-formyl isomers with hydriodic acid in acetic anhydride met with a failure, apparently similar black complex products being isolated.

4,6-Dimethoxy-3-formyl-β-methylcoumarinic acid (X). One gram of 5,7-dimethoxy-8-formyl-4-methylcoumarin and 10 cc. of 10% sodium hydroxide were heated together on a steam bath for 0.5 hr. when the substance slowly went into solution. The mixture was cooled, carefully acidified, and the substance which separated was crystallized from alcohol to yield 0.8 g. of white needles, m.p. 212° (dec.). It gives a purple red coloration with alcoholic ferric chloride, and dissolves in sodium bicarbonate with faint effervescence.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.6; H, 5.3. Found: C, 58.9; H, 5.5.

5,7-Dimethoxy-6-formyl-4-methylcoumarin was recovered on dissolving the product in sodium hydroxide on a steam bath, cooling, and then acidifying.

5,7-Dimethoxy-6-hydroxy-8-formyl-4-methyl-coumarin (XI). 5,7-Dimethoxy-8-formyl-4-methylcoumarin (1.25 g.) was dissolved in 10 cc. of 10% sodium hydroxide by warming on a steam bath and the solution was cooled to 0°. A solution of 1.35 g. of potassium persulfate in 27 cc. of water was then added dropwise while the reaction mixture was mechanically stirred. It was left overnight in a refrigerator, just acidified, and the coumarinic acid, m.p. 212°, which separated was removed by filtration. The filtrate was heated on a steam bath for 1 hr. with more hydrochloric acid. The contents were cooled and extracted with ether (charcoal), and the ether was evaporated to furnish a product which crystallized from alcohol as brown needles, m.p. 225–226°. It does not give any coloration with alcoholic ferric chloride and dissolves in alkali giving an orange yellow solution.

Anal. Calcd. for $C_{13}H_{12}O_6$: C, 59.1; H, 4.6. Found: C, 59.3; H, 4.8.

8-Formyl-4-methyl-5,6,7-trimethoxycoumarin (XIII), was obtained as a light yellow oil on methylation of XI. It did not solidify either in a refrigerator or in a desiccator under vacuum.

It furnished an orange-red *2,4-dinitrophenylhydrazone*, crystallized from acetic acid in needles, m.p. 232°.

Anal. Calcd. for $C_{20}H_{18}N_4O_9$: N, 12.2. Found: N, 12.6.

8-Formyl-4-methyl-5,6,7-trimethoxycoumarin (XIII). A mixture of 1.2 g. of 4-methyl-5,6,7-trimethoxycoumarin,[5] 1.7 g. of *N*-methylformanilide, 1.5 cc. of phosphorus oxychloride and 10 cc. of *o*-dichlorobenzene, was heated on a steam bath for 1 hr. with intermittent shaking. Saturated solution of sodium acetate was added and the contents were steam-distilled to remove *o*-dichlorobenzene. A brown pasty substance separated. It was filtered, while hot, through cotton wool, and the filtrate, on cooling, gave the unreacted coumarin. The pasty material was taken up in ether and the extract treated with activated charcoal. On removing charcoal and evaporating ether, the light yellow oil was isolated. Most of it decomposed when distilled under vacuum. It was characterized by the preparation of a 2,4-dinitrophenylhydrazone (m.p. 231–232°) which did not depress the melting point of the 2,4-dinitrophenylhydrazone obtained in the previous case.

6-Formyl-5-hydroxy-4-methylcoumarin (XV, R = H). A mixture of 1.8 g. of 5-hydroxy-4-methylcoumarin, 2.0 g. of *N*-methylformanilide, 2 cc. of phosphorus oxychloride, and 15 cc. of *o*-dichlorobenzene, was heated on a steam bath for 2 hr. After adding sodium acetate solution and steam-distilling, the brown product which separated was found to be the unreacted coumarin. The contents were filtered hot, and the filtrate afforded the aldehyde on cooling. It was crystallized from alcohol to yield 0.2 g. of thin white needles, m.p. 220°. It gives a purple red coloration with alcoholic ferric chloride and dissolved in alkali giving an orange-red solution.

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.7; H, 3.9. Found: C, 65.0; H, 3.8.

5,6-Dihydroxy-4-methylcoumarin (XVII, R = H). To a solution of 0.2 g. of 6-formyl-5-hydroxy-4-methylcoumarin in 2 cc. of 2% sodium hydroxide at 0°, 1.5 cc. of 6% hydrogen peroxide was added dropwise, and the reaction mixture was left at 0° for 1 hr. It was acidified and the product which separated was crystallized from alcohol in thin shining yellow needles, m.p. 248°. It did not depress the melting point of 5,6-dihydroxy-4-methylcoumarin prepared according to Dalvi, Desai, and Sethna.[6]

4,7-Dimethyl-8-formyl-5-hydroxycoumarin (XVI, R = CH_3) and *4,7-dimethyl-6-formyl-5-hydroxycoumarin* (XV, R = CH_3). The mixture of 1.9 g. of 4,7-dimethyl-5-hydroxycoumarin, 2.0 g. of *N*-methylformanilide, 2.0 cc. of phosphorus oxychloride, and 15 cc. of *o*-dichlorobenzene, was heated on steam bath for 2 hr. The crude product obtained on working up as in earlier cases was refluxed with alcohol and filtered. The product left over as insoluble was crystallized from acetic acid (charcoal) as 0.15 g. of thin white flocculent needles of 4,7-dimethyl-8-formyl-5-hydroxycoumarin, m.p. >315°. It does not give any coloration with alcoholic ferric chloride and dissolves in sodium hydroxide to give a yellow solution.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.1; H, 4.6. Found: C, 66.4; H, 4.9.

The filtrate on cooling gave a product which was fractionally crystallized to give a small quantity of 4,7-dimethyl-6-formyl-5-hydroxycoumarin, m.p. 218°, along with a large amount of the unreacted coumarin. It gives a blood-red coloration with alcoholic ferric chloride and dissolves in alkali giving an orange yellow solution.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.1; H, 4.6. Found: C, 66.0; H, 4.4.

4,7-Dimethyl-8-formyl-5-methoxycoumarin was obtained by methylation of XVI (R = CH_3) and crystallized from acetic acid in thin white needles, m.p. 262°.

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.2; H, 5.2. Found: C, 67.5; H, 5.0.

5,6-Dihydroxy-4,7-dimethylcoumarin (XVII, R = CH_3). One ml. of 6% hydrogen peroxide was added dropwise to a solution of 0.1 g. 4,7-dimethyl-6-formyl-5-hydroxycoumarin

in 2 cc. of 2% sodium hydroxide at 0°, and the mixture was left for 1 hr. It was acidified and the product which separated was crystallized from alcohol in light yellow needles, m.p. 260°. It did not depress the melting point of an authentic specimen of 5,6-dihydroxy-4,7-dimethylcoumarin prepared according to Parikh and Sethna.[1]

Acknowledgment. The authors thank Dr. R. C. Shah, National Chemical Laboratory, Poona, for his keen interest in this work.

BOMBAY, INDIA

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY INSTITUTE OF SCIENCE]

Stabilities of Nitrohydroxy Chalcones and Flavanones. Role of Hydrogen Bonding

S. SESHADRI AND P. L. TRIVEDI

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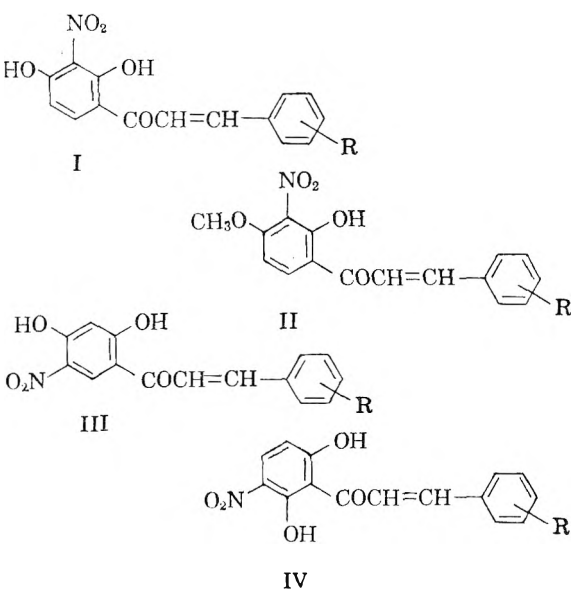
The cyclization of nitro-substituted chalcones to the flavanones has been studied for the first time. The effect of the nitro group on the reaction has been studied and it has been shown that the chelation of the nitro group with the 2′-hydroxyl group is an important factor in determining the stability of the chalcone. The properties of the chalcones and the flavanones have been studied and discussed.

The isomerization of nitro-substituted chalcones to flavanones does not appear to have been studied at all. The present work was, therefore, undertaken with a view to investigating the influence of the nitro group on the reaction.

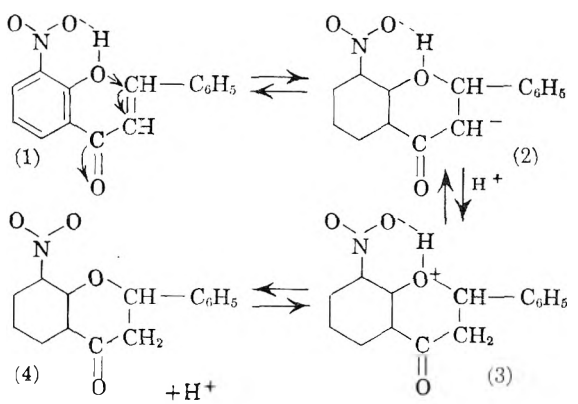
A number of new chalcones as well as a few known chalcones were prepared from nitro derivatives of 2,4-dihydroxyacetophenone and 2,6-dihydroxyacetophenone. The chalcones, prepared by the "cold alkaline condensation" method, were of four types, I–IV.



The cyclization of the chalcones was carried out by refluxing in aqueous alcoholic hydrochloric acid (3%). The flavanones were separated from the chalcones by fractional crystallization from suitable solvents. The times of refluxing and the yields of flavanones are set out in Table II.

All the flavanones were readily reconverted to the chalcones by warming with alkali solution and reacidifying. The flavanones from chalcones Ia–Ih were very unstable towards strongly acid solution, being completely converted to the chalcones in fifteen minutes. The flavanones of type III were more stable since only a part of the flavanone had reverted to the chalcone after boiling for an hour. The Group IV flavanones were unaffected by strongly acid solution.

The results obtained show that the nitro group has a profound influence on the behavior of nitrochalcones. The slow rate of cyclization of Group I chalcones and the high instability of the flavanone Ia towards acid solution indicate that the nitro group has a stabilizing effect on the chalcone. This effect is probably exerted in the manner shown.



The chelation of the *ortho* nitro group will prevent proton elimination at the last stage and retard the cyclization. On the same basis, the tendency of (4) to take up a proton will be much greater than the tendency of (3) to lose one and this accounts for the instability of the flavanone ring in acid medium. Crawford and Rasburn[1] have observed a similar stabilizing effect of the nitro group in 3-nitrocouma-

(1) M. Crawford and J. W. Rasburn, *J. Chem. Soc.*, 2155 (1956).

TABLE I

LIST OF CHALCONES PREPARED AND THEIR PROPERTIES

No.	Chalcone	Yield, %	H_2SO_4 Coloration	M.P., °C.	Formula	Analysis N, % Calcd.	Found
Ia	2′,4′-Dihydroxy-3′-nitro	20	Orange-red	173[a]	$C_{15}H_{11}NO_5$	4.91	4.96
Ib	2′,4′-Dihydroxy-3′-nitro-2-methoxy	25	Dark red	192[b]	$C_{15}H_{13}NO_6$	4.44	4.39
Ic	2′,4′-Dihydroxy-3′-nitro-4-methoxy	20	Red	172[c]	$C_{16}H_{13}NO_6$	4.44	4.43
Id	2′,4′-Dihydroxy-3′-nitro-4-methoxy	25	Dark red	215–216[b]	$C_{16}H_{13}NO_6$	4.44	4.37
Ie	2′,4′-Dihydroxy-3′-nitro-3,4-methylenedioxy	25	Purple-red	218[b]	$C_{16}H_{11}NO_7$	4.26	4.03
If	2′,4′-Dihydroxy-3′-nitro-4-methyl	20	Red	175[c]	$C_{16}H_{13}NO_5$	4.68	4.70
Ig	2′,4′-Dihydroxy-3′-nitro-3,4-benzo	5	Dark red	225[b]	$C_{19}H_{13}NO_5$	4.18	3.88
Ih	2′,4′-Dihydroxy-3,3′-dinitro	5	Deep yellow	227[d]	$C_{15}H_{10}N_2O_6$	8.51	8.67
IIa	2′-Hydroxy-4′-methoxy-3′-nitro	60	Orange-red	232[b]	$C_{16}H_{13}NO_5$	4.68	4.88
IIb	2′-Hydroxy-4,4′-dimethoxy-3′-nitro	60	Red	223–225[b]	$C_{17}H_{15}NO_6$	4.26	4.20
IIIa	2′,4′-Dihydroxy-[e] 5′-nitro	60	Orange-red	188–189[c]	—	—	—
IIIb	2′,4′-Dihydroxy-[e] 5′-nitro-4-methoxy	60	Dark red	160–162[c]	—	—	—
IVa	2′,6′-Dihydroxy-3′-nitro	15	Orange-red	163–165[c]	$C_{15}H_{11}NO_5$	4.91	5.02
IVb	2′,6′-Dihydroxy-3′-nitro-2-methoxy	15	Dark red	175–176[c]	$C_{16}H_{13}NO_6$	4.44	4.31
IVc	2′,6′-Dihydroxy-3′-nitro-3-methoxy	15	Red	140–141[c]	$C_{16}H_{13}NO_6$	4.44	4.40
IVd	2′,6′-Dihydroxy-3′-nitro-4-methoxy	20	Dark red	165[c]	$C_{16}H_{13}NO_6$	4.44	4.60
IVe	2′,6′-Dihydroxy-3′-nitro-3,4-methylenedioxy	25	Violet	182[b]	$C_{16}H_{11}NO_7$	4.26	4.05

[a] Alcohol. [b] Acetic acid. [c] Benzene. [d] Nitrobenzene. [e] *Cf.* V. G. Kulkarni and G. V. Jadhav, *J. Indian Chem. Soc.*, **31**, 746 (1954).

rinic acids. The nonformation of flavanone from the chalcones of group II shows that the chelation of the nitro group with the 3′-hydroxyl group is firmer in these chalcones than in the Group I chalcones.

The slowness of cyclization of Group III chalcones is the result of the retarding influence of the nitro group on the reaction. The greater stability of the flavanone of this group towards acid shows that the nitro group has no longer the effect it exerted in flavanone Ia.

The effect of substitution in the R nucleus on the stability of the chalcones of types I and III is noteworthy. The yield of flavanone from the chalcone decreases considerably with introduction of substituents and this effect is especially pronounced in Group I chalcones. The nature of the substituent seems to be of no importance. The conclusion is, therefore, reached that the substituent exerts a purely steric effect. The flavanone structure becomes more unstable with increased loading of the 2-phenyl nucleus and hence lower yields of the flavanone are obtained. The abrupt fall in the yields of flavanones from Group I chalcones, with substitution of the R nucleus, seems to be due to a combination of effect of chelation and the steric effect exerted by the substituent.

The Group IV chalcones are remarkable for the ready isomerization to the flavanones. This behavior is attributable to the presence of a 6′-hydroxyl group.[2] It, therefore, appears that the activating influence of the 6′-hydroxyl group is not appreciably masked by the retarding effect of the nitro group. The group IV flavanones have been assigned the constitution of 5-hydroxy-6-nitroflavanones and not 5-hydroxy-8-nitroflavanones. The formation of the latter would involve cyclization at the chelated hydroxyl group and this, as has been shown, is a difficult process. The stability in these flavanones in acid medium is only to be expected,

(2) Shinoda and Sato, *J. Pharm. Soc. Japan*, **48**, 933 (1928).

TABLE II

CYCLIZATION TO THE FLAVANONES

Flavanone	Chalcone Cyclized	Volume of Alcohol	Volume,[a] Strength of HCl	Time of Reaction	Yield, % of Flavanone	M.P., °C.	H_2SO_4 Color	Analysis N, % Calcd.	Found
7-Hydroxy-8-nitro	Ia	60	60, 6%	6 days	35	184[b]	Yellow	4.91	4.80
7-Hydroxy-8-nitro-2′-methoxy	Ib	150	80, 9%	6 days	3	181–183[c]	Red	4.44	4.41
7-Hydroxy-8-nitro-3′-methoxy	Ic	80	80, 6%	6 days	5	174–175[c]	Yellow	4.44	4.26
7-Hydroxy-8-nitro-4′-methoxy	Id	150	80, 9%	6 days	5	163–165[c]	Crimson	4.44	4.39
7-Hydroxy-8-nitro-3′,4′-methylenedioxy	Ie	150	80, 9%	6 days	2	172–173[c]	Crimson	4.26	4.55
	If	60	60, 6%	6 days	[d]				
	Ig	200	40, 18%	6 days	[d]				
	Ih	80	80, 6%	6 days	[d]				
	IIa	150	80, 9%	6 days	[d]				
	IIb	200	40, 18%	6 days	[d]				
7-Hydroxy-6-nitro	IIIa	180	90, 9%	6 days	35	154–156[c]	Yellow	4.91	4.99
7-Hydroxy-6-nitro-4′-methoxy	IIIb	225	40, 18%	6 days	15	172[c]	Orange	4.44	4.20
5-Hydroxy-6-nitro	IVa	100	50, 9%	4 hr.	80	155–156[e]	Yellow	4.91	4.80
5-Hydroxy-6-nitro-2′-methoxy	IVb	150	80, 9%	4 hr.	80	181–183[e]	Red	4.44	4.54
5-Hydroxy-6-nitro-3′-methoxy	IVc	100	50, 9%	4 hr.	80	142–143[e]	Yellow	4.44	4.44
5-Hydroxy-6-nitro-4′-methoxy	IVd	150	80, 9%	4 hr.	80	148[c]	Red	4.44	4.70
5-Hydroxy-6-nitro-3′,4′-methylenedioxy	IVe	150	80, 9%	4 hr.	80	169–171[e]	Purple	4.26	4.39

[a] Volume in ml. per gram of chalcone. [b] Cryst. from alcohol. [c] Cryst. from benzene. [d] No flavanone could be isolated. [e] Cryst. from ethyl acetate and alcohol mixture.

in view of the ease with which they are formed from the chalcone in acid medium.

All the flavanones are converted to the chalcones in alkali solution. T. R. Seshadri[3] has shown that flavanones which do not contain a 5-hydroxyl group break up in alkaline solution to the chalcones. The 5-hydroxyflavanones alone are unaffected by alkali, and this stability has been attributed to the chelation of the 5-hydroxyl group with the carbonyl group of the flavanone ring. In the case of the 5-hydroxy-6-nitroflavanones, the 5-hydroxyl group is not capable of exerting its stabilizing effect on the flavanone because it is chelated with the 6-nitro group.

EXPERIMENTAL

2,4-Dihydroxy-3-nitroacetophenone,[4] m.p. 103°, was obtained by the Friedel-Crafts acetylation of 2-nitroresorcinol. To a solution of anhydrous aluminum chloride (12 g.) in nitrobenzene (80 ml.) was added 2-nitroresorcinol (6.4 g.) and to this mixture was added acetic anhydride (4.1 ml.). The reaction mixture was heated on a steam bath for 4 hr., the aluminum chloride decomposed by ice-cold dilute hydrochloric acid and the nitrobenzene removed by steam distillation. The residue in the flask was crystallized from hot water as silky grey needles which turned yellow on drying.

2-Hydroxy-4-methoxy-3-nitroacetophenone,[4] m.p. 211–212°, was obtained by refluxing 2,4-dihydroxy-3-nitroacetophenone (4 g.) in acetone (60 ml.) with dry potassium carbonate (12 g.) and dimethyl sulfate (2 ml.) for 24 hr. The acetone was removed and the alkaline solution extracted with ether. The alkaline solution was acidified and the solid obtained crystallized from acetic acid.

2,4-Dihydroxy-5-nitroacetophenone,[5] m.p. 142°, was prepared by nitration of resacetophenone.

2,6-Dihydroxy-3-nitroacetophone,[5] m.p. 119°, was prepared by Friedel-Crafts acetylation of 4-nitroresorcinol.

Preparation of the chalcones. The chalcones were prepared by adding potassium hydroxide solution to a cooled mixture of molecular proportions of the acetophenone and the requisite aromatic aldehyde in alcohol (2 ml. per g. of ketone) and leaving the reaction mixture at room temperature (30°) with intermittent shaking. After the reaction period was over, the mixture was diluted with ice-cold water and acidified by concentrated hydrochloric acid. The product after filtration and repeated washing was generally crystallized from acetic acid. (Alcohol was used for chalcones Ia and If. Chalcone Ig was washed with warm acetic acid and crystallized from nitrobenzene.) The chalcone thus obtained was washed with alcohol and crystallized further from suitable solvents (given in Table I).

The strength and amount of potassium hydroxide solution used per gram of ketone, and the time of reaction were as follows. Chalcone groups I and III: 2 g. of potassium hydroxide in 7 ml. water for 6 days. Chalcone group II: 2 g. potassium hydroxide in 2 ml. water for 24 hr. Chalcone group IV: 2 g. potassium hydroxide in 5 ml. water for 24 hr. in the case of IVa, IVd, and IVe, and for 9 hr. in the case of IVb and IVc.

The chalcones varied in color from yellow to deep red. The characteristic sulfuric acid colorations are set out in Table I.

(3) M. Narsimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **27A**, 223 (1948).

(4) R. M. Naik, unpublished work, Ph.D. thesis, Bombay University (1955).

(5) R. M. Naik and V. M. Thakor, *Proc. Indian Acad. Sci.*, **37A**, 774 (1953).

Cyclization. The chalcones were refluxed in aqueous alcoholic hydrochloric acid (3%) solution or suspension. The amounts of alcohol and hydrochloric acid used varied with the solubility of the chalcone and are given in Table II.

Different methods were adopted for isolating the flavanone depending on the nature of the chalcone.

Groups I *and* II. The reaction mixture was cooled well and the chalcone that had separated was filtered. The filtrate was concentrated under reduced pressure till turbidity appeared. It was then cooled and diluted. The solid obtained was fractionally crystallized from benzene to get the flavanone. In the case of Chalcone Ia, the reaction mixture was diluted and the mixture of chalcone and flavanone separated by virtue of the higher solubility of the chalcone in alcohol. The mixture was triturated with cold alcohol and filtered. The white residue was crystallized from alcohol when the pure flavanone separated.

Group III. The reaction mixture was cooled to about 45° and the yellow chalcone that had separated was filtered. The filtrate was cooled in ice when the crude flavanone separated which was crystallized from benzene.

Group IV. The reaction mixture was cooled and the solid that separated was recrystallized from a mixture of alcohol and ethylacetate to get the pure flavanone.

All the flavanones were white or very pale yellow in color. They did not give the magnesium-hydrochloric acid test and many of them gave colors other than yellow with concentrated sulfuric acid (see Table II). Groups I and III flavanones gave pale brown colors with alcoholic ferric chloride, while the isomeric chalcones gave deep brownish red colors. Both the chalcones and flavanones of group IV gave red colors with alcoholic ferric chloride.

Tests for stability of flavanones. (a) The flavanone (0.1 g.) was warmed with sodium hydroxide solution (10 cc.; 5%) for 10 min. and acidified. All the flavanones gave back the chalcone when thus treated. (b) The flavanone (0.1 g.) was refluxed in alcohol (10 cc.) with concentrated hydrochloric acid (10 cc.). Flavanone Ia was completely converted into the chalcone in 15 min. Only part of flavanone IIIa had reverted to the chalcone even after refluxing for an hour. Flavanone IVa was unaffected.

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BOMBAY, INDIA

[CONTRIBUTION FROM THE RESEARCH LABORATORY, LEPETIT S.P.A., MILAN]

Cinnamic and 2-Thienylacrylic Derivatives

ALBERTO VECCHI AND GAETANO MELONE

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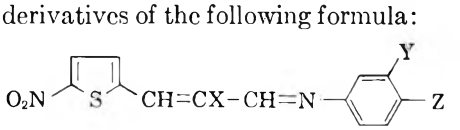
As a further development of previous studies on two exceptionally active antibacterial substances, β-(5-nitro-2-thienyl)-acrolein and its α-bromo derivative, the effects of introducing a 5-cyano group instead of the 5-nitro group and of a nitro instead of the aldehyde group were studied. Similar substitutions were tried in the benzene analogs. Furthermore, 4-cyanocinnamylidene acetaldehyde and 4-methylsulfonyl derivatives of the benzene series have been prepared. Outstanding antifungal activity was displayed by α-bromo-β-(5-cyano-2-thienyl)acrolein, α-bromo-4-cyanocinnamaldehyde, and their Schiff's bases with *p*-aminobenzoic acid, as well as by 1-(5-nitro-2-thienyl)-2-nitroethylene and 1-(5-nitro-2-thienyl)-2-bromo-2-nitroethylene. Other members of the described classes were also highly active.

In continuation of our previous work on cinnamic and 2-thienylacrylic derivatives,[1-3] which was suggested by a consideration of the marked biological interest of aromatic acroleins[4] and confirmed by a paper of Affonso and Khorana[5] on halogenated derivatives of cinnamic and *p*-nitrocinnamic acid, we have now synthesized a series of new compounds having structural resemblance to the acroleins already described.

The considerable interest aroused by the prior work is shown by several publications of Japanese scientists concerning furan analogs of the series.[6-12] Strict furan analogs of the thiophene compounds described in our previous papers have been recorded, such as β-(5-nitro-2-furyl)acrolein[6] and many functional derivatives thereof.

In view of the slight water solubility of the β-(5-nitro-2-thienyl)acroleins,[1] which prevented their use by the parenteral route and their absorption by the gastro-enteric tract, we have prepared functional derivatives of the following formula:



I	X = H,	Y = H,	Z = COOH
II	X = H,	Y = OH,	Z = COOH
III	X = H,	Y = H,	Z = SO_3H
IV	X = H,	Y = H,	Z = SO_2NH_2
V	X = Br,	Y = H,	Z = COOH[1]
VI	X = Br,	Y = H,	Z = SO_2NH_2
VII	X = Br,	Y = H,	Z = $SO_2NHCOCH_3$

(1) G. Carrara, R. Ettorre, F. Fava, G. Rolland, E. Testa and A. Vecchi, *J. Am. Chem. Soc.*, 76, 4391 (1954).

(2) G. Rolland and M. T. Timbal, *Atti VI Congresso Int. Microbiologia Roma*, 1953, vol. I, sect. 2, p. 629.

(3) G. Carrara, E. Ginoulhiac, G. Rolland, and M. T. Timbal, *Il Farmaco, Sci. ed.*, 9, 39 (1954).

(4) E. Koeser and J. Houben, *Fortschritte der Heilstoffchemie*, 2 Abt., Berlin, Leipzig, 1932, p. 254.

(5) A. Affonso and M. L. Khorana, *Indian J. Pharm.*, 14, 3 (1952).

(6) T. Toda and I. Mifuchi, *Tuberculosis*, 28, 19 (1953).

(7) T. Sasaki, *Pharm. Bull. (Japan)*, 2, 123 (1954).

(8) M. Ikeda, *J. Pharm. Soc. Japan*, 75, 628 (1955).

(9) M. Ikeda, *J. Pharm. Soc. Japan*, 75, 631 (1955).

(10) A. Ohyama, *Bull. Inst. Chem. Research Kyoto Univ.*, 34, 25 (1956).

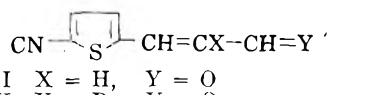
(11) M. Ikeda, *Ann. Rept. Fac. Pharm. Kanazawa Univ.*, 3, 25 (1953).

(12) S. Yasuda, *Ann. Rept. Fac. Pharm. Kanazawa Univ.*, 3, 30 (1953).

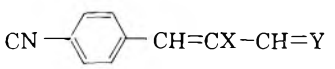
Unfortunately, no substantial improvement in solubility was achieved, so we tried to overcome this difficulty by forming salts with hydrophilic bases, such as hydroxyethylamine, piperazine, and morpholine. These salts, however, when dissolved in water quickly hydrolyzed (in some instances after a few minutes) with precipitation of the acidic moiety.

The antibacterial activity on a molar basis of the compounds of this class was generally slightly lower than that of the corresponding aldehydes. Table I is representative of these and all results obtained *in vitro* with the compounds of the present paper.

Another untoward feature of the free nitroaldehydes is the brown coloration they impart to the tissue proteins, which impaired also their topical use in ointments and alcohol solutions. Since this property could be attributed to the simultaneous presence of bromine, nitrothiophene, and aldehyde groups in the molecule, an attempt was made to prepare analogs bearing a cyano instead of a nitro group. The cyano group being electronegative, the polarity of the molecule should not be markedly different, and the antibacterial activity should be maintained. The same substitution was tried also for the benzene analogs for the purpose of comparison; the following series of compounds were thus prepared:



VIII X = H, Y = O
IX X = Br, Y = O
X X = Br, Y = NC_6H_4COOH-*p*

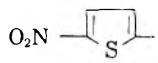


XI X = H, Y = O
XII X = Br, Y = O
XIII X = H, Y = CH—CHO
XIV X = H, Y = $NNHCSNH_2$
XV X = Br, Y = $NNHCSNH_2$
XVI X = Br, Y = NC_6H_4COOH-*p*

The expected equivalence of cyano and nitro analogs was substantially confirmed for the simplest members of the benzene series, since the antibacterial activity of compounds XI and XII paralleled that of 4-nitrocinnamaldehyde and α-bromo-4-nitrocinnamaldehyde. In the thiophene series, however, the cyano compounds were somewhat less active, although this disadvantage was balanced by the fact that skin coloration was almost totally eliminated. More extensive details on this subject will be published elsewhere.[13]

Compound XIII does not properly belong to the present class, and was only prepared for the purpose of ascertaining whether a lengthening of chain with the insertion of a second double bond would improve antibacterial activity. However XIII was practically devoid of activity. The thiosemicarbazones, as expected, were only active on *Mycobacterium tuberculosis var. hominis H37Rv*.

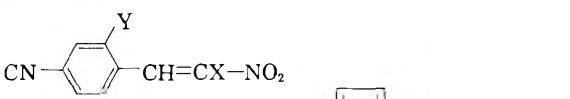
As a further development of the present study, in view of the interesting antibacterial and antifungal properties of β-nitrostyrenes, β-nitrovinylfurans, and β-nitrovinylthiophenes as described in several works,[14-22] 1-(5-nitro-2-thienyl)-2-nitroethylene (XVII) and 1-(5-nitro-2-thienyl)-2-bromo-2-nitroethylene (XVIII) were prepared and compared with the corresponding known benzene analogs (XIX and XX).[23]



XVII X = H
XVIII X = Br

Whereas in any case the halogenated compounds were generally more active, it can be observed that benzene derivatives were superior for their antibacterial activity (except for H37Rv), while thiophene compounds reached higher values of antifungal effectiveness, XVII being of the utmost interest in this respect.

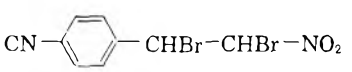
Moreover, analogs of these last compounds in which the ring nitro group was substituted by a cyano group were prepared, giving compounds XXI–XXIV



XXI X = H Y = H XXIII X = H
XXII X = Br Y = H XXIV X = Br
XXV X = Br Y = NO_2

whereby a slightly higher antibacterial and antifungal activity of the benzenes was ascertained.

The introduction of a ring nitro group in XXII (compound XXV) gave a fairly active compound; also compound XXVI,



XXVI

(13) M. T. Timbal, unpublished results.

(14) J. C. McGowan, P. W. Brian, and H. G. Hemming, *Ann. Applied Biol.*, **35**, 25 (1948).

(15) P. W. Brian, J. F. Grove and J. C. McGowan, *Nature*, **158**, 876, 1946.

(16) O. Dann and E. F. Moeller, *Ber.*, **82**, 76 (1949).

(17) O. Schales and H. A. Graefe, *J. Am. Chem. Soc.*, **74**, 4486 (1952).

(18) F. C. Bocobo, A. C. Curtis, W. D. Block, and E. R. Harrell, *Proc. Soc. Exptl. Biol. Med.*, **85**, 220 (1954).

(19) A. C. Curtis, F. C. Bocobo, E. R. Harrel and W. D. Block, *Arch. Dermatol. and Syphilol.*, **70**, 786 (1954).

(20) A. C. Haitric, R. Pratt, Y. Okano, and W. D. Kumbler, *Antibiotics & Chemotherapy*, **6**, 290 (1956).

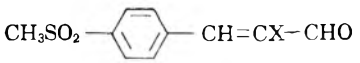
(21) F. C. Bocobo, A. C. Curtis, W. D. Block, E. R. Harrel, E. E. Evans, and R. F. Haines, *Antibiotics & Chemotherapy*, **6**, 385 (1956).

(22) E. E. Evans, R. F. Haines, A. C. Curtis, F. C. Bocobo, W. D. Block, and E. R. Harrell, *J. Invest. Dermatol.*, **28**, 43 (1957).

(23) T. Posner, *Ber.*, **31**, 657 (1898); R. Flürscheim, *J. prakt. Chem.* [2] **66**, 16 (1902).

obtained as an intermediate of the preparation of XXII, retained a good order of activity.

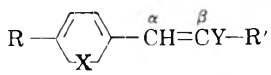
Our work has been concluded with the synthesis of compounds XXVII and XXVIII, structurally related to the derivatives, made by Affonso and Khorana,[5] but bearing a methylsulfonyl group at position 4. This substitution has been suggested by the considerable activity of the *p*-methylsulfonyl analog of chloramphenicol.[23,24]



XXVII X = H
XXVIII X = Br

While XXVII was practically devoid of any *in vitro* activity, the introduction of the bromine atom brought a marked degree of antibacterial and antifungal activity.

From an inspection of a generic formula embracing most of the compounds prepared in this and in the other papers it can be concluded with respect to the antibacterial and antifungal activity:



1. The carbon atom at position β from the ring must be totally substituted, since where Y is hydrogen a considerable decrease of activity results. The presence of a bromine atom at β is of great importance; however, a methyl group[17] or chlorine may be substituted for it thus obtaining fairly active compounds.

2. Compounds in which R′ is a nitro group are generally slightly more active than in the case of R′ being an aldehyde carbonyl. Also in this case the β carbon atom must be totally substituted, as stated in item 2.

3. No substantial difference in activity is found when R is a cyano instead of a nitro group.

4. In any case, thiophene compounds, except in some isolated instances, have somewhat superior activity when compared with the benzene analogs.

EXPERIMENTAL

N-[γ-(*5-Nitro-2-thienyl*)*acrylidene*]-*p-aminobenzoic acid* (I). A mixture of 2 g. β-(5-nitro-2-thienyl)acrolein[1] and 100 ml. anhydrous ethanol was refluxed on a steam bath in a 250-ml. round bottom flask to complete solution, then 1.5 g. *p*-aminobenzoic acid were quickly added in one portion and refluxing was continued. After a few minutes complete solution occurred followed by precipitation of brick red crystals. After 10 min. the mixture was filtered hot by suction, and the solid on the filter was washed with hot anhydrous ethanol and dried. The yield was 2.65 g. (67%) m.p. 221–23°.

Anal. Calcd. for $C_{14}H_{10}N_2O_4S$: N, 9.26; S, 10.60. Found: N, 9.22; S, 10.61.

By strictly analogous procedures the following compounds were prepared.

N-[γ-(*5-Nitro-2*)*thienyl*)*acrylidene*]-*4-aminosalicylic acid* (II). Yield, 75%; m.p. 187–188° (dec.).

Anal. Calcd. for $C_{14}H_{10}N_2O_6S$: N, 8.80; S, 10.07. Found: N, 8.32; S, 9.65.

N-[γ-(*5-Nitro-2-thienyl*)*acrylidene*]*sulfanilic acid* (III). Yield, 64%; m.p. above 300°.

Anal. Calcd. for $C_{13}H_{10}N_2O_5S_2$: N, 8.28; S, 18.95. Found: N, 7.99; S, 18.20.

N^4-[γ-(*5-Nitro-2-thienyl*)*acrylidene*]*sulfanilamide* (IV). Yield, 52%; m.p. 198–199°.

Anal. Calcd. for $C_{13}H_{11}N_3O_4S_2$: N, 12.45; S, 19.00. Found: N, 12.10; S, 19.50.

N^4-[β-*Bromo*-γ-(*5-nitro-2-thienyl*)*acrylidene*]*sulfanilamide* (VI). From α-bromo-β-(5-nitro-2-thienyl)acrolein[1] and sulfanilamide. Yield, 47% m.p. 163–164°.

Anal. Calcd. for $C_{13}H_{10}BrN_3O_4S_2$: N, 10.09; S, 15.40. Found: N, 9.82; S, 15.25.

N^1-*Acetyl-N*^{4}-[β-*bromo*-γ-(*5-nitro-2-thienyl*)*acrylidene*]-*sulfanilamide* (VII). Acetic acid was used as a solvent in this case. Yield, 36%; m.p. 217° (dec.).

Anal. Calcd. for $C_{15}H_{12}BrN_3O_5S_2$: N, 9.16; Br, 17.43; S, 13.99. Found: N, 8.95; Br, 17.62; S, 14.02.

In addition, the hydroxyethylamine (V), piperazine (Va), and morpholine (Vb) salts of *N*-[β-bromo-γ-(5-nitro-2-thienyl)acrylidene]-*p*-aminobenzoic acid, a compound already described in our previous work,[1] were prepared. Va and Vb could not be subjected to microbiological experimentation in view of their insolubility.

2-Methyl-5-cyanothiophene (XXIX). A mixture of 255 ml. anhydrous pyridine, 26.2 g. cuprous cyanide, and 34.9 g. 2-methyl-5-iodothiophene[25] were refluxed in a round bottom flask on an oil bath under vigorous stirring for 8 hr. Pyridine was then removed by distillation *in vacuo*, and the residual dark mixture of oil and crystals was extracted with four 150-ml. portions of hot ethyl acetate. The combined organic extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the dark oily residue was distilled from a Claisen flask to yield a light orange liquid, b.p. 87–90°/10 mm. n_D^{20} 1.5512. Yield, 14 g. (73%).

Anal. Calcd. for C_6H_5NS: N, 11.38; S, 26.03. Found: N, 10.96; S, 25.78.

5-Cyano-2-thiophenecarboxaldehyde diacetate. Into a well stirred mixture of 14.0 g. of 2-methyl-5-cyanothiophene, 175 ml. acetic anhydride, and 175 ml. glacial acetic acid, previously cooled to below 20°, 25 ml. concd. sulfuric acid were added dropwise taking care that the temperature did not exceed 25°. The mixture was then cooled to below 5° and 31.2 g. chromium trioxide were added in small portions with stirring for 2 hr. without exceeding 8°. Stirring was continued for an additional 30 min. between 10 and 12°, and the mixture was poured into 400 ml. of ice water. The precipitated crystals were collected by suction, washed with cold water, and dried *in vacuo* at 40° to yield, 15.3 g. (56%) of material, m.p. 74–75°.

Anal. Calcd. for $C_{10}H_9NO_4S$: N, 5.85. Found: N, 5.90.

5-Cyano-2-thiophenecarboxaldehyde (XXX). The above product (15.3 g.) was suspended in a mixture of 60 ml. water, 60 ml. 95% ethanol, and 4.5 ml. concd. sulfuric acid and refluxed for 20 min. The solution was treated with charcoal and filtered when hot. On cooling, long white needles separated, which were collected by suction, washed with water, and dried *in vacuo* at 40°. An additional crop was obtained on concentration of the mother liquor; yield, 8.45 g. (51.5% calculated on 2-methyl-5-cyanothiophene); m.p. 96–97°.

Anal. Calcd. for C_6H_3NOS: N, 10.21; S, 23.38. Found: N, 10.25; S, 23.15.

The antibacterial activity of the intermediate compounds XXIX and XXX are also tabulated in Table I.

β-(*5-Cyano-2-thienyl*)*acrolein* (VIII). This product was

(24) R. A. Cutler, R. J. Stenger, and C. M. Suter, *J. Am. Chem. Soc.*, 74, 5475 (1952).

(25) E. Grischkewitsch-Trochimowski, *J. Russ. Phys. Chem. Soc.*, 43, 804 (1911).

TABLE I

MINIMAL INHIBITORY CONCENTRATION, γ/ML.

	Compound	*Micrococcus aureus*	*Streptococcus faecalis*	*Escherichia coli*	*Proteus vulgaris*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*	H37 Rv (With Serum)	*Trichophyton mentagrophytes*	*Candida albicans*
I		10	20	20	5	>100	10	2	5	10
II		10	20	20	10	>100	10	0.5	10	10
III		10	50	20	10	>100	20	10	10	20
IV		10	20	20	5	>100	20	10	5	10
V		5	10	10	5	50	10	10	5	10
VI		5	10	10	10	20	10	5	2	5
VII		5	10	10	5	10	10	5	1	5
VIII		100	>100	>100	100	>100	100	50	100	50
IX		5	20	20	10	10	20	5	2	5
X		10	100	50	5	20	20	5	0.5	5
	Ethanolamine salt of X.	10	100	50	10	20	20	5	0.5	5
XI		100	100	100	50	>100	100	10	10	50
XII		10	20	10	5	50	10	5	0.5	5
XIII		100	>100	>100	>100	>100	>100	10	20	50
XIV		>100	>100	>100	>100	>100	>100	10	>100	>100
XV		>100	>100	>100	>100	>100	>100	5	50	>100
XVI		10	10	10	5	50	10	10	0.2	10
	Ethanolamine salt of XVI	10	10	20	5	>100	20	20	0.5	50
XVII		20	100	50	20	100	50	1	0.3	0.5
XVIII		10	50	20	20	50	50	2	0.5	1
XIX	*p*-$NO_2C_6H_4CH{=}CHNO_2$	20	100	20	10	>100	20	20	2	2
XX	*p*-$NO_2C_6H_4CH{=}CBrNO_2$	5	20	10	5	5	20	20	1	2
XXI		10	50	20	10	100	10	20	2	1
XXII		5	20	10	10	5	20	20	1	2
XXIII		50	50	50	20	>100	20	10	1	5
XXIV		10	20	10	10	10	20	5	1	5
XXV		10	50	20	10	20	20	...	1	2
XXVI		50	50	10	10	5	20	20	2	2
XXVII		100	>100	>100	100	>100	>100	50	100	>100
XXVIII		10	50	20	5	>100	20	50	20	2
XXIX	2-Methyl-5-cyanothiophene	>100	>100	>100	>100	>100	>100	>100	>100	>100
XXX	5-Cyano-2-thiophenecarboxaldehyde	>100	>100	>100	>100	>100	>100	100	100	100
α-Bromo-β-(5-nitro-2-thienyl)-acrolein		5	20	2	2	10	2	1	1	5
α-Bromo-5-nitrocinnamaldehyde		5	10	10	5	50	5	1	1	5
Chloramphenicol		5	5	5	1	>100	5	12,5	>100	>100
4-Amino-salicylic acid		>100	>100	>100	>100	>100	>100	5	>100	>100

prepared with the same technique as described for β-(5-nitro-2-thienyl)acrolein.[1] Yield, 43%; m.p. 128–130°.

Anal. Calcd. for C_3H_5NOS: N, 8.58; S, 19.64. Found: N, 8.26; S, 19.48.

α-Bromo-β-(5-cyano-2-thienyl)acrolein (IX) was prepared as described for α-bromo-(5-nitro-2-thienyl)acrolein.[1] Yield, 77%; m.p. 152–154°.

Anal. Calcd. for C_8H_4BrNOS: 5.78; Br, 33.00. Found: N, 5.62; Br, 33.10.

4-[β-Bromo-γ-(5-cyano-2-thienyl)acrylideneamino]benzoic acid (X). A suspension of 12.3 g. of IX in 230 ml. anhydrous ethanol was refluxed until complete solution was obtained, then 8 g. 4-aminobenzoic acid were added in one portion under stirring. Heating was continued for some minutes, whereby complete solution occurred followed by gradual precipitation of yellow needles. After cooling in ice bath the crystals were collected by suction and dried on a steam bath. Yield, 7.3 g. (41%); m.p. 298° (dec.).

Anal. Calcd. for $C_{15}H_9BrN_2O_2S$: N, 7.75; Br, 22.12. Found: N, 7.70; Br, 22.06.

The hydroxyethylamine salt had m.p. 173–175° (dec.).

4-Cyanocinnamaldehyde (XI). This product was prepared starting from 4-cyanobenzaldehyde as described for 4-nitrocinnamaldehyde.[26] Yield, 41%; m.p. 136–138°.

Anal. Calcd. for $C_{10}H_7NO$: N, 8.91. Found: N, 9.10.

Thiosemicarbazone (XIV), m.p. 218° (dec.).

α-Bromo-4-cyanocinnamaldehyde XII was prepared starting from XI as described for α-bromo-4-nitrocinnamaldehyde.[27] Yield, 82%; m.p. 158–159°.

Anal. Calcd. for $C_{10}H_6BrNO$: N, 5.93; Br, 33.85. Found: N, 5.93; Br, 33.81.

Thiosemicarbazone (XV), m.p. 207–208° (dec.).

4-(β-Bromo-4-cyanocinnamylideneamino)benzoic acid (XVI) was prepared as described above for X. M.p. 217° (dec.).

Anal. Calcd. for $C_{17}H_{11}BrN_2O_2$: N, 7.88; Br, 22.49. Found: N, 7.68; Br, 22.27.

Hydroxyethylamine salt, m.p. 152–155°.

4-Cyanocinnamylideneacetaldehyde (XIII). A mixture of 3.8 g. XI and 15 ml. acetaldehyde was cooled to about 6–8°, then 0.6 ml. 25% potassium hydroxide solution in methanol was added, whereby the temperature rose to about 30°. After cooling 10 ml. acetic anhydride was added and the mixture was refluxed for 1 hr. After cooling, addition of 30 ml. water and 3.5 ml. concd. hydrochloric acid, refluxing for 0.5 hr. and cooling, the precipitated product was collected by suction and recrystallized from 50% ethyl alcohol. Yield (after 2 recrystallizations), 1.2 g. (27.2%); m.p. 153–155°.

Anal. Calcd. for $C_{12}H_9NO$: N, 7.64. Found: N, 7.41. Bromometric assay: 98.3%.

1-(5-Nitro-2-thienyl)-2-nitroethylene (XVII). To a well-stirred and cooled mixture of 5.82 g. 5-nitro-2-thiophenecarboxaldehyde and 3.7 ml. nitromethane, 1.2 ml. 25% potassium hydroxide solution in methanol were added, whereby the temperature reached 30°. It was cooled to 15°, 21 ml. acetic anhydride was added, and the mixture was refluxed for 30 min. After cooling a solution of 7.5 ml. concd. hydrochloric acid in 60 ml. water was added, the mixture was refluxed for 10 min., cooled, and filtered by suction. The solid was recrystallized from water. Yield, 1.1 g. M.p. 102–104°.

Anal. Calcd. for $C_6H_4N_2O_4S$: N, 13.99; S, 16.01. Found: N, 13.27; S, 15.84.

1-(5-Nitro-2-thienyl)-2-bromo-2-nitroethylene (XVIII). This compound was prepared as described for α-bromo-β-(5-nitro-2-thienyl)acrolein,[1] starting from XVII. M.p. 172–174°.

Anal. Calcd. for $C_6H_3BrN_2O_4S$: N, 10.03; Br, 28.63; S, 11.48. Found: N, 9.83; Br, 28.42; S, 11.30.

4-Cyano-β-nitrostyrene (XXI). This compound was prepared as described for XVII, except that refluxing with diluted hydrochloric acid was avoided. Yield, 47%; m.p. 186–188°.

Anal. Calcd. for $C_9H_6N_2O_2$: C, 62.06; H, 3.47; N, 16.08. Found: C, 61.92; H, 3.80; N, 15.96.

1-(4-Cyanophenyl)-2-nitro-1,2-dibromoethane (XXVI). A mixture of 2 g. XXI and 1.84 g. bromine was sealed in a glass tube and heated in a water bath at 100° for 1.5 hr. After cooling and opening of the tube the thick brown-red liquid was taken up in 10 ml. glacial acetic acid, whereby thin yellowish crystals separated which were collected by suction, washed with acetic acid, then with water, and recrystallized from anhydrous ethanol. Yield, 2.1 g. (55%); m.p. 141–143°.

Anal. Calcd. for $C_9H_5Br_2N_2O_2$: N, 8.38; Br, 47.85. Found: N, 8.38; Br, 48.00.

4-Cyano-β-bromo-β-nitrostyrene (XXII). Two grams XXVI were dissolved in hot glacial acetic acid (6 ml.), then 0.415 g. anhydrous potassium carbonate were added in portions. The mixture was heated on a boiling water bath for 15 min., then cooled, whereby a yellow precipitate formed which was collected by suction, washed well with water, and dried in an oven. Yield, 1.2 g. (79%); m.p. 148–150° (from anhydrous ethanol).

Anal. Calcd. for $C_9H_5BrN_2O_2$: N, 11.07; Br, 31.57. Found: N, 10.80; Br, 30.95.

4-Cyano-2,β-dinitrostyrene. This compound was prepared as described for XVII; m.p. 133–135°.

Anal. Calcd. for $C_9H_5N_3O_4$: N, 19.17. Found: N, 18.86.

4-Cyano-β-bromo-2,β-dinitrostyrene (XXV). The above compound (0.3) was admixed with 0.22 g. bromine in a sealed glass tube and heated for 1 hr. at 100° in a boiling water bath. The resulting brown-reddish residue was dissolved in 3 ml. hot glacial acetic acid and mixed with 0.1 g. anhydrous potassium carbonate. After heating to 100° for an additional 15 min. the mixture was cooled, filtered from some insoluble material, and diluted with an equal volume of water. The flocculent yellow precipitate was dissolved by heating and the solution allowed to cool. The precipitate was collected by suction and recrystallized from 95% ethanol. Yield, 0.22 g. (54%); m.p. 103–104°.

Anal. Calcd. for $C_9H_4BrN_3O_4$: N, 14.09. Found: N, 12.95.

1-(5-Cyano-2-thienyl)-2-nitroethylene (XXIII). This compound was prepared as described for XXI, starting from XXX. Yield, 77%; m.p. 181–182°.

Anal. Calcd. for $C_7H_4N_2O_2S$: N, 15.54; S, 17.79. Found: N, 15.45; S, 17.48.

1-(5-Cyano-2-thienyl)-2-bromo-2-nitroethylene (XXIV). A mixture of 8.2 g. XXIII and 7.7 g. bromine was heated for 20 min. on a boiling water bath in a round-bottom flask fitted with a reflux condenser. After cooling and addition of 45 ml. glacial acetic acid the preparation was carried on as described for XXV using 3.2 g. anhydrous potassium carbonate. Yield, 8.8 g. (75%) of light yellow crystals melting at 151–153° (from 95% ethanol).

Anal. Calcd. for $C_7H_3BrN_2O_2S$: N, 10.81; Br, 30.84. Found: N, 10.82; Br, 30.60.

4-Methylsulfonylcinnamaldehyde (XXVII). This product was prepared as described for 4-nitrocinnamaldehyde,[26] except that refluxing with dilute hydrochloric acid was avoided; the product crystallizing directly from acetic anhydride. M.p. 207–208°.

Anal. Calcd. for $C_{10}H_{10}O_3S$: C, 57.12; H, 4.79. Found: C, 57.37; H, 4.97.

α-Bromo-4-methylsulfonylcinnamaldehyde (XXVIII) was prepared starting from XXVII as described for α-bromo-4-nitrocinnamaldehyde.[27] Yield, 75%; m.p. 102–104°.

Anal. Calcd. for $C_{10}H_9BrO_3S$: Br, 27.63; S, 11.08. Found: Br, 27.68; S, 10.87.

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MILAN, ITALY

(26) H. Fecht, *Ber.*, **40**, 3898 (1907).

(27) A. Einhorn and F. Gehrenbeck, *Ann.*, **253**, 351 (1886).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, AIN SHAMS UNIVERSITY, ABBASSIA]

Products of Interaction of Acetylacetone, *p*-Benzoquinones, and Pyridine

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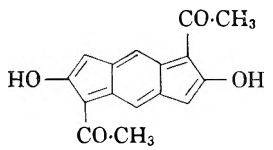
Condensation of chloranil and acetylacetone in the presence of pyridine gives the pyrrocolinequinone (Va). This compound is a useful intermediate in the preparation of nonsymmetrically substituted benzodipyrrocolinequinones of the type IIb and IIIb.

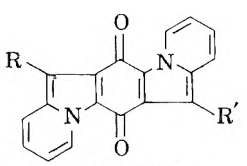
Recently, Islam and Raphael[1] proposed the benzodipyrrocolinequinone structure (IIa) for the product of interaction of acetylacetone, *p*-benzoquinone and pyridine which was previously formulated by Ionescu[2] as the indacene derivative (I).



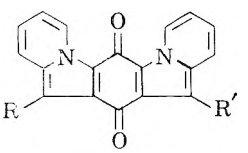
I

The formation of IIa, or the other possible isomeric structure (IIIa), was conceived as a bilateral version of a type of condensation which has already been described in the case of naphthoquinone, ethyl acetoacetate, and pyridine.[3,4]

While the establishment of this proposed structure was in progress, Tilak and Venkiteswaran[5] published the results of their work on the condensation of acetylacetone, chloranil, and pyridine. They isolated two products, a red-brown substance which was proved to be IIa and a dark green substance for which they gave the isomeric structure (IIIa). They also pointed out that the product obtained by Ionescu from *p*-benzoquinone was identical with the dark green substance obtained from chloranil and hence assigned to it the *cis* structure (IIIa).

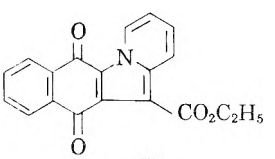


IIa; R = R′ = $CO{\cdot}CH_3$
IIb; R = $CO{\cdot}CH_3$; R′ = $CO_2C_2H_5$



IIIa; R = R′ = $CO{\cdot}CH_3$
IIIb; R = $CO{\cdot}CH_3$; R′ = $CO_2C_2H_5$
IIIc; R = R′ = H

The presence of the quinone nucleus in IIIa is established in the present investigation by reductive acetylation. In the presence of excess of hydroxylamine hydrochloride, IIIa gives a dioxime. It is suggested that the side-chain carbonyl groups will react preferentially since they are less hindered sterically. Pratt, Luckenbaugh, and Erickson,[3] obtained also a monoxime from the phthaloylpyrrocoline (IV) and considered the carbonyl group farthest from the nitrogen atom to be more reactive.



IV

An attempt to remove the acetyl groups by means of a Beckmann rearrangement of the dioxime, followed by hydrolysis and deamination, failed. Fusion of IIIa with a mixture of zinc chloride, sodium chloride and zinc dust, or heating it with phosphoric acid and zinc dust gave IIIc which retained the quinone nucleus as confirmed by reductive acetylation.

The failure of IIIc to give an oxime supports the above suggestions that the acetyl carbonyl groups are those responsible for the formation of the dioxime in IIIa. The ultraviolet absorption spectra of IIIa and IIIc (*cf.* Fig. 1) show that they possess analogous structures.

When the reaction between chloranil and acetylacetone was carried out in the presence of a limited amount of pyridine (1–2 moles of pyridine for each mole of chloranil), a mixture of a yellowish green and violet substances was obtained. The former compound (A) which possesses a quinone nucleus, has the empirical formula $C_{16}H_{11}NO_4Cl_2$

(1) A. M. Islam and R. A. Raphael, *Chemistry & Industry*, **50**, 1635 (1955).
(2) M. V. Ionescu, *Bull. soc. chim. France*, **41**, 1094 (1927).
(3) E. F. Pratt, R. W. Luckenbaugh, and R. L. Erickson, *J. Org. Chem.*, **19**, 176 (1954).
(4) E. F. Pratt, *et al.*, *J. Am. Chem. Soc.*, **79**, 1212 (1957).
(5) B. D. Tilak and M. R. Venkiteswaran, *J. Sci. Ind. Research (India)*, **15B**, 561 (1956).

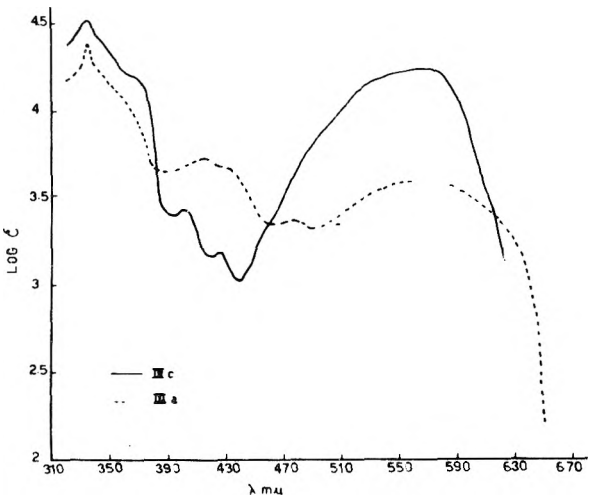


FIGURE 1.

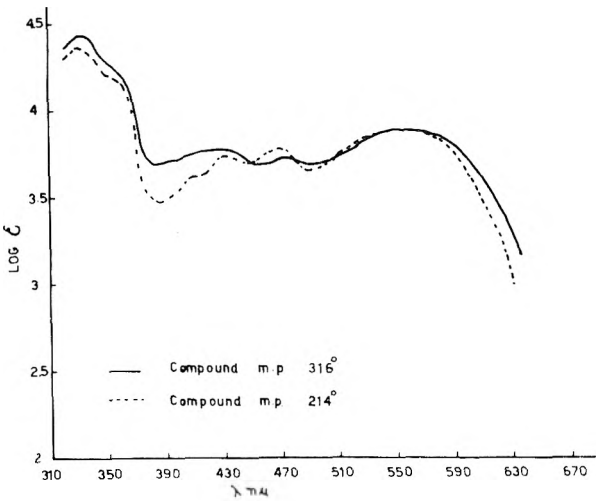
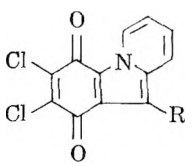


FIGURE 2.

and is still under investigation. The latter compound, which contains also a quinone nucleus, analyzed for the benzopyrrocolinequinone (Va). Treatment of Va with acetylacetone and pyridine gives a dark green solid proved to be benzodipyrrocolinequinone (IIIa) by melting point and mixed melting point determinations and also by identical ultraviolet absorption spectra.



Va; R = $CO{\cdot}CH_3$
Vb; R = $CO_2C_2H_5$

Reaction between Va, ethyl acetoacetate, and pyridine gives a mixture of two substances. One, m.p. 214°, has a dark green color and gives a blue color with concentrated sulfuric acid. The second substance which has a lighter shade, melts at 316° and gives an olive green color with concentrated sulfuric acid.

It has been observed[5] that *cis*- and *trans*-benzodipyrrocolinequinones give with concentrated sulfuric acid green and blue to violet colors, respectively. In accordance with these observations, which seem to be a general rule, the substance which melts at 214° should have the *trans* structure (IIb), and the substance m.p. 316° should have the *cis* structure (IIIb).

The same mixture of IIb and IIIb is also obtained when the benzopyrrocolinequinone (Vb)[5] is treated with acetylacetone and pyridine. The identity of IIb and IIIb obtained from Va with those obtained from Vb is proved by melting point and mixed melting point determinations and also by identical ultraviolet absorption spectra (*cf.* Fig. 2).

The ready conversion of either Va or Vb to the benzodipyrrocolinequinones IIb and IIIb, illustrates a direct route for the formation of non-symmetrically substituted benzodipyrrocolinequinones which are difficult to obtain otherwise.

EXPERIMENTAL[6]

Interaction of acetylacetone and p-benzoquinone. The benzodipyrrocolinequinone (IIIa) was essentially prepared according to the directions of Ionescu.[2] The crude product was purified by sublimation at 320°/0.2 mm., and had m.p. 364°.

Anal. Calcd. for $C_{22}H_{14}N_2O_4$: C, 71.35; H, 3.81; N, 7.56. Found: C, 71.19; H, 3.85; N, 7.28.

Reductive acetylation of IIIa. A mixture of 0.6 g. of IIIa, 0.1 g. of fused sodium acetate, and 0.2 g. of zinc dust in 15 ml. acetic anhydride was heated under reflux for 4 hr. The cold reaction mixture was poured into ice-cold water and the precipitate filtered off. Recrystallization from acetic acid gave 0.4 g. (55%) of the diacetate as brown nodules which did not melt up to 300° (dec.).

Anal. Calcd. for $C_{26}H_{22}N_2O_6$: C, 68.41; H, 4.42; N, 6.14. Found: C, 68.15; H, 4.71; N, 6.10.

Oximation of IIIa. A mixture of 0.5 g. of IIIa and 0.5 g. (4 moles) of hydroxylamine hydrochloride in 30 ml. of dry pyridine was heated at 100° for 3 hr. Most of the pyridine was removed under reduced pressure and the residue was extracted with chloroform. Evaporation of the chloroform gave 0.1 g. (18%) of the dioxime. It was crystallized from dilute pyridine in dark red prisms, which did not melt up to 320° (dec.).

Anal. Calcd. for $C_{22}H_{16}N_4O_4$: N, 13.99; Found: N, 14.21.

Zinc dust reduction of IIIa. (*a*) A mixture of 4 g. of IIIa, 4.8 g. of zinc dust, and 4.8 g. of sodium chloride was finely ground together. The mixture was transferred to a 250-ml. conical flask, mixed with 28 g. of fused pulverized zinc chloride, then heated at 300° for 5 min. The cooled reaction mixture was boiled with water, then extracted continuously with benzene. The dried and concentrated benzene solution was chromatographed over alumina; a deep blue band was obtained which gave on elution a dark violet solid. On crystallization from benzene-petroleum ether (b.p. 40–60°), 0.2 g. (6.6%) of IIIc was obtained as violet silky needles which did not melt up to 360°.

Anal. Calcd. for $C_{18}H_{10}N_2O_2$: C, 75.51; H, 3.52; N, 9.79. Found: C, 75.56; H, 3.49; N, 9.67.

The substance was soluble in most organic solvents and gave a yellowish green color with concentrated sulfuric acid.

(6) Melting points are not corrected. All ultraviolet absorption spectral determinations were carried out in *p*-dioxane.

(*b*) IIIa (1 g.) was dissolved in 100 ml. of concentrated phosphoric acid and 0.2 g. of zinc dust was added. The solution was heated at 100–110° for 2 hr. with the frequent addition of fresh zinc dust. The cold reaction mixture was poured into ice-cold water and the precipitate filtered off. Recrystallization from benzene-petroleum ether (b.p. 40–60°) gave 0.4 g. (52%) of IIIc as violet needles which did not melt up to 360°.

Anal. Calcd. for $C_{18}H_{10}N_2O_2$: C, 75.51; H, 3.52; N, 9.79. Found: C, 75.39; H, 3.43; N, 10.01.

The substance gave a yellowish green color with concentrated sulfuric acid, and had an absorption spectrum identical with IIIc obtained from the above experiment. Reductive acetylation of IIIc gave a yellow unstable product which could not be satisfactorily purified. It turned violet when heated to 200–220°, and did not melt up to 360°.

Attempted oximation of IIIc was unsuccessful. The recovered substance had an absorption spectrum identical with IIIc.

Interaction of chloranil, acetylacetone, and pyridine. To a solution of 1 g. of chloranil and 4 ml. of acetylacetone in 200 ml. of boiling ethyl alcohol was added 12 drops of pyridine; the color of the solution changed immediately to violet. The solution was concentrated to half its volume, cooled, and the resultant precipitate filtered off. Recrystallization from ethyl alcohol gave 0.3 g. of the benzopyrrocolinequinone (Va) as violet needles, m.p. 246–248°.

Anal. Calcd. for $C_{14}H_7Cl_2O_3$: C, 54.54; H, 2.27; N, 4.54; Cl, 23.05. Found: C, 54.81; H, 2.42; N, 4.48; Cl, 22.49.

The filtrate from the above experiment was concentrated, cooled, and the resultant precipitate filtered off. Recrystallization from methyl alcohol gave 0.6 g. of A as yellowish green needles, m.p. 196° (decomposition; violet melt).

Anal. Calcd. for $C_{16}H_{11}Cl_2NO_4$: C, 54.54; H, 3.12; N, 3.97; Cl, 20.17. Found: C, 54.58; H, 3.28; N, 4.00; Cl, 20.42.

The substance gave an olive green color with concentrated sulfuric acid. Its solution in alcohol showed green fluorescence.

Reductive acetylation of Va. A mixture of 0.5 g. of Va, 0.1 g. of fused sodium acetate, and 0.1 g. of zinc dust in 15 ml. of acetic anhydride was heated under reflux for 15 min. After being filtered from the zinc dust, the reaction mixture was cooled, poured into ice-cold water, and the precipitate filtered off. On crystallization from acetic acid 0.4 g. (62%) of the diacetate was obtained as yellow needles, which changed color at 210° and melted at 244° (violet melt).

Anal. Calcd. for $C_{18}H_{13}Cl_2NO_5$: C, 54.82; H, 3.38; N, 3.55; Cl, 18.02. Found: C, 55.22; H, 3.60; N, 3.78; Cl, 19.17.

Reductive acetylation of A. Acetylation of A as in the above experiment, gave the diacetate (75%) which crystallized from ethyl acetate in light yellow needles, m.p. 212–214°.

Anal. Calcd. for $C_{20}H_{17}Cl_2NO_6$: C, 54.79; H, 3.88; N, 3.19; Cl, 16.21. Found: C, 55.05; H, 3.49; N, 3.16; Cl, 17.13.

Acetylation of A with acetyl chloride was unsuccessful.

Interaction of Va, *acetylacetone, and pyridine.* A mixture of 0.2 g. of Va, 2 ml. of acetylacetone, 2 ml. of pyridine, and 50 ml. of absolute ethyl alcohol was heated under reflux for 20 min. The cold reaction mixture was filtered off, and the product crystallized from diethylaniline to give 0.1 g. (42%) of a green solid, m.p. 364°, undepressed when mixed with an authentic sample of IIIa. The substance gave an olive green color with concentrated sulfuric acid and had an absorption spectrum identical with IIIa.

Interaction of Va, *ethyl acetoacetate, and pyridine.* A mixture of 0.5 g. of Va, 2 ml. of ethyl acetoacetate, 2 ml. of pyridine, and 50 ml. of absolute ethyl alcohol was heated under reflux for 45 min. The solution was concentrated to half its volume, cooled, and the resultant precipitate filtered off. The product was extracted with boiling acetone and the solution filtered from an insoluble residue. On concentration of the reddish violet acetone solution, 0.12 g. of IIb was obtained as green needles, m.p. 214°.

Anal. Calcd. for $C_{23}H_{16}N_2O_5$: C, 68.99; H, 4.03; N, 7.00. Found: C, 68.81; H, 4.24; N, 6.76.

The substance gave a deep blue color with concentrated sulfuric acid. Its solution in *p*-dioxane was red.

Crystallization of the acetone-insoluble residue from the above experiment from *p*-dioxane gave 0.27 g. of IIIb as green needles, m.p. 316°.

Anal. Calcd. for $C_{23}H_{16}N_2O_5$: C, 68.99; H, 4.03; N, 7.00. Found: C, 69.31; H, 4.07; N, 7.20.

The substance gave an olive green color with concentrated sulfuric acid. Its solution in *p*-dioxane was reddish violet.

Interaction of Vb, *acetylacetone, and pyridine.* A mixture of 0.5 g. of Vb,[5] 2 ml. of acetylacetone, 2 ml. of pyridine, and 50 ml. of absolute ethyl alcohol was heated under reflux for 30 min. The precipitate was filtered from the cold reaction mixture and the product extracted with acetone. The acetone solution upon concentration gave 0.15 g. of IIb as green needles, m.p. 214°, undepressed when mixed with a sample of IIb obtained from the above experiment. The substance gave a deep blue color with concentrated sulfuric acid and had an absorption spectrum identical with IIb obtained above.

The acetone-insoluble part of the product weighed 0.25 g. It crystallized from *p*-dioxane in green needles, m.p. 316°, undepressed when mixed with a sample of IIIb obtained from the above experiment. The substance gave an olive green color with concentrated sulfuric acid and had an absorption spectrum identical with IIIb obtained above.

CAIRO, EGYPT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, CAIRO UNIVERSITY]

Reactions of Hydroxyxanthones. IV.[1] Action of Lithium Aluminum Hydride and of Diazomethane on Hydroxyxanthones

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Received June 10, 1957

Treatment of 1-hydroxy-9-xanthones (I and II) and their benzoyl and/or benzenesulfonyl derivatives with lithium aluminum hydride led to the formation of the corresponding xanthene derivatives (IVa and V), respectively. Similar results were obtained with the benzenesulfonyl derivative of 1-hydroxybenzo[b]xanthen-12-one (IIIb), reduction of which yielded 1-hydroxybenzo[b]xanthene (VI).

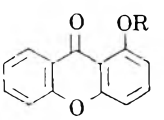
1-Methyl-4-hydroxythiaxanthene-5,5-dioxide (VIIIa) now has been obtained by the oxidation of the product which is obtained on treatment of 1-methyl-4-hydroxy- (VIIa), and 1-methyl-4-benzoyloxy-10-thiaxanthenones (VIIb) with lithium aluminum hydride.

Whereas methylation of 4-hydroxy-9-xanthenone could be effected with ethereal diazomethane, methylation of 1-hydroxy-9-xanthenone could only be brought about by the action of ethereal diazomethane in presence of methanol.

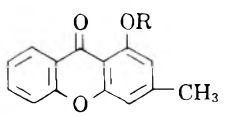
It has been found that when certain aromatic ketones containing amino or methoxyl groups *ortho* or *para* to the carbonyl group are reduced under forcing conditions with excess of lithium aluminum hydride at elevated temperatures for long periods, hydrogenolysis occurs to a methyl or methylene group.[2] Recently, similar behavior has been reported in the xanthone series. Thus reduction of xanthones, *e.g.*, 9-xanthenone, 1,2-benzo-, and 3,4-benzo-9-xanthenones[3] and 10-thiaxanthenone with lithium aluminum hydride proceeds one step further to give the corresponding xanthenes.[4] Halogen-substituted-9-xanthenones, *e.g.*, 2-chloro-, and 4-chloro-9-xanthenones undergo reduction with the same reagent leading to the formation of xanthene in every case with the loss of halogen.[5] The reaction was carried out in all cases in boiling ether-benzene solution.[3,5]

The reduction of hydroxy-9-xanthenones and their benzoyl and/or benzenesulfonyl derivatives with lithium aluminum hydride under similar conditions now has been investigated. Thus, when 1-hydroxy-9-xanthenone (Ia) and 1-hydroxy-3-methyl-9-xanthenone (IIa) are allowed to react with the same reagent in boiling ether-benzene solution for three hours and kept aside at room temperature overnight, followed by hydrolysis, the corresponding xanthene derivatives, namely, 1-hydroxy-(IVa) and 1-hydroxy-3-methylxanthene (V), are obtained respectively in an almost quantitative yield. Fractional crystallization of the reaction products does not reveal the presence of the corresponding hydrols.[6]

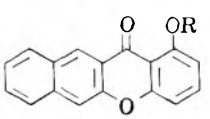
Reduction of the benzenesulfonyl derivative of 1-hydroxy-9-xanthenone (Ic) and of 1-hydroxybenzo-[b]xanthene-12-one (IIIb) with the same reagent, under the same experimental conditions, effects the cleavage of the ester, with the formation of the corresponding hydroxyxanthene derivative (IVa and VI respectively) together with thiophenol. Simi-



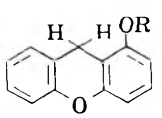
Ia, R=H
b, R=CH_3
c, R=$SO_2C_6H_5$



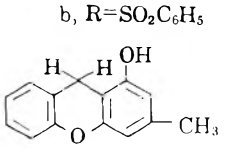
IIa, R=H
b, R=COC_6H_5



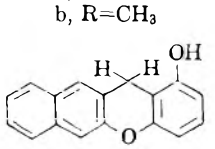
IIIa, R=H
b, R=$SO_2C_6H_5$



IVa, R=H
b, R=CH_3



V



VI

(1) For Part III *cf.* A. Mustafa and O. H. Hishmat, *J. Am. Chem. Soc.*, **79**, 2225 (1957).

(2) *Cf.* the hydrogenolysis of *p*-aminobenzophenone [L. H. Conover and D. S. Tarbell, *J. Am. Chem. Soc.*, **72**, 3586 (1950)], 2-formyl-, and 2-acetylpyrroles [A. Treibs and H. Scherer, *Ann.*, **577**, 139 (1952); A. Treibs and H. Derra-Scherer, *Ann.*, **589**, 188 (1954); W. Herz and C. F. Courtney, *J. Am. Chem. Soc.*, **76**, 576 (1954)], 3-formyl-, 3-acetyl, and 3-benzoylpyrroles [A. Treibs and H. Scherer, *loc. cit.*; E. D. Rossiter and J. E. Saxton, *J. Chem. Soc.*, 3654 (1953)]; 4-oxo-1,2,3,4-tetrahydroquinoline [W. S. Johnson and B. G. Buell, *J. Am. Chem. Soc.*, **74**, 4517 (1952)], spiro[cyclopentane-1,2′-indolin)-3′-one (B. Witkop, *J. Am. Chem. Soc.*, **72**, 614 (1950); W. Witkop and J. B. Patrick, *Experientia*, **6**, 183 (1950)], 2-methyl-2-(2′-methyl-3′-indolyl)indoxyl [B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 713 (1951)], as well as derivatives of acridone [G. M. Badger, J. H. Seidler, and B. Thomson, *J. Chem. Soc.*, 3207 (1951)].

(3) A. Mustafa and M. K. Hilmy, *J. Chem. Soc.*, 1343 (1952).

(4) *Cf.* the reduction of decussatin methyl ether (1,2,5,6-tetramethoxy-9-xanthenone) to the xanthene derivative when boiled with excess of lithium aluminum hydride in ether for 12 hr. [R. C. Shah, A. B. Kulkarni, and C. G. Joshi, *J. Sci. Ind. Research (India)*, **13B**, 185 (1954)].

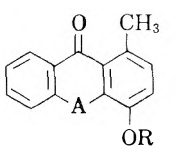
(5) A. Mustafa, W. Asker, and M. E. E. Sobhy, *J. Am. Chem. Soc.*, **77**, 5121 (1955).

(6) *Cf.* the reduction of xanthone to xanthhydrol with the same reagent [R. Mirza and R. Robinson, *Nature*, **166**, 997 (1950)].

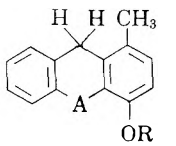
larly, V was produced by the action of lithium aluminum hydride on 1-benzoyloxy-3-methyl-9-xanthenone (IIb).

Whereas the esters of hydroxy-9-xanthenones, *e.g.* (Ic), are readily cleaved by the action of lithium aluminum hydride, the ether linkage in 1-methoxy-9-xanthenone (Ib) is stable toward the same reagent.[4,7] Thus, 1-methoxyxanthene (IVb) is obtained when (Ib) is allowed to react with the same reagent. IV was proved to be identical with the product, obtained by the action of dimethyl sulfate on an acetone solution of IVa in the presence of anhydrous potassium carbonate.

1-Methyl-4-hydroxy-10-thiaxanthenone (VIIa) undergoes reduction with lithium aluminum hydride to give an oily substance, probably 1-methyl-4-hydroxythiaxanthene, which upon treatment with hydrogen peroxide in glacial acetic acid gives 1-methyl-4-hydroxythiaxanthene-5,5-dioxide (VIIIa). The same substance was also obtained by the oxidation of the oily substance, obtained by reduction of 1-methyl-4-benzoyloxy-10-thiaxanthenone (VIIb) with the same reagent. Treatment of 1-methoxy-4-benzoyloxy-10-thiaxanthenone-5,5-dioxide (VIId) with amalgamated zinc dust, acetic and hydrochloric acids under the experimental conditions described by Fehnel[8] for the preparation of thiaxanthene-5,5-dioxide, led to the formation of a solid substance, which upon hydrolysis with alcoholic sodium hydroxide gave VIIIa.



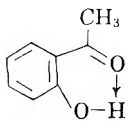
VIIa, R = H; A = S
b, R = COC_6H_5; A = S
c, R = H; A = SO_2
d, R = COC_6H_5; A = SO_2



VIIIa, R = H; A = SO_2
b, R = COC_6H_5; A = SO_2

Whereas VIIa is stable toward the action of hydrogen peroxide in glacial acetic acid, under conditions which bring about the oxidation of 10-thiaxanthenone to 10-thiaxanthenone-5,5-dioxide, 1-methyl-4-benzoyloxy-10-thiaxanthenone (VIIb) is readily oxidized with the same reagent to VIId in an almost quantitative yield. The reduction of VIId with lithium aluminum hydride, under conditions similar to those used for VIIb, led to the formation of an oily substance which upon oxidation with hydrogen peroxide in acetic acid gave VIIIa.

Reactions with diazomethane. It has been pointed out that certain *o*-hydroxy compounds are not methylated by an ethereal solution of diazomethane, *e.g.*, alizarin-2-methyl ether,[9] 9,10-dihydroxynaphthalene-11,12-quinone,[10] and *o*-hydroxyketones, *e.g.*, *o*-hydroxyacetophenone.[11] This stability is also shown by *o*-hydroxybenzophenone, 1-hydroxy-, 1,5-dihydroxy-, and 1,4-dihydroxyanthraquinones, and by the 4-methyl ether of resacetophenone.[11]



IX

The generally accepted reason[12] for the stability of *o*-hydroxyketones and related compounds toward diazomethane is the formation of a chelated ring system (*e.g.* IX in the case of *o*-hydroxyacetophenone).

We now have investigated the behavior of Ia, an *o*-hydroxyketone,[13] toward the action of ethereal diazomethane solution. Thus, when Ia is treated with an excess of the same reagent, it is recovered almost completely. But, when methyl alcohol was added to the reaction mixture, Ib was obtained together with unchanged Ia. This reaction finds a parallel in the stability of *o*-hydroxy compounds, *e.g.*, *o*-hydroxyacetophenone toward ethereal diazomethane solution, and their ready methylation in presence of methanol.[11]

Whereas, Ia is stable or almost stable toward the action of ethereal diazomethane solution, 4-hydroxy-9-xanthenone is methylated with an excess of the same reagent to give 4-methoxy-9-xanthenone.

EXPERIMENTAL

Action of lithium aluminum hydride. General procedure. Solvents dried over sodium were used. To 0.7 g. of lithium aluminum hydride (New Metals and Chemicals, Ltd., London) was added 50 ml. of ether. After 15 min. a benzene solution (30 ml.) containing 1 g. of each of Ia-c, IIa-b, and IIIb was added portionwise. The reaction mixture was refluxed for 3 hr. and then kept overnight at room temperature. After treatment with cold aqueous ammonium chloride solution the ethereal solutions were worked up as follows: The solid residues which were obtained after washing with light petroleum (b.p. below 40°; 40 ml.) were crystallized from a suitable solvent to yield the xanthene derivatives listed in Table I.

In the case of Ic and IIIb evaporation of the light petroleum washings gave an oily residue which was identified as thiophenol *via* the preparation of its benzoyl derivative (melting point and mixed melting point with phenylthiobenzoate).

(7) *Cf.* the stability of anisole toward the action of lithium aluminum hydride [P. Karrer, O. Rüttner, *Helv. Chim. Acta*, **33**, 812 (1950)].

(8) E. A. Fehnel, *J. Am. Chem. Soc.*, **71**, 1063 (1949).

(9) J. Herzig and K. Klimosch, *Monatsh.*, **30**, 535 (1909).

(10) A. Schönberg and R. Moubasher, *J. Chem. Soc.*, 366 (1944).

(11) A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 746 (1946).

(12) *Cf.* H. V. Sidgwick and R. K. Callow, *J. Chem. Soc.*, **125**, 527 (1924); A. G. Perkin and R. C. Storey, *J. Chem. Soc.*, 233 (1928).

(13) The hydroxyl group in position "1" in hydroxy-9-xanthenone results in the formation of stable chelated compounds, *e.g.*, with nickel acetate and pyroboroacetate (O. Dimroth, *Ann.*, **446**, 97 (1926).

TABLE I

XANTHENES OBTAINED BY REDUCTION OF XANTHONES

Starting Material	Product[a]	M.P.,[b] °C.	Yield, %	Solvent for Cryst.[c]	Color with H_2SO_4	Formula	Analysis, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Ia	IVa	144.5	82	A	Yellow-orange turning red	$C_{13}H_{10}O_2$	78.78	78.25	5.05	5.43
Ic	IVa	144.5	80	A	Yellow-orange turning red	$C_{13}H_{10}O_2$	78.78	78.62	5.05	4.98
Ib	IVb	70–71.5	85	B	Orange-red turning violet	$C_{14}H_{12}O_2$	79.24	79.26	5.66	5.46
IIa	V	137–138	77	A	Reddish-orange	$C_{14}H_{12}O_2$	79.24	79.65	5.66	5.97
IIb	V	137–138	72	A	Reddish-orange					
IIIb	VI	240	86	C	Reddish-brown turning red	$C_{17}H_{12}O_2$	82.26	81.99	4.84	5.38

[a] All are soluble in aqueous sodium hydroxide solution except IVb. [b] Melting points are uncorrected. [c] A, petroleum ether (b.p. 80–100°); B, petroleum ether (b.p. 40–60°); C, ethyl alcohol.

Action of lithium aluminum hydride on: (a) *1-Methyl-4-benzoyloxy-10-thiaxanthenone* (VIIb). One gram of VIIb[14] was similarly treated with lithium aluminum hydride, followed by decomposition with a cold aqueous ammonium chloride solution containing a few drops of hydrochloric acid. Evaporation of the ethereal extract gave an oily residue; solution of the latter in glacial acetic acid was then treated with hydrogen peroxide (*ca.* 1 ml.) and was heated for 1 hr. (steam bath). The solid that separated on addition of a few drops of water to the cooled solution, was collected and crystallized from petroleum ether (b.p. 80–100°) as colorless crystals (*ca.* 0.56 g.), m.p. 141–142°.

Anal. Calcd. for $C_{14}H_{12}O_2S$: C, 64.61; H, 4.61; S, 12.31. Found: C, 64.61; H, 4.69; S, 11.93.

1-Methyl-4-hydroxythiaxanthene-5,5-dioxide (VIIIa) dissolves readily in aqueous sodium hydroxide solution and develops a brownish red color when treated with concentrated sulfuric acid.

(b) *1-Methyl-4-hydroxy-10-thiaxanthenone* (VIIa). Similar treatment of 1.5 g. of VIIa with lithium aluminum hydride under the general conditions led to the formation of an oily product which upon oxidation with hydrogen peroxide as described above gave VIIIa (*ca.* 0.62 g.); identified by melting point and mixed melting point.

(c) *1-Methyl-4-benzoyloxy-10-thiaxanthenone-5,5-dioxide* (VIId). A solution of 2 g. of VIIb in glacial acetic acid (30 ml.) was treated with hydrogen peroxide (5 ml.) under the same experimental conditions described above. The crystals that separated upon cooling the reaction mixture were collected and crystallized from acetic acid as colorless crystals, m.p. 236°. The yield was almost quantitative.

Anal. Calcd. for $C_{21}H_{14}O_5S$: C, 66.67; H, 3.70; S, 8.46. Found: C, 66.27; H, 3.82; S, 8.42.

1-Methyl-4-benzoyloxy-10-thiaxanthenone-5,5-dioxide (VIId) is insoluble in cold aqueous sodium hydroxide solution and gives a deep yellow color with concentrated sulfuric acid. When refluxed with alcoholic sodium hydroxide solution (10%) for 15 min., it gave a deep orange solution which upon acidification with dilute hydrochloric acid deposited pale yellow crystals of 1-methyl-4-hydroxy-10-thiaxanthenone-5,5-dioxide (VIIc), m.p. 185°. Recrystallization from alcohol did not raise the m.p. Yield is *ca.* 70%.

Anal. Calcd. for $C_{14}H_{10}O_4S$: C, 61.31; H, 3.65; S, 11.68. Found: C, 61.17; H, 3.62; S, 11.54.

VIIc is soluble in hot aqueous sodium hydroxide solution and gives an orange color changing to red when treated with concentrated sulfuric acid.

Treatment of 1.1 g. of VIId with lithium aluminum hydride by the general experimental procedure gave an oily product which upon oxidation with hydrogen peroxide in acetic acid, as described above, produced VIIIa (m.p. and mixed m.p.). Yield is *ca.* 82%.

Reduction of VIId *with zinc amalgam, acetic acid, and hydrochloric acid mixture.* A procedure similar to that described by Fehnel[8] for the preparation of thiaxanthene-5,5-dioxide was followed. A reaction mixture of 0.5 g. of VIId, 1.23 g. of zinc amalgam, 8 ml. of glacial acetic acid, and 2.5 ml. of hydrochloric acid was refluxed for 3 hr. The solid that separated out during the reaction was separated from the unchanged zinc and was crystallized from acetic acid as colorless crystals, m.p. 252° (*ca* 0.3 g.). This was subjected directly to treatment with boiling alcoholic sodium hydroxide (10%; 30 ml.) for 15 min. The resulting orange alkaline solution gave, upon acidification with dilute hydrochloric acid and cooling, colorless solid which was crystallized from petroleum ether (b.p. 80–100°) as colorless crystals, m.p. 140°. It was identified as VIIIa (melting point and mixed melting point). The yield was almost quantitative.

Action of ethereal diazomethane solution on: (a) *1-Hydroxy-9-xanthenone* (Ia). An ethereal solution of 0.6 g. of Ia[15] was treated with excess of cold freshly distilled diazomethane solution (prepared from 8 g. of nitrosomethylurethane), and the mixture was left for 48 hr. at 0°. The ether was then evaporated. The product was identified as starting material by melting point and mixed melting point. (Yield was almost quantitative.)

The above experiment was repeated, but one ml. of methyl alcohol was added. The ethereal solution of the reaction mixture was washed with dilute aqueous sodium hydroxide solution (10%) when a canary yellow solid (sodium salt of Ia) separated. The ethereal layer was then washed with water thoroughly, dried, and evaporated. The colorless solid, so obtained, was crystallized from petroleum ether (b.p. 80–100°) as colorless crystals (*ca.* 0.43 g.), m.p. 136°. Identification as 1-methoxy-9-xanthenone was carried out by melting point and mixed melting point determination.[16]

Acidification of a suspension of the canary yellow solid in water gave yellow substance which upon crystallization yielded yellow needles (*ca.* 0.12 g.) which were identified as Ia (melting point and mixed melting point).

(b) *4-Hydroxy-9-xanthenone.* Treatment of a suspension of 0.5 g. of 4-hydroxy-9-xanthenone[17] in 50 ml. of dry ether with ethereal diazomethane solution, prepared as above,

(14) R. N. Sen and S. C. Sen-Gupta, *J. Indian Chem. Soc.*, **6**, 267 (1929).

(15) K. S. Pankajamani and T. R. Seshadri, *J. Sci. Ind. Research (India)*, **13B**, 396 (1954).

(16) J. Tambor, *Ber.*, **43**, 1883 (1910).

(17) F. Ullmann and M. Zlokasoff, *Ber.*, **38**, 2118 (1905).

in the absence of methyl alcohol resulted in the partial disappearance of the insoluble solid. The reaction mixture was filtered from the unchanged material and the ethereal solution was washed with cold aqueous sodium hydroxide solution (to remove any unchanged material), then with water, dried, and evaporated. The colorless solid, so obtained, was crystallized from ethyl alcohol as colorless crystals, *ca.* 0.15 g., m.p. 169°. It was identified as 4-methoxy-9-xanthenone (melting point and mixed melting point[17]).

Acidification of the alkaline washings gave trace of unchanged 4-hydroxy-9-xanthenone.

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[CONTRIBUTION FROM THE ENTOMOLOGY RESEARCH DIVISION, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

Synthesis of *beta*-(3,4-Methylenedioxyphenyl)tropic Acid and Its Derivatives. A Contribution to the Chemistry of the Perkin Reaction

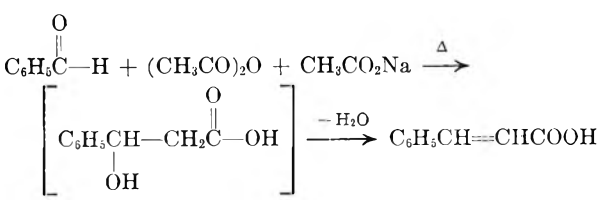
B. H. ALEXANDER AND W. F. BARTHEL

Received June 7, 1957

The belief that the Perkin synthesis involves an intermediate addition compound of the "aldol" type has been accepted since Perkin first described the reaction. Fittig reported the isolation of such an "aldol," but his compound was incapable of losing water, and therefore not a true intermediate. Hauser and Breslow prepared a true "aldol," and with their preparation the "aldol" view of the Perkin synthesis was regarded as established experimentally. Our synthesis of β-(3,4-methylenedioxyphenyl)tropic acid in good yield provides another example of a true "aldol" postulated in the Perkin reaction.

In connection with insecticide studies at Beltsville, Md., β-(3,4-methylenedioxyphenyl)tropic acid (V) and β-(3,4-methylenedioxyphenyl)atropic acid (VII) were synthesized and several of their esters tested as synergists for house flies. The synthesis of V in 65% yield provides another example of an "aldol"[1] intermediate postulated in the Perkin reaction.

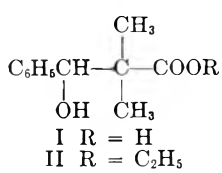
Although the history of this interesting reaction dates from Perkin's synthesis of coumarin in the year 1868, uncertainty existed as to the roles of the acid anhydride and the sodium salt in the formation of "aldol" intermediates until just recently. Some textbooks in organic chemistry are still in opposition to Perkin's[2] original views that this synthesis of cinnamic acid involves the condensation of the aldehyde with the anhydride, the acid salt acting catalytically:



These writings on the subject follow the views of Fittig,[3] who by an incorrect interpretation of his data believed that the Perkin synthesis occurs between the aldehyde and the sodium salt of the acid in two stages: first an "aldol" is formed, *i.e.*, condensation took place between the aldehyde and the alpha carbon of the acid and then water was lost by the action of the anhydride.

The results of this investigation and a number of others provide substantial evidence in favor of Perkin's original view. Michael and Hartman[4] presented strong evidence that reaction was between the aldehyde and the anhydride in the production of intermediate "aldols." Studies by Breslow and Hauser[5] have led them to conclude that "there no longer need be any doubt that the anhydride condenses in the Perkin synthesis," and not the sodium salt.

Since the "aldol" view of the Perkin reaction has now received considerable support, its further substantiation by the actual isolation of the intermediate "aldols" becomes important. Fittig[6] reported the preparation of 2,2-dimethyl-3-phenylhydracrylic acid (I).



Muller and co-workers[7] were unable to repeat this synthesis. Hauser and Breslow[1] were successful and prepared the ethyl ester (II) of I in 30% yield using

(1) H. B. Watson, *Ann. Repts. Chem. Soc. (London)*, **36**, 210 (1939), and C. R. Hauser and D. S. Breslow, *J. Am. Chem. Soc.*, 61, 793 (1939), used the term "aldol" to represent *beta*-hydroxy intermediates.

(2) W. H. Perkin, *J. Chem. Soc.*, 388 (1877); **53**, 181 (1868).

(3) R. Fittig, *Ann.*, 195, 169 (1879); 216, 97 (1883); **227**, 48 (1885); *Ber.*, **14**, 1824 (1881); **16**, 1436 (1883); **27**, 2658 (1897).

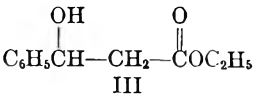
(4) A. Michael and R. N. Hartman, *Ber.*, **34**, 918 (1901); A. Michael, *J. Prakt. Chem.*, 60, 364 (1899).

(5) D. S. Breslow and C. R. Hauser, *J. Am. Chem. Soc.*, 61, 786 (1939).

(6) R. Fittig and H. W. Jayne, *Ann.*, 216, 115 (1883); R. Fittig and P. Ott, *Ann.*, **227**, 48, 61 (1885).

(7) E. Muller, H. Gawlick, and W. Kreutzmann, *Ann.* **515**, 97 (1935); E. Muller, *Ann.*, **491**, 251 (1931).

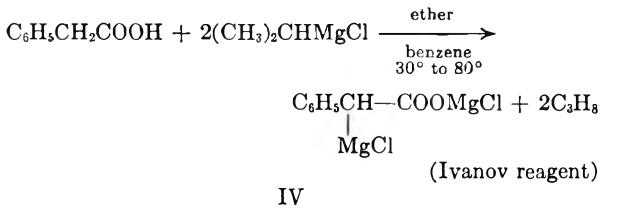
sodium triphenylmethyl as the condensing agent. However, II and I are not true intermediates in the Perkin reaction because normal elimination of water does not occur. They isolated then the true "aldol," ethyl phenylhydroxypropionate (III), in 26% yield by stopping



III

their condensation after a reaction time of only one minute.

Another example of such a ture "aldol" has been prepared in this laboratory. Kalnin[8] had observed that inorganic and organic bases, for example potassium carbonate and triethylamine, may be substituted for the aliphatic acids salts in the Perkin reaction. We therefore heated potassium carbonate, piperonal, sodium phenylacetate, and acetic anhydride at 180° for 2 hr., and VII resulted in 46% yield. It followed that VII must have come from the intermediate V. Since V is related to tropic acid and because esters of tropic acid have been found useful in insecticide studies,[9] V was synthesized. This was accomplished by reacting phenylacetic acid and isopropyl magnesium chloride to give the Ivanov reagent[10] IV.



IV

The Ivanov reagent was heated with piperonal in the presence of benzene, and V was produced in 65% yield. This procedure is general and other "aldols," which have been difficult to isolate, may now be synthesized.[11] Treatment of V with acetic anhydride gave VII in 97% yield. A mixed melting point with VII from the Kalnin modification (the use of potassium carbonate) showed them to be identical. VIII, where R is methyl, was prepared in 83% yield with methanolic hydrogen chloride. De Schuttenbach[12] prepared this ester in 20% yield by the condensation of benzaldehyde with methyl α-(3,4-methylenedioxyphenyl) acetate in the presence of granulated sodium in toluene. VI was produced in quantitative yield from V. X where R′ is methyl or ethyl and R″ is acetyl or propionyl was prepared from VI in two steps with an overall yield of 36 to 56%.

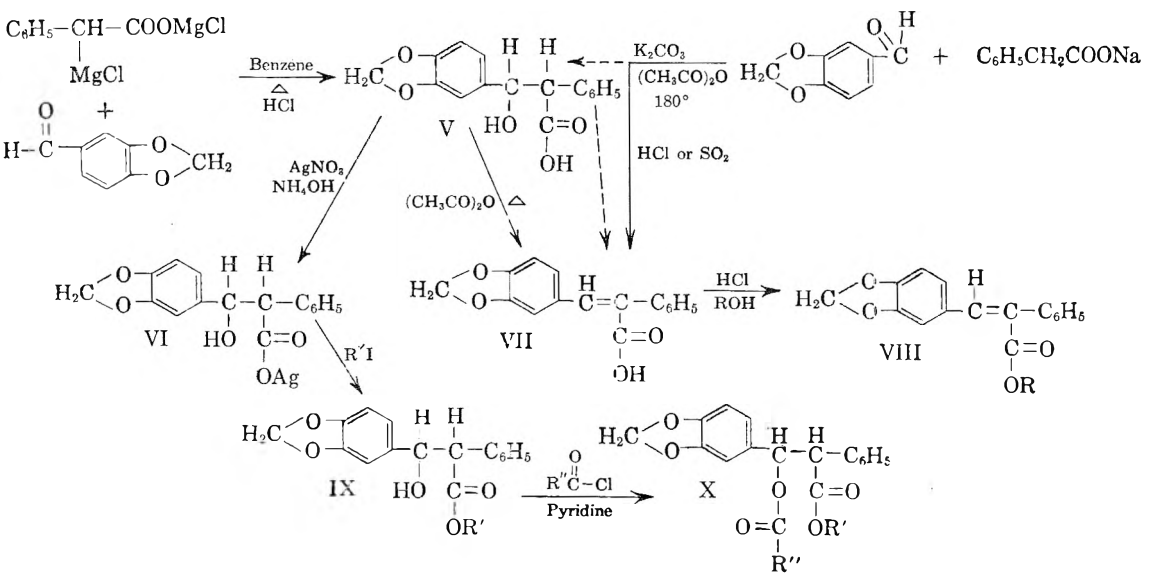
EXPERIMENTAL

β-(3,4-Methylenedioxyphenyl)tropic acid (V), was prepared according to the directions of Blicke *et al.*;[10] piperonal dissolved in benzene was substituted for their paraformaldehyde; m.p. 169° (dec.), recrystallized from 50% aqueous alcohol; yield 65%.

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 66.82; H, 5.02.

β-(3,4-methylenedioxyphenyl)atropic acid, (VII), was prepared from V (0.4 mole) by stirring with 95% acetic anhydride (900 ml.) and anhydrous sodium acetate (0.9 mole) at 100° for 1 hr. It was cooled at 25° and poured into cracked ice. On standing crystallization occurred; m.p. 232–235° (lit. 231–232°) recrystallized from alcohol; yield 97%.

VII was also prepared by the Kalnin modification from sodium phenylacetate, acetic anhydride, potassium carbonate, pyridine, and piperonal in 46% yield. The procedure of Hauser and Patterson[13] was followed.



(8) P. Kalnin, *Helv. Chim. Acta.*, **11**, 977 (1928).

(9) W. V. King, *U.S.D.A. Agricultural Handbook* 69, 397 pp. (1954).

(10) D. Ivanov and S. Spassov, *Bull. soc. chim. France*, **49**, 19 (1931); F. F. Blicke, H. Raffelson, and B. Barna, *J. Am. Chem. Soc.*, **74**, 253 (1952); H. E. Zimmerman and M. D. Traxler, *J. Am. Chem. Soc.*, **79**, 1920 (1957).

(11) C. S. Rondestvedt, Jr., and M. E. Rowley, *J. Am. Chem. Soc.*, **78**, 3804 (1956).

(12) Y. de Schuttenbach, *Ann. chim.*, **6**, 53 (1936).

(13) C. R. Hauser and M. Patterson, *Org. Reactions*, Vol. **1**, 252 (1942).

β-(3,4-Methylenedioxyphenyl)atropic acid, methyl ester (*VIII*, $R = CH_3$), was prepared from V (0.15 mole) by refluxing with 3% methanolic hydrogen chloride (200 ml.) for 4 hr.; m.p. 110–111° (lit. 106–107°) recrystallized from alcohol; yield 83%.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.34; H, 5.00. Found: C, 72.34; H, 4.93.

β-(3,4-Methylenedioxyphenyl)atropic acid, ethyl ester (*VIII*, $R = C_2H_5$) was prepared as the methyl ester (described above); m.p. 100–102° (lit. 104°) recrystallized from alcohol; yield 56%.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.80; H, 5.38.

β-(3,4-Methylenedioxyphenyl)tropic acid, silver salt (*VI*), was prepared as follows: V, 200 g. (0.7 mole), was stirred in water, 1800 ml., at 5°. Concentrated ammonium hydroxide, 80 ml. (0.7 mole) was added until the solution was just neutral to indicator paper. Silver nitrate, 121 g. (0.71 mole) was then added slowly and the mixture was kept at 5° overnight. After filtering, the residue was washed with cold water and then it was air-dried in the dark. The product was further dried *in vacuo* over phosphorus pentoxide. Yield 272 g., or 99% of theory.

β-(3,4-Methylenedioxyphenyl)tropic acid, methyl ester, acetate (*X*, *R′ and R″* $= CH_3$), was prepared from VI. Methyl iodide (0.084 mole) was added dropwise to VI (0.076 mole) in 250 ml. of ether with stirring. The mixture was refluxed 18 hr. and then was filtered. Pyridine, 18 ml., was added to the filtrate and while stirring there was added acetyl chloride (0.1 mole). The mixture was refluxed for 4 hr. and then kept at room temperature overnight. Ether and 5% aqueous hydrochloric acid were added and two layers separated. The ether layer was washed with 5% hydrochloric acid, water, 5% sodium bicarbonate, and then with saturated sodium chloride. After removal of the ether, crystallization occurred. Recrystallized twice from alcohol, the compound melted at 122–123°; yield 54%.

Anal. Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.73; H, 5.14.

β-(3,4-Methylenedioxyphenyl)tropic acid, methyl ester, propionate (*X*, $R' = CH_3$, $R'' = C_2H_5$), was prepared from VI as described except that propionyl chloride was used instead of acetyl chloride; m.p. 82°–83° after recrystallization from alcohol; yield 56%.

Anal. Calcd. for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.03; H, 5.60.

β-(3,4-Methylenedioxyphenyl)tropic acid, ethyl ester, acetate (*X*, $R' = C_2H_5$, $R'' = CH_3$) was prepared as described above; m.p. 108°–110° after recrystallization from alcohol; yield 36%.

Anal. Calcd. for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.02; H, 5.66.

Acknowledgment. The authors gratefully acknowledge the aid of Ray W. Ihndris. All microanalyses were performed by Kathryn Gerdeman, of the Chemistry Department, University of Maryland.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FORDHAM UNIVERSITY]

Sulfonation of Phenanthrene by Dioxane-Sulfotrioxide[1]

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Phenanthrene is converted by dioxane-sulfotrioxide to 1-, 2-, 3- and 9-phenanthrene sulfonic acids. The salts of these isomeric acids are isolated in yields of 5–7%, 4–6%, 27–32% and 24–30%, respectively.

Earlier reports[2] on the sulfonation of phenanthrene in which sulfuric acid was used indicated the need for temperatures of 120–125° for a short reaction time. Losses due to polysulfonation and sulfone formation had to be accepted and only the phenanthrene-2- and the phenanthrene-9-sulfonates were isolated. At lower temperatures, very long reaction times were needed. The yields were still unsatisfactory although some phenanthrene-1- and phenanthrene-9-sulfonates were isolated. Table I summarizes this earlier work.

The fractionation and isolation of the isomers were a long and tedious process especially when all four isomers resulted from the sulfonation.

Suter *et al.*[3] have reported facile sulfonation of naphthalene by dioxane-sulfotrioxide. This reagent turned out to be well suited for the monosulfonation of phenanthrene. Generally, 94–96% of the phenanthrene was converted into water soluble material during the sulfonation and over 90% of the water soluble product could be precipitated as an insoluble sodium salt by the addition of a saturated solu-

TABLE I

Author	Temp., °C.	Reaction Time, Hrs.	Yields, % of Phenanthrene Sulfonates -1-	-2-	-3-	-9-
Fieser[a]	120–125	3–7	...	17–21	24–26	...
	60	72	4–8	18	19	13
Werner[b]	120–130	5	...	12	18.6	...
	100	8	...	7	9–11	4
Sanqvist[c]	20	400	...	...	...	7–14.6
Ioffe[d]	...	...	...	17–37	...	...

[a] *Cf.* Ref. 4. [b] A. Werner, B. Löwenstein, A. Wack, T. Frey, M. Kunz, K. Rekner, A. Ney, H. Heil, A. Scherrer, H. Schwabacher, J. Kunz, and A. Grob, *Ann.*, **321**, 248 (1902). [c] H. Sandqvist, *Ann.*, **392**, 76 (1912). [d] I. S. Ioffe, *J. Gen. Chem.* (*U.S.S.R.*), **3**, 448 (1933), *Chem. Abstr.*, **28**, 1694 (1934).

(1) Presented before the Division of Organic Chemistry, AMERICAN CHEMICAL SOCIETY, 130th Meeting, Atlantic City, September 1956.

(2) References to earlier reports are given by L. E. Fieser, *Org. Syntheses*, Coll. Vol. II, 482 (1943).

(3) C. M. Suter, P. B. Evans, and J. M. Kiefer, *J. Am. Chem. Soc.*, 60, 538 (1938).

tion of sodium chloride, indicating that little, if any, polysulfonation had occurred. The isolation of 72–75% combined yield of pure salts of the isomeric monosulfonic acids is additional evidence for the preponderance of monosulfonation.

The sulfonation was carried out at various temperatures between 0° and 60° with no significant change in the relative yields of the four isomers. In order to maintain a high conversion, the reaction time had to be lengthened as the reaction temperature was lowered. These data are summarized in Table II. The reported instability[3] of dioxane-sulfotrioxide at 75° limited the highest temperature in this investigation to 60°.

TABLE II

SULFONATION OF PHENANTHRENE BY DIOXANE-SULFOTRIOXIDE

Temp., °C.	Time, Hrs.	Yields, % of Phenanthrene Sulfonates -1-	-2-	-3-	-9-
0	30	5	5	25	24
20	20	5	6	30	28
40	7	6	5.5	30	29
50	5	6.5	6	32	30
60	3	6.5	4.8	32	28

In the course of working out the fractionation of the isomers, a rather simple procedure was developed. Three new observations helped in this regard: (*a*) Sodium phenanthrene-1-sulfonate crystallized in comparatively pure form from an aqueous solution saturated with ether while the other isomers remained in solution. The ether seemed to suppress the crystallization of the other isomeric salts. (*b*) Most of the potassium phenanthrene-3-sulfonate crystallized at 60° from a solution one-fourth saturated with potassium chloride at 25°, while the 2- and 9-isomers remained in solution. (*c*) Potassium phenanthrene-9-sulfonate was quite soluble in boiling methanol while the 2- and 3-isomers were nearly insoluble in this solvent. Certain features of the Fieser fractionation were combined with the observations stated above to develop the procedure which we finally adopted for the isolation of the pure isomeric phenanthrene sulfonates.

The purity and identity of the isolated sulfonates was established by the formation of crystalline toluidine salts whose melting points corresponded closely with those reported by Fieser.[4]

An interesting comparison of the yields of the isomeric sulfonates with reactivities at the five available positions as determined by quantum mechanical methods is represented in Table III. The relative yield of the 1-isomer is seen to be less than that predicted from the calculations while the relative yield of the 3-isomer is significantly greater than the calculated reactivity would indicate. The obvious steric hindrance at the 4 position almost certainly accounts for the apparent failure of sulfonation at this position.

TABLE III

COMPARISON OF CALCULATED REACTIVITY AT THE FIVE AVAILABLE POSITIONS IN PHENANTHRENE WITH YIELDS OF ISOMERIC PHENANTHRENE SULFONATES

Position	Frontier Electron Density Distribution[5]	Free Valence[6]	Polarization Energy[6]	Yields, % of Sulfonates
1	0.231	0.134	2.30	6–7
2	0.004	0.086	2.50	4–6
3	0.148	0.079	2.41	27–32
4	0.110	0.122	2.39	0
9	0.344	0.133	2.30	28–30

EXPERIMENTAL

Sulfonation of phenanthrene. To a solution of 100 ml. (1.1 mole) of purified dioxane[7] in 350 ml. of dry ethylene dichloride in an ice-packed 2-liter, 3-necked flask fitted with a stirrer, condenser, and dropping funnel, there was slowly added from the dropping funnel 88 g. (1.1 mole) of sulfur trioxide[8] while the reaction mixture was stirred vigorously.

After the sulfur trioxide had been added, the dropping funnel was removed and 178 g. (1 mole) of pure phenanthrene,[9] m.p. 98°, was added to the contents of the flask through a powder funnel. The temperature of the reaction mixture was raised to 50° at which temperature it was maintained for 5 hr. The same procedure was followed when the reaction was run at temperatures other than 50°, except that the times were changed to those indicated in Table II.

Isolation of the pure salts of the isomeric phenanthrene sulfonic acids. Sodium phenanthrene-1-sulfonate. The sulfonation mixture was extracted with 2.2 liters of cold water. The ethylene dichloride was evaporated. This yielded 6–10 g. of water insoluble material. The supernatant, straw-colored aqueous layer was extracted with 400 ml. of ether, brought to pH 6 with a 10% aqueous solution of sodium hydroxide, cooled to 10°, and allowed to stand with occasional agitation at this temperature for 30 min. A little ether was added to maintain saturation by this solvent. The glistening plates which separated were collected on a Buchner funnel and recrystallized from boiling water to yield 17–20 g. (6–7%) of sodium phenanthrene-1-sulfonate. The toluidine salt was prepared by dissolving 0.15 g. of the sulfonate in 15 ml. of boiling water with 0.10 g. of *p*-toluidine hydrochloride. The

(4) L. F. Fieser, *J. Am. Chem. Soc.*, 51, 2460 (1929).

(5) K. Fukui, T. Yonezawa, and H. Shingu, *J. Chem. Phys.*, 20, 723 (1952).

(6) F. H. Burkitt, C. A. Coulson, and H. C. Longuet-Higgins, *Trans. Faraday Soc.*, 47, 553 (1951).

(7) E. Eigenberger, *J. prakt. Chem.* [2] 230, 75 (1931).

(8) Sulfan B, General Chemical Co.

(9) The method of Bachmann [*J. Am. Chem. Soc.*, 57, 557 (1935)] was used to purify 90% phenanthrene (Gesellschaft f. Teerverwertung b.H. Duisberg-Meiderich, Germany) after which all colored impurities were removed by solution of the powdered phenanthrene in petroleum ether and column chromatography of the solution on aluminum oxide (non-alkaline grade, Alupharm Chemicals, 322 Lafayette Street, New Orleans, La.). The effluent from the column was continuously distilled and the distillate was used to dissolve the phenanthrene. The colored impurities were retained on the alumina and the snow white phenanthrene was recovered in over 90% yield from the continuously concentrating effluent. The melting point was 98°.

crystalline product separated upon cooling and when recrystallized from boiling water melted at 265–267°.[10] The toluidine salts of the other isomers were similarly prepared.

Potassium phenanthrene-3-sulfonate. The filtrate from which the sodium phenanthrene-1-sulfonate had been separated was heated to 90°, 800 ml. of a solution of potassium chloride, saturated at 25°, added, and the temperature allowed to drop to 60° where it was held for 30 min. The crystalline product was collected on a Buchner funnel and recrystallized from boiling water. The yield was 80–90 g. (27–30%). The toluidine salt melted at 218–219°.

Potassium phenanthrene-9-sulfonate. To the filtrate from which the potassium phenanthrene-3-sulfonate had been separated, there was added 400 ml. of a saturated solution of potassium chloride and the mixture refrigerated at 4° overnight. The precipitate was collected, dried, and digested first with 800 ml., and then with 400 ml. of boiling methanol. The combined methanol extracts were evaporated. The residue dissolved in 1 liter of boiling water was treated with 25 ml. of a 10% solution of barium chloride dihydrate. The mixture was held at the boiling temperature for 10 min. and then filtered on a preheated Buchner funnel. The precipitate which was a small amount of barium phenanthrene-2-sulfonate was retained. The filtrate was treated with 60 ml. of 5*M* sulfuric acid, digested at the boiling point for 10 min., and filtered to remove barium sulfate. To this filtrate there was added 150 ml. of a 20% solution of hydrated ferrous sulfate in 2% sulfuric acid. After this was allowed to stand in the cold overnight, the greenish crystals which formed were separated and recrystallized from boiling water to which was added a small amount of sulfuric acid and ferrous sulfate solution. The purified ferrous phenanthrene-9-sulfonate was suspended in 200 ml. of boiling water and treated with an equivalent amount of a 20% solution of potassium hydroxide. After digesting at the boiling point for 15 min. the mixture was filtered to remove iron hydroxide and the filtrate allowed to stand in the refrigerator overnight. The yield of recrystallized salt was 83–89 g. (28–30%). The toluidine salt melted at 230–232°.

Sodium phenanthrene-2-sulfonate. The alcohol-insoluble residue from which the 9-isomer had been extracted was dissolved in 1 liter of boiling water and 100 ml. of a 10% solution of barium chloride dihydrate was added. After digesting the mixture at the boiling point for 10 min., the barium phenanthrene-2-sulfonate was collected on a hot Buchner funnel and combined with the material obtained during the isolation of the potassium phenanthrene-9-sulfonate. The filtrate upon cooling deposited crystalline flakes of barium phenanthrene-3-sulfonate. The barium salts were separately converted to the free acids by treatment with 5% sulfuric acid. Subsequently the barium sulfate was removed and the respective solutions neutralized with a 25% solution of sodium hydroxide to yield crude sodium phenanthrene-2-sulfonate and with 25% solution of potassium hydroxide to yield 5–7 g. (*ca.* 2%) of the potassium phenanthrene-3-sulfonate. The latter was obtained in pure form. The 2-isomer, purified by recrystallization from boiling water was obtained in yields of 12–18 g. (4–6%). The toluidine salt melted at 283–285°.

NEW YORK 58, N. Y.

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

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FORDHAM UNIVERSITY]

Syntheses and Absorption Spectra of *cis*- and *trans*-9,10-Diaryl-9,10-dihydro-9,10-phenanthrenediols[1]

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The syntheses and characterization of a series of *cis*- and *trans*-9,10-diaryl-9,10-dihydro-9,10-phenanthrenediols are described in which the 9,10-diaryl substituents vary in bulk (aryl = 4-methylphenyl, 2,4-dimethylphenyl, 2,4,6-trimethylphenyl, 2,3,5,6-tetramethylphenyl, and 1-naphthyl). Each *cis-trans* isomeric pair was configurationally related by oxidation to the same 2,2′-diaroylbiphenyl, and conversion to the same acid-catalyzed rearrangement product. Intramolecular hydrogen bonding measurements of the *cis*-diol series in the 3 micron region show $\Delta\nu$(OH) shifts of 38 cm.$^{-1}$ to 69 cm.$^{-1}$ In the *trans* series, only the *trans*-di(1-naphthyl) diol showed any hydrogen bonding [$\Delta\nu$(OH) = 36 cm.$^{-1}$]. These infrared measurements are interpreted in terms of the non-bonded steric effects of the aryl substituents upon the O—C—C angles at the 9,10-positions. A preferred conformation is suggested for the *trans*-di(1-naphthyl) diol. Interplanar angles of the biphenyl moiety calculated from ultraviolet absorption data show only a slight increase in both the *cis*- (32–36°) and *trans*-series (30–34°).

The molecule of 9,10-dihydrophenanthrene can be regarded as having a collinear biphenyl skeleton with a 2,2′-two-carbon-atom bridge. The two benzene rings are twisted at an angle of about 20° in order to accommodate the two methylene groups without appreciable distortion.[3]

As part of a study of *cis*- and *trans*-configurations about this two-carbon-atom bridge, we have prepared and characterized a series of *cis*- and *trans*-9,10-diaryl-9,10-dihydro-9,10-phenanthrenediols (II) in which the 9,10-diaryl substituents vary in bulk.

The general methods used in the synthesis and

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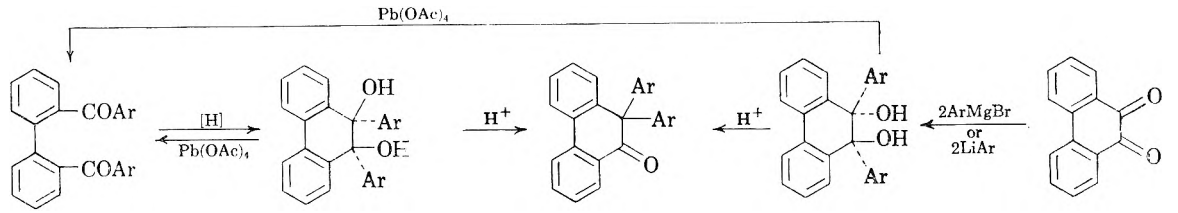
(2) Ballistics Research Laboratory, Aberdeen Proving Ground, Md.

(3) G. H. Beaven, D. M. Hall, M. S. Lesslie, and E. E. Turner, *J. Chem. Soc.*, 854 (1952).

interconversion of these diol racemates are shown in the diagram.



Ia: Ar = 4-methylphenyl
Ib: Ar = 2,4-dimethylphenyl
Ic: Ar = 2,4,6-trimethylphenyl
Id: Ar = 2,3,5,6-tetramethylphenyl
Ie: Ar = 1-naphthyl

cis-IIa: Ar = *p*-tolyl
cis-IIb: Ar = *m*-xylyl
cis-IIc: Ar = mesityl
cis-IId: Ar = duryl
cis-IIe: Ar = 1-naphthyl

IIIa: Ar = *p*-tolyl
IIIe: Ar = 1-naphthyl

trans-IIa: Ar = *p*-tolyl
trans-IIb: Ar = *m*-xylyl
trans-IIe: Ar = 1-naphthyl

The *cis*-diols were prepared by a Zn dust-KOH,[4,5] Mg-MgI_2[6-8] and/or Na-Hg[4,5] reduction of the appropriate 2,2′-diaroylbiphenyl (I) (Table I) which was obtained by a Friedel-Crafts aroylation with diphenoyl chloride (Table IV). The *trans*-diols were synthesized by a Grignard[5,9,10] or aryllithium reaction on phenanthrenequinone (Table I). These methods of syntheses are not unequivocal. For example in the preparation of the *cis*-di-(*p*-tolyl) diol (IIa) and the *cis*-di(1-naphthyl) diol (IIe), the Zn-dust-KOH technique gave a not unexpected separable mixture of both *cis* and *trans* isomers.[4,5] However, since four of the six *cis*-diol isomers listed in Table I were prepared by at least one alternate method of 2,2′-diaroylbiphenyl reduction, we believe that this method generally yields the *cis* isomer. Further metallo-organic reductions of phenanthrenequinone are known to yield *trans*-diols.[6,9-11] Many unsuccessful attempts were made to prepare the *trans*-dimesityl diol (IIc) and *trans*-diduryl diol (IId) by this latter technique. *cis*-9,10-Dihydro-9,10-phenanthrenediol was prepared by an OsO_4 hydroxylation of phenanthrene,[12] and a Na-Hg reduction of 2,2′-biphenyldialdehyde,[13] while the unsubstituted *trans*-diol was synthesized by a $LiAlH_4$ reduction of phenanthrenequinone.[14]

Where possible the *cis*- and *trans*-diols were configurationally related as follows. Each diol of a *cis-trans* isomeric pair gave the same oxidation product, the 2,2′-diaroylbiphenyl (I) on treatment with $Pb(OAc)_4$. Further, *cis*- and *trans*-9,10-dihydro-9-10-phenanthrenediols, and each diol of *cis-trans* pair IIa, IIb, and IIe was converted to an identical acid-catalyzed rearrangement product. The unsubstituted diols, IIa, and IIe gave the expected pinacol rearrangement product, respectively, 9,10-dihydro-9-phenanthrone, 10,10-di(*p*-tolyl)-9,10-dihydro-9-phenanthrone (IIIa), and 10,10-di-(1-naphthyl)-9,10-dihydro-9-phenanthrone (IIIe). The infrared spectra of phenanthrones IIIa and IIIe were quite similar. Both showed strong carbonyl absorption at 5.92 microns, and an intense carbonyl conjugated aryl band at 6.27 microns.[15] On the basis of combustion analyses, molecular weight determination, and infrared and ultraviolet absorption data, IIIb seems to be a dimeric rearrangement product formed by loss of one molecule of water from two molecules of the diol.[16]

All *cis*-diols with the exception of *cis*-diduryl diol (IId) gave a color change with potassium tetramethylosmate (Table V). This negative test for *cis*-IId is probably due to its insolubility in methanol. It was quantitatively recovered by filtration from the methanolic solution of potassium tetramethylosmate. *trans*-Diols gave no reaction. This color test is based on the formation of cyclic osmic esters and is specific for *cis*-diols in the 9,10-dihydrophenanthrene and 9,10-dihydropyrene series.[10,12] Color

(4) W. E. Bachmann and E. J. Chu, *J. Am. Chem. Soc.*, **57**, 1095 (1935).
(5) W. E. Bachmann, *J. Am. Chem. Soc.*, **54**, 1969 (1932).
(6) R. F. Brown, *J. Am. Chem. Soc.*, **76**, 1279 (1954).
(7) R. C. Fuson and C. Hornberger, *J. Org. Chem.*, **16**, 637 (1951).
(8) R. C. Fuson and R. O. Kerr, *J. Org. Chem.*, **19**, 372 (1954).
(9) T. Zincke and W. Troppe, *Ann.*, **362**, 242 (1908).
(10) R. Criegee, E. Höger, G. Huber, P. Kruck, F. Marktscheffel, and H. Schellenberger, *Ann.*, **599**, 81 (1956).
(11) H. M. Crawford, M. Lumpkin, M. McDonald, *J. Am. Chem. Soc.*, **74**, 4087 (1952); R. C. Fuson and P. Tomboulian, *J. Am. Chem. Soc.*, **79**, 956 (1957).
(12) R. Criegee, B. Marchand, and H. Wannowius, *Ann.*, **550**, 99 (1942).
(13) Additional evidence for a *cis*-diol synthesis in a Na-Hg reduction.
(14) J. Booth, E. Boyland, and E. E. Turner, *J. Chem. Soc.*, 1188 (1950).
(15) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 61.
(16) Assignment and proof of structure of IIIb and the acid-catalyzed rearrangement products obtained from IIc and IId will be the subject of a separate communication. It is pertinent to this work only that the *cis*- and *trans*-IIb diols gave the same rearrangement product.

TABLE I

9,10-DIARYL-9,10-DIHYDRO-9,10-PHENANTHRENEDIOLS (II)

Reactant	Procedure	Diol	Yield, %		Diol, M.P., °C.		Phenanthrone, M.P., °C.
			cis	*trans*	*cis*	*trans*	
Phenanthrene	OsO_4	*cis*-9,10-Dihydro-9,10-phenanthrenediol	70		177–178[12]		147–149[b]
2,2′-Biphenyldialdehyde	Na-Hg	*cis*-9,10-Dihydro-9,10-phenanthrenediol	20		177–178		
Phenanthrenequinone	$LiAlH_4$	*trans*-9,10-Dihydro-9,10-phenanthrenediol		85		185–187[14]	
Ia	Zn-KOH	*cis*- and *trans*-Di(*p*-tolyl) diol (IIa)	50	20	212–213[5]	140–142[5]	162–163[c]
Ia	Na-Hg	*cis*-Di(*p*-tolyl) diol (IIa)	55		212–213		
Phenanthrenequinone	ArMgBr	*trans*-Di(*p*-tolyl) diol (IIa)		44		140–142	
Ib	Na-Hg	*cis*-Di(*m*-xylyl) diol (IIb)	40		147–148		104–105[d]
Ib	Mg-MgI_2	*cis*-Di(*m*-xylyl) diol (IIb)	14		147–148		
Phenanthrenequinone	LiAr	*trans*-Di(*m*-xylyl) diol (IIb)		0.7		130–131	
Ic	Mg-MgI_2	*cis*-Dimesityl diol (IIc)	24		200–201.5[8]		
Id	Mg-MgI_2	*cis*-Diduryl diol (IId)[a]	68[a]		231–232[a]		
Ie	Zn-KOH	*cis*- and *trans*-Di(1-naphthyl) diol (IIe)	20	38	205–206[4]	263–264[5,f]	286–287[e]
Ie	Na-Hg	*cis*-Di(1-naphthyl) diol (IIe)	25		205–206[4]		
Phenanthrenequinone	ArMgBr	*trans*-Di(1-naphthyl) diol (IIe)		64		263–264	

[a] This *cis*-diol was generously supplied by Prof. R. C. Fuson, Univ. of Illinois. Yield and m.p. data from Ref. 7. [b] 9,10-Dihydro-9-phenanthrone. [c] 10,10-Di(*p*-tolyl)-9,10-dihydro-9-phenanthrone (IIIa). [d] This rearrangement product (IIIb) is not a phenanthrone. See Ref. 16. [e] 10,10-Di(1-naphthyl)-9,10-dihydro-9-phenanthrone (IIIe); Bachmann and Chu[5] report a m.p. of 258.5–259°. However, their carbon analysis was 0.6% low. [f] Most recently, W. I. Awad and A. R. A. Raouf, *J. Org. Chem.*, **22**, 881 (1957) report a melting point of 261°.

changes were also observed with potassium triacetylosmate for the *cis*-diols. The *trans*-diols gave various shades of the original blue color of the reagent. As expected from Criegee's work, the reaction was reversible only with the *trans*-diols. On addition of a solution of potassium acetate in acetic acid to the *trans*-diol osmic acid diester, the characteristic deep blue color of the reagent, triacetylosmate, was reformed. The diesters of the *cis*-diols did not react with potassium acetate.[10,12]

Infrared absorption spectra. Intramolecular hydrogen bonds. Using LiF optics to obtain high resolution, Kuhn[17] has found two hydroxyl absorption bands in the 3 micron region for a number of dihydroxy compounds, the higher frequency band due to unbonded OH and the lower frequency band due to intramolecularly bonded OH. The measurements were made at dilutions such that intermolecular bonding did not occur. The separation between these bands, $\Delta\nu$(OH), is a measure of the strength of the hydrogen bond and varies inversely with distance between the OH groups—the stronger the bond, the shorter is the distance between the two OH groups, and the greater is $\Delta\nu$.[18]

Our data are summarized in Table II. In the *cis* series of compounds, all of the compounds have an internal hydrogen bond. As the steric requirements of the aryl substituents in the 9 and 10 positions increase the OH groups are forced closer together. The hydrogen bonding observed for *cis*-IIc, *cis*-IId, and *cis*-IIe diols is the strongest yet reported for *cis*- or *trans*-1,2-diols.[17,19] In the *trans* series of compounds only the *trans*-di(1-naphthyl)diol (IIe) has a hydrogen bond. Thus in the *trans* compounds a

TABLE II

FREQUENCY OF HYDROXYL BANDS IN THE INFRARED (CM.$^{-1}$)

Compound	Free OH	Bonded OH	$\Delta\nu$(OH) *cis*	$\Delta\nu$(OH) *trans*
cis-9,10-Dihydro-9,10-phenanthrenediol[17]	3605	3547	38	
trans-9,10-Dihydro-9,10-phenanthrenediol[17]	3605			0
cis-Di(*p*-tolyl) diol (IIa)	3595	3548	47	
trans-Di(*p*-tolyl) diol (IIa)	3552			0
cis-Di(*m*-xylyl) diol (IIb)	3595	3539	56	
trans-Di(*m*-xylyl) diol (IIb)	3595			0[a]
cis-Dimesityl diol (IIc)	3594	3525	69	
cis-Diduryl diol (IId)	3594	3529	65	
cis-Di(1-naphthyl) diol (IIe)	3595	3532	63	
trans-Di(1-naphthyl) diol (IIe)	3596	3560		36

[a] This compound showed one broad band in contrast to the sharp bands obtained for all other compounds. We feel that this compound may have two-OH bands which are unresolved and hence appear as one broad band.

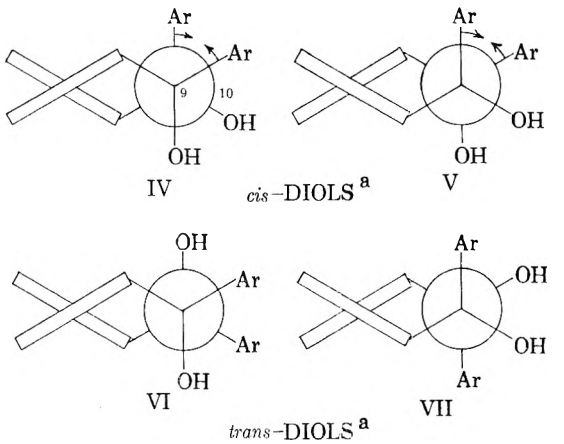
(17) L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952); **76**, 4323 (1954).

(18) R. M. Badger and S. H. Bauer, *J. Chem. Phys.*, **5**, 839 (1937); R. M. Badger, *J. Chem. Phys.*, **8**, 288 (1940); W. Gordy, *J. Chem. Phys.*, **7**, 167 (1939); W. Gordy and S. C. Stamford, *J. Chem. Phys.*, **8**, 170 (1940).

(19) (a) E. E. Eliel and C. Pillar, *J. Am. Chem. Soc.*, **77**, 3600 (1955). (*b*) A. R. H. Cole and P. R. Jeffries, *J. Chem. Soc.*, 4391 (1956).

hydrogen bond occurs only when the aryl substituents in the 9 and 10 positions are very large.

In the two possible low-energy skew conformations IV and V, for the *cis*-diols, one OH group is equatorial and the other is axial. These two OH groups are never more than 60° out of phase. There are two ways in which the OH groups can be brought closer together: (1) by rotation around the C—C bond between positions 9 and 10 as indicated by the arrows, and (2) by decreasing the O—C—C bond angles at the same positions.



[a] These convenient conformational symbols for the two-carbon bridge system in the *cis*- and *trans*-9,10-diaryl-9,10-dihydro-9,10-phenanthrenediols are adapted from those originally reported by Professor Kurt Mislow for a four-carbon bridge system in lectures presented at the AAAS Symposium on Organic Reaction Mechanisms, December 1956, N. Y. Academy of Science, January 1957, and the N. Y. American Chemical Society Meeting-in-Miniature, February 1957, and from Professor Melvin S. Newman's projectional formulas, *J. Chem. Ed.*, **32**, 344 (1955).

Since in the rotation around the C-C bond, the biphenyl system approaches a planar (eclipsed) conformation in which the aryl groups are opposed,[20] increasing the size of the aryl groups would increase the distance between the OH groups. This is contrary to our experimental findings and we must therefore conclude that the OH groups are brought closer together by a decrease of the O—C—C bond angles. An examination of molecular models shows that there is considerable steric interference between the two aryl groups and between the aryl groups and the biphenyl moiety in the *cis* isomers of IIc, IId, and IIe. This steric interference can be relieved by increasing the Ar—C—C bond angles at positions 9 and 10 which at the same time decreases the O—C—C bond angles. This alteration of bond angles seems to be another example of the Thorpe-Ingold deformation theory which states that when one of the angles at a carbon atom is increased, the opposite angle is decreased.[21] The deformation suggested by this interpretation of the data involves bringing an equatorial OH bond and an axial OH bond closer together, and it is known that this type of deformation involves considerably less strain than bringing two equatorial bonds together.[19a] The ultraviolet data are in accord with this view since the increase in the Ar—C—C bond angle should be much more effective in bringing the hydrogen-bonded OH groups together than in forcing the two phenyl rings of the biphenyl system closer together (*i.e.*, less effective in increasing the interplanar angle).

The two skew conformations for the *trans*-diols show both OH groups as axial (VI) or equatorial (VII). A necessary but not sufficient condition for hydrogen bonding in these compounds is that the OH groups be in equatorial positions. Thus, for example, in *trans*-1,2-cyclohexanediol, the azimuthal angle formed by the two OH groups is 60°, and this compound has an internal hydrogen bond. In the 9,10-dihydro-9,10-phenanthrenediols, the biphenyl interplanar angle causes the azimuthal angle between C—O bonds to be much larger than 60°, and as a consequence, the distance between the OH groups is much larger than in *trans*-1,2-cyclohexanediol. In *trans*-9,10-dihydro-9,10-phenanthrenediol,[17] *trans*-9,10-dimethyl-9,10-dihydro-9,10-phenanthrenediol,[10] *trans*-IIa, and *trans*-IIb diols, there is no internal hydrogen bond, and there is no reason for the OH groups to exist in any preferred conformation. We must conclude therefore that the presence of the very large naphthyl groups forces *trans*-diol IIe into conformation VII. Further, a hydrogen bond is produced by enlarging the Ar—C—C angles with the consequent decrease in the O—C—C angles at position 9 and 10, thereby bringing the OH groups close enough together to form a hydrogen bond of approximately the same strength as that in *trans*-1,2-cyclohexanediol.

Ultraviolet absorption spectra. Interplanar angles. Many workers have pointed out that electronic spectra are a much more sensitive index of steric effects in a molecule in its equilibrium state than is optical resolvability.[22] Indeed, Braude[23a,b,c,d,e] and his students, and most recently Truce and Emrick[24] have used ultraviolet absorption data to calculate interplanar angles (θ) from ϵ values at λ_{max} of the biphenyl-type band (K-band). Table III summarizes similar results on the *cis*- and *trans*-diols IIa-IIe, *cis*- and *trans*-9,10-dihydro-9,10-phenanthrenediol, 9,10-dihydrophenanthrene, and the reference compound, fluorene. Both *cis*- and *trans*-diols re-

(20) Conformational isomers IV and V are also enantiomers.

(21) J. W. Baker, *Tautomerism*, G. Rutledge and Sons, Ltd., London, 1934, p. 179.

(22) W. Klyne, *Progress in Stereochemistry*, Vol. I, Academic Press, Inc., New York, N. Y., 1954, Ch. 4.

(23) (a) E. A. Braude and C. F. Sondheimer, *J. Chem. Soc.*, 3754 (1955); (b) E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 3766 (1955); (c) E. A. Braude and C. F. Sondheimer, *J. Chem. Soc.*, 3773 (1955); (d) E. A. Braude and W. F. Forbes, *J. Chem. Soc.*, 3776 (1955); (e) E. A. Braude, *Experientia*, Vol. XI, 457 (1955).

(24) W. E. Truce and D. D. Emrick, *J. Am. Chem. Soc.*, **78**, 6130 (1956).

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA (BIPHENYL BANDS) AND INTERPLANAR ANGLES (θ)[a]

Compound	λ_{max} (mμ)		ϵ_{max}		$\epsilon/\epsilon^\circ = \cos^2\theta$		θ	
	cis	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*
Fluorene[b]	262		20,000		1.00		0	
9,10-Dihydrophenanthrene[c]	264		17,400		0.87		21°	
9,10-Dihydro-9,10-phenanthrenediol[d]	269	267	16,000	15,000	0.80	0.75	26°	30°
IIa	277	278	14,300	13,500	0.71	0.68	32°	34°
IIb	268	270	13,800	13,600	0.69	0.68	33°	34°
IIc	277		13,200		0.66		35°	
IId	276		13,000		0.65		36°	
IIe	278	278	28,000	26,900	1.40	1.34	—	—

[a] The data refers variously to absolute ethanol or cyclohexane solutions. Since measurements are solvent independent—our work and that reported by Beaven *et al.* (Ref. 3)—the comparison seems justified. [b] Our λ_{max} and ϵ_{max} data for the fluorene reference compound is in agreement with that reported by R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Organic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 311, but differs slightly from that reported by E. A. Braude and W. F. Forbes[23d] who obtained their data from W. V. Mayneord and E. M. F. Roe, *Proc. Roy. Soc.*, A185, 634 (1937). [c] Generously supplied by Prof. Donald D. Phillips, Cornell University. [d] Our values agree with those reported by R. N. Beale and E. Roe, *J. Chem. Soc.*, 2884 (1951).

vealed the expected bathochromic shift and decrease in ϵ which Braude[23e] has ascribed to partly forbidden transitions between the non-planar ground states and near-planar excited states enforced by the "locking" effect of the two-carbon-atom bridge. The insignificant increase in interplanar angles in going from the *cis*-di(*p*-tolyl) diol (IIa) to the *cis*-diduryl diol (IId) however, indicates that the increasing steric repulsions of the aryl substituents have a much greater effect on the hydroxyl groups than the biphenyl moiety. The bond angle distortion results almost wholly in an increase in H-bonding and only a negligible increase in interplanar angle.

It is unfortunate that the irrelevant extinction of *trans*-IIe diol with the suggested conformation VII, had a separate naphthalene absorption which overlapped the displaced K-band of biphenyl.

The total effect of the 9,10-bridgehead hydroxyl and aryl substituents on the interplanar angles is approximately equivalent to placing a methoxyl or methyl "handle" in the 4,5-position of 9,10-dihydrophenanthrene.[2,22,23e] Since Wittig and Zimmerman[25] have demonstrated indirectly that the molecule 4,5-dimethyl-9,10-dihydrophenanthrene is dissymmetric, it may not be presumptuous here to note the intriguing possibility of similar optical behavior in the substituted two-carbon-atom bridged biphenyls reported herein.[26]

EXPERIMENTAL[27]

Hydroxyl absorption measurements were made by Dr. Lester P. Kuhn at the Ballistics Research Laboratory, Aberdeen Proving Ground, Md. with a Perkin-Elmer Model 12B Spectrometer equipped with a LiF prism. See Ref. 17 for details of sample preparation. The ultraviolet spectra were run in a Beckmann Quartz Spectrophotometer Model DU using 1 cm. quartz cells. The reported ϵ values are the average of three to six measurements at diol concentrations ranging from 0.005 g./liter to 0.015 g./liter in either ethanol or cyclohexane.

2,2′-Diaroylbiphenoyl (I). The appropriate diketones were obtained directly by a Friedel-Crafts aroylation with 2,2′-diphenoylchloride (Table IV). Nightingale, Heiner, and French[28] used this procedure to prepare 2,2′-di(4-methylbenzoyl)biphenyl (Ia) and 2,2′-di(2,4-dimethylbenzoyl)-biphenyl (Ib) in unreported yields. We have extended their technique to the preparation of 2,2′-di(2,4,6-trimethylbenzoyl)biphenyl (Ic), 2,2′-di(2,3,5,6-tetramethylbenzoyl)-biphenyl (Id), and 2,2′-di(1-naphthoyl)biphenyl (Ie). Thus, 8.0 g. anhydrous $AlCl_3$ (0.06 mole) were added to a stirred mixture of 100 ml. tetrachloroethane, 5.6 g. (0.02 mole) diphenoyl chloride, and 6.71 g. (0.05 mole) durene. After complete addition of the $AlCl_3$ (20 min.), the mixture was refluxed for 15 min. and then stirred at room temperature for 10 hr. The resulting dark brown mixture was hydrolyzed with 200 g. ice and 15 ml. concd. HCl. The solid which separated was filtered and air dried. The tetrachloride layer of the two phase system was separated and dried over anhydrous $CaSO_4$. Filtration, followed by evaporation of the solvent to dryness gave a dark colored solid. The combined solids (5.51 g., 58%) were recrystallized from toluene (charcoal) and finally from propanol to give 2.8 g. (26%) of Id, m.p. 253–255°. The structures of Ia, Ib, Ic, Id, and Ie have previously been established by unequivocal syntheses which culminated with a chromic acid oxidation of either the appropriate 9,10-diarylphenanthrene[7] or the 9,10-diaryl-

(25) G. Wittig and H. Zimmerman, *Ber.*, **86**, 629 (1953).

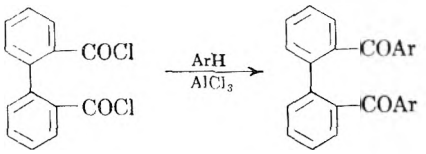
(26)[11] If the biphenyl system is rigidly twisted, six stereomeric forms are possible in theory: (±)-*cis*, (±)-*trans* A, and (±)-*trans* B; if on the other hand the biphenyl system readily passes through a planar (or equivalent) conformation, only three stereomeric forms will be isolable, *cis*, and (±)-*trans*.[11] The first reported evidence for this concept has been the result of the elegant work of Prof. Kurt Mislow and his students, New York University, who have observed racemization of the *cis*-diastereomer of 1,2,3,4-dibenzo-1,3-cyclooctadiene and mutarotation of one of the two possible *trans*-forms [*Trans. N. Y. Academy of Science*, 19, 298 (1957)]. Although Prof. Mislow's compound contains a four-carbon-atom bridge, the theoretical arguments for this concept can be applied with no modification to compounds with only a two-carbon-atom bridge.

(27) All melting points are uncorrected. The microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(28) D. Nightingale, H. E. Heiner, and H. E. French, *J. Am. Chem. Soc.*, 72, 1875 (1950).

TABLE IV

2,2'-DIAROYLBIPHENYLS



2,2'-Diaroylbiphenyl	Mole Ratio ArH/Diphenoylchloride/$AlCl_3$	Reaction Solvent	Time, Hrs.	Yield,[a] %	2,2-Diaroylbiphenyl M.P., °C.	Recrystallizing Solvent	Lit. M.P., °C.
Ia	27.9/1.0/2.7	Toluene	8–12[b]	70	136–137	EtOH	136.5–137[4,28]
Ib	23.5/1.0/3.0	*m*-Xylene	3[b]	61	129–131	EtOH	126.5–127[28]
Ic	20.0/1.0/3.0	Mesitylene	5[b]	59	226–228[d]	EtOH	219–220[28]; 226–228[7]
Id	2.5/1.0/3.0	Tetrachloroethane	10[b]	26	253–255[e]	C_6H_6	255–256[8]
Ie	2.5/1.0/3.0	CS_2	5[c]	12	198–200	HOAc	200[4]

[a] All yield figures are the average of at least two runs. [b] Reactions run at room temperature. [c] Reaction run at 0–5°C. [d] Our melting point agrees with that reported by R. C. Fuson and C. Hornberger,[7] and differs from that reported by D. Nightingale, H. Heiner, and H. E. French.[23] [e] For purposes of comparison, a sample of 2,2'-diduroylbiphenyl was generously provided by Prof. R. C. Fuson, University of Illinois. His method of preparation is found in Ref. 8.

9,10-dihydro-9,10-phenanthrenediol,[4,5,8] or by an Ullman reaction on the aryl-2-bromophenyl ketone.[4,5,8,28]

2,2'-Biphenyldialdehyde. Pale yellow needles from 70% ethanol, m.p. 61–62°.[29]

Phenanthrenequinone. Orange needles from ethanol, m.p. 208–210°.[30]

cis-9,10-Dihydro-9,10-phenanthrenediol was obtained in 70% yield from phenanthrene, OsO_4 and pyridine[12] as white, fine silk needles from toluene, m.p. 177–178°. Alternatively this compound was prepared by treatment of 2,2-biphenyldialdehyde with Na-Hg.[4,5] Thus 0.5 g. (0.0024 mole) 2,2'-biphenyldialdehyde was shaken for 1 week with 11.5 g. of 5% Na-Hg (0.025 g. atom Na) in 50 ml. absolute ether. Hydrolysis of this mixture with dilute acetic acid (1:10), separation of the two resulting layers, and evaporation of the ether layer gave a yellow oil. Careful agitation of this oil with several ml. of cold 95% ethanol dissolved the oil and left crystalline plates, m.p. 135–138° which were immediately filtered. Several recrystallizations from *n*-propyl alcohol (charcoal) raised the m.p. to 177–178° which was not depressed on admixture with a sample prepared by the osmylation technique. The yield of pure diol was 0.1 g. (20%).

trans-9,10-Dihydro-9,10-phenanthrenediol was obtained in 85% yield from the $LiAlH_4$ reduction of phenanthrenequinone,[14] as white, fine silk needles from cyclohexane, m.p. 185–187°.

cis-9,10-Di(p-tolyl)-9,10-dihydro-9,10-phenanthrenediol (*cis*-IIa). Bachmann's[4,5] procedures were generally followed: 3.0 g. of Ia (0.0077 mole) was dissolved in 120 ml. of 95% ethanol. Nine g. of Zn dust, and 15 ml. of 40% KOH solution were then added and the mixture was refluxed (stirring) for 8 hr. After filtration, the Zn-dust residue was extracted twice with 25 ml. portions of hot ethanol and the combined filtrates poured into ice HCl-mixture. The precipitated solid was filtered, washed with water, and thoroughly air-dried before recrystallization from propanol. The first fraction was separated and after several recrystallizations from propanol (charcoal), yielded 1.5 g. (0.0038 mole, 50%) of *cis*-IIa, m.p. 212–213°. The solubilities of *cis*-IIa and *trans*-IIa are reversed in acetone. Therefore, the combined filtrates of these recrystallizations were evaporated to dryness, and recrystallized from acetone to yield 0.6 g. (0.0015 mole, 20%) of *trans*-IIa, m.p. 140–142°.

Alternatively, the Na-Hg reduction of Ia gave *cis*-IIa, m.p. 212–213° in 55% yield, undepressed on admixture with *cis*-IIa diol prepared by the Zn-dust reduction.

trans-9,10-Di(p-tolyl)-9,10-dihydro-9,10-phenanthrenediol (*trans*-IIa). The Grignard reagent was prepared in the usual manner: 50 ml. of anhydrous ether, 5.5 g. of Mg turnings, 8 ml. of bromotoluene, and a crystal of I_2 were stirred and gently heated until the Grignard reaction had commenced. Three portions of 8 ml. each of bromotoluene (total 0.24 mole) were then added alternately with three portions of 10 ml. each of anhydrous ether. The mixture was refluxed for 15 min. and then cooled. Fifty ml. of dry benzene was added to the prepared Grignard reagent, and with cooling, 17 g. (0.079 mole) of phenanthrenequinone was added (stirring) in 4 portions sufficient to maintain a vigorous reflux, after which the solution was refluxed for 5 hr. After cooling, the complex was hydrolyzed by pouring it into a mixture of 200 g. ice and 300 ml. concd. HCl. The water layer was separated and the solid material at the two-layer interface was filtered. The benzene-ether layer was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The oil residue was digested with a few ml. of cold ethanol to remove the oily impurity. The solid residue was combined with the solid material from the interface and the whole was twice recrystallized from ethanol (charcoal) to yield 13.5 g. (44%) of *trans*-IIa, m.p. 140–142°. The mother liquor contains 4,4'-dimethylbiphenyl as a very soluble by-product. It was obtained by slow evaporation of the solvent ethanol to dryness in an evaporating dish. The center portion of the solid residue in the dish was again dissolved in ethanol and the process repeated several times to give 1.0 g. (0.0055 mole, 4.5% conversion based on bromotoluene) of 4,4'-dimethylbiphenyl, m.p. 120–121° (lit. m.p. 121–122°).[31]

With benzene as a recrystallizing solvent, a low melting benzene-diol adduct, m.p. 103–104°, was formed. Combustion analyses gave consistently and reproducibly high carbon and hydrogen analyses. All attempts to remove the benzene were unsuccessful. The adduct was ultimately identified as such by its infrared spectrum which was virtually superimposable upon that of *trans*-diol IIa with a single exception of strong benzene band at 14.82 microns.[32]

cis-9,10-Di(m-xylyl)-9,10-dihydro-9,10-phenanthrenediol (*cis*-IIb). The procedure of Fuson and Hornberger[7] was followed. Thus, 2.02 g. of I_2 was added under a nitrogen

(29) W. J. Schmitt, E. J. Moriconi, and W. F. O'Connor, *J. Am. Chem. Soc.*, **77**, 5640 (1955).

(30) R. Wendland and J. LaLonde, *Org. Syntheses*, **34**, 76 (1954).

(31) F. Ullman and G. M. Meyer, *Ann.*, **332**, 44 (1904).

(32) We are indebted to Dr. R. L. Wagner, Chas. Pfizer and Co., Inc. for the infrared (CS_2) and ultraviolet (cyclohexane) solution spectra of these compounds.

atmosphere over a 15-min. period to a well stirred, initially heated mixture of 19.0 ml. of dry *n*-butyl ether, 23.0 ml. of dry toluene, and 2.12 g. Mg filings. The solution gradually became colorless as the reaction proceeded. After 15 min., a solution of 2.2 g. (0.00525 mole) of 2,2′-di(2,4-dimethylbenzoyl)biphenyl (Ib) in 19.0 ml. toluene was added over a period of $^1/_2$ hr. Color changes of solution were: yellow after one-half of Ib had been added, violet after 3 hr. reflux and light brown to gray after 4 hr. reflux. Refluxing and stirring was continued overnight (15-hr. total) after which the solution appeared faintly yellow. The reaction product was decanted from the Mg and the solution poured into 20 g. ice and 25 ml. concd. HCl. The Mg residue was extracted with 30 ml. dry ethyl ether and the solution added to the ice–HCl mixture. The organic layer was extracted three times with water, dried over $CaSO_4$, and after filtration, evaporated to dryness. The residual oil was digested with anhydrous methanol and evaporated until crystallization occurred to yield 0.50 g. of crude *cis*-diol IIb. Recrystallization from ethyl alcohol (4 wk.) or n-hexane (15 min.) (charcoal) gave 0.30 g. (14%) of *cis*-IIb, m.p. 147–148°. Alternatively, *cis*-IIb was prepared in 40% yield, m.p. 147–148° from a Na-Hg reduction of Ib. A mixed melting point of the diols prepared by the alternate methods showed no depression.

Anal. Calcd. for $C_{30}H_{28}O_2$: C, 85.70; H, 6.71. Found: C, 85.76; H, 6.67.

trans-9,10-Di(m-xylyl)-9,10-dihydro-9,10-phenanthrenediol (*trans*-IIb). The *m*-xylyllithium was prepared under a nitrogen atmosphere in the usual manner.[33] To a solution of 1.6 g. of freshly prepared 1-bromo-2,4-dimethylbenzene[34] in 25 ml. anhydrous ether was added 1.4 g. (0.20 g.-atom) of lithium wire. The remainder of the bromoxylene (13.4 g.; total 0.088 mole) dissolved in 50 ml. of dry ether was added dropwise as soon as the initially vigorous reaction had subsided (1 hr.). Several runs were made at ice-bath temperatures, but the reaction proceeded most conveniently at room temperature. The *m*-xylyllithium was then filtered through an L-shaped tube loosely plugged with glass wool into a dry 250-ml. three-neck flask, also under a nitrogen atmosphere. To the almost clear solution, cooled to 0° with an ice-salt bath was added (stirring) 4.3 g. (0.021 mole) of phenanthrenequinone suspended in 50 ml. of benzene. The mixture was stirred overnight at room temperature. Hydrolysis of the complex intermediate was accomplished by adding the suspension to 100 g. ice and 5 ml. dilute HCl. The benzene-ether layer was then separated, dried, and evaporated to dryness. The resulting oil contained large amounts of phenanthrenequinone which remained undissolved after digesting the oil with several ml. of ether. Filtration of the insoluble phenanthrenequinone, and subsequent evaporation of the ether solution left an oil. This oil was treated with 40 ml. of dry petroleum ether (30–60°) and then 5–10 ml. of dry ether until all of the oil had dissolved leaving the crude white diol. This was filtered and recrystallized (charcoal) three times to yield 58 mg. (0.7%) of *trans*-diol (IIb) white needles, m.p. 130–131°.

Anal. Calcd. for $C_{30}H_{28}O_2$: C, 85.70; H, 6.71. Found: C, 85.58; H, 6.62.

All attempts to prepare this compound by the normal Grignard reaction using a wide variety of concentrations, temperatures, and isolation procedures led to no identifiable diol.

cis-9,10-Dimesityl-9,10-dihydro-9,10-phenanthrenediol (*cis*-IIc). Fuson's directions[8] for preparing *cis*-IIc were followed using a nitrogen atmosphere throughout. It was obtained in 24% yield, m.p. 200–201° from methanol.

cis-9,10-Diduryl-9,10-dihydro-9,10-phenanthrenediol (*cis*-IId). This compound, m.p. 231–232° was generously supplied by Prof. R. C. Fuson and was used directly in all measurements and reactions.

cis-9,10-Di(1-naphthyl)-9,10-dihydro-9,10-phenanthrenediol (*cis*-IIe). This compound, m.p. 205–206°,[4] from propanol, was prepared in the same manner as *cis*-IIa *via* Zn-dust–KOH reduction (20% yield) and Na-Hg reduction (25%) of 2,2′-di(1-naphthoyl)biphenyl (Ie). In the former reduction, a 38% yield of the *trans*-isomer was also obtained.

trans-9,10-Di(1-naphthyl)-9,10-dihydro-9,10-phenanthrenediol (*trans*-IIe). This compound, m.p. 263–264°, from isopropyl alcohol, was prepared in 64% yield by a Grignard reaction on phenanthrenequinone,[4] in the same manner as in the preparation of *trans*-Ia. A mixed melting point of the *trans* isomer prepared in this manner and by the Zn-dust–KOH reduction of Ie showed no depression.

Color tests with Criegee's Reagents.[10,12] Potassium tetramethylosmate (0.001*M*) and potassium triacetylosmate (0.001*M*) solutions were prepared, respectively, in absolute methanol and glacial acetic acid as directed.[12] The color tests were conveniently run with 0.5 ml. of the reagent and approximately 10^{-6} mole of the diol. Results are summarized in Table V.

TABLE V

COLOR CHANGES WITH CRIEGEE'S REAGENTS[a]

Compound	Potassium Tetramethylosmate		Potassium Triacetylosmate	
	cis	*trans*	*cis*[b]	*trans*[b]
9,10-Dihydro-9,10-phenanthrenediol	Pale green	Green	Pale violet	Deep blue
IIa	Yellow	No reaction	Yellow	Deep blue
IIb	Yellow	No reaction	Deep violet	Deep blue
IIc	Deep blue		Deep violet	
IId	No reaction[c]		Pale violet	
IIe	Yellow-green	No reaction	Deep violet	Deep blue

[a] The colors reported are those which appeared after the solutions of reagent and diol were in contact 30 min. [b] To show the reversibility of this reaction on treatment of the reagent-diol solution with potassium acetate in acetic acid, the recorded color is that which appears after the potassium acetate in acetic acid has been added. [c] *cis*-Diol (IId) is insoluble in MeOH solvent used for reagent preparation.

Diol oxidation with lead tetraacetate. The 2,2′-diaroylbiphenyls, respectively, Ia, Ib, and Ie were obtained from each of *cis-trans* isomeric diol pairs by warming a benzene or acetic acid solution of excess lead tetraacetate and each diol (25–50 mg.) of the series, IIa, IIb, and IIe, for 15–30 min. in a steam bath. Similarly, *cis*-IIc and *cis*-IId, gave, respectively, Ic and Id.

Acid-catalyzed rearrangements. Each diol of the *cis-trans* isomeric pairs 9,10-dihydro-9,10-phenanthrenediol, IIa, IIb, and IIe, was dissolved in the minimum volume of hot glacial acetic acid to which was added 2–3 drops of concd.

(33) *Organic Reactions*, Vol. VII, p. 286 (1954).

(34) Preparation identical to that for bromomesitylene, L. I. Smith, *Org. Syntheses*, Vol. II, p. 95 (1943).

sulfuric acid. The solution was heated on a steam bath for 15–30 min. In all cases, the *cis*-diols reacted visibly more rapidly than the *trans*-diols. A few drops of water were sufficient to precipitate the rearrangement product if this had not occurred at the end of 30 min. The product was filtered, washed with water, and recrystallized. In this manner, the following four rearrangement products were obtained:

9,10-Dihydro-9-phenanthrone, m.p. 147–149° (lit. m.p., 152°)[35] from ethanol, was obtained from both *cis*- and *trans*-9,10-dihydro-9,10-phenanthrendiol. It is unstable on standing in air or in solution and changes color from pale yellow to pink to red in a relatively short time. After rapid filtration, a single pale yellow crystal was quickly selected for melting point determination. The time interval between commencement of the rearrangement process and the melting point determination approximated 20 min.

10,10-Di(p-tolyl)-9,10-dihydro-9-phenanthrone (IIIa), m.p. 163–164.5° from absolute ethanol was obtained in 90% yield from *cis*-IIa and in 80% yield from *trans*-IIa.

Anal. Calcd. for $C_{28}H_{22}O$: C, 89.80; H, 5.92. Found: C, 89.69; H, 5.88.

Bachmann[4] prepared IIIa, m.p. 158–159° by a similar pinacol rearrangement using iodine and glacial acetic acid.

10,10-Di(1-naphthyl)-9,10-dihydro-9-phenanthrone (IIIe), m.p. 286–287°[36] from absolute ethanol was obtained in 90% yield from *cis*-IIe and in 35% yield from *trans*-IIe.

Anal. Calcd. for $C_{34}H_{22}O$: C, 91.46; H, 4.97. Found: C, 91.45; H, 5.33.

The infrared spectra of phenanthrones IIIa and IIIe are quite similar and show identical absorption bands, attributed to aromatic ketones at 5.92, 6.27, and 7.90 microns, and to aromatic substituents at 6.90, 7.18, 12.62, 13.03, 13.26, 13.66, and 14.40 microns.[37]

Rearrangement Product (IIIb), m.p. 104–105° from ethanol was obtained in 95% yield from *cis*-IIb and in 90% yield from *trans*-IIb.

Anal. Calcd. for $C_{60}H_{54}O_3$: C, 87.55; H, 6.61; Mol. wt., 823. Found: C, 87.56; H, 6.71; Mol. wt., 881 ± 10% (Signer-Barger).

The infrared spectrum of IIIb showed a weak band at 2.95μ (OH), moderate bands at 6.23μ, 6.92μ, 8.13, 9.25, and 10.57μ (aryl substituents), and strong bands at 6.01μ and 13.65μ; λ_{max} 253 mμ, ϵ_{max} 68,200.

Acknowledgment. The authors take pleasure in thanking the Research Corp. for grants initiating and supporting this work. Special thanks are due to William J. Schmitt, S. J., Woodstock College, Woodstock, Md. whose serendipity led us to this investigation.

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(35) F. R. Japp and A. Findlay, *J. Chem. Soc.*, 1121 (1897).

(36) See Table I, Ref. (e).

(37) We are indebted to Mr. Daniel McCarthy for the infrared spectra (KBr) disk for these compounds.

[CONTRIBUTION FROM THE LOS ALAMOS SCIENTIFIC LABORATORY, UNIVERSITY OF CALIFORNIA]

gem-Dinitro Esters. I. Preparation and Some Reactions of α-Hydroxy-β,β-dinitropropionic and -butyric Acids

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The preparation of α-hydroxy-β,β-dinitro-propionic and -butyric acids by the condensation of dinitromethane and 1,1-dinitroethane, respectively, with glyoxylic acid, their esterification and acylation, and some of their physical properties are described.

As part of a study of the chemistry and properties of *gem*-dinitro esters, several α-hydroxy-β,β-dinitro acids and esters were prepared by the condensation of 1,1-dinitroparaffins with glyoxylic acid derivatives.

The condensation of nitroparaffins with carbonyl compounds to form nitro alcohols was first reported by Henry[2] in 1895. Subsequent studies of this reaction, primarily using mononitroparaffins, were reviewed by Hass and Riley.[3] Chattaway and Witherington[4] successfully used the hydrate of a carbonyl compound in this same condensation to obtain nitro alcohols. Shechter and Conrad[5] prepared α-hydroxy-β-nitropropionic acid by the condensation of nitromethane with glyoxylic acid in aqueous solution.

In the present investigation α-hydroxy-β,β-dinitrobutyric acid (I) was prepared by the acid-catalyzed condensation of 1,1-dinitroethane with glyoxylic acid hydrate. It was also obtained, although in lower yield, in the attempted preparation of 2,2,5,5-tetranitro-3,4-hexanediol by the reaction of 1,1-dinitroethane with a commercial grade of glyoxal.[6] The α-hydroxy acid was stable in acidic or neutral media but it rapidly reacted with two moles of base to form glyoxylate and dinitroethane anions. Esterification with ethanol or methanol in the presence of sulfuric acid was normal in contrast

(1) Present address: Stanford Research Institute, Menlo Park, Calif.

(2) L. Henry, *Compt. rend.*, 120, 1265 (1895).

(3) H. B. Hass and E. F. Riley, *Chem. Revs.*, 32, 406 (1943).

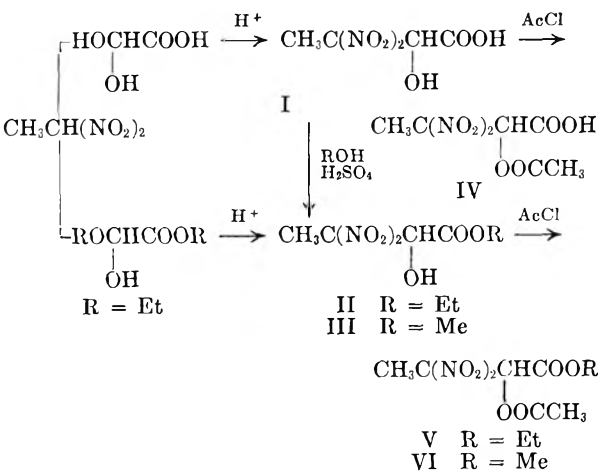
(4) F. D. Chattaway and P. Witherington, *J. Chem. Soc.*, 1178 (1935).

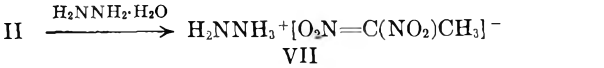
(5) H. Shechter and F. Conrad, *J. Am. Chem. Soc.*, 75, 5612 (1953).

(6) α-Hydroxy-β,β-dinitrobutyric acid could arise in one of several ways, for instance, by oxidation of an intermediate condensation product as α-hydroxy-β,β-dinitrobutyraldehyde or by preliminary oxidation of the glyoxal to glyoxylic acid, followed by normal condensation. The mechanism of this reaction, however, was not investigated.

to that of the propionic analog, giving the corresponding ethyl and methyl esters II and III; the former ester was also prepared by the condensation of 1,1-dinitroethane with ethyl glyoxylate hemiacetal. The nitro acid, however, was recovered unchanged after warming with concentrated sulfuric or polyphosphoric acid showing no evidence of lactide or polyester formation. Attempted preparation of the α-bromo acid by reaction with phosphorus tribromide gave instead, a phosphate ester which was free of bromine. Acetylation of the nitro acid and esters gave α-acetoxy-β,β-dinitrobutyric acid (IV) and the corresponding ethyl and methyl α-acetoxy esters V and VI. α-Trifluoroacetoxy-β,β-dinitrobutyric acid (VIII) was readily prepared by the action of trifluoroacetic anhydride on the acid but it was comparatively unstable.

Ethyl α-hydroxy-β,β-dinitrobutyrate (II) was also rapidly cleaved to the anion of 1,1-dinitroethane by hydrazine hydrate or even dry ammonia. The α-acetoxy derivatives were more stable toward bases than were the free hydroxyl compounds. α-Acetoxy-β,β-dinitrobutyric acid (IV) reacted as a monobasic acid although excess alkali slowly produced the 1,1-dinitroethane anion. Hydrazine hydrate and dry ammonia each cleaved the α-acetoxy esters from which low yields of 1,1-dinitroethane hydrazinium or ammonium salts were isolated.





α-Hydroxy-β,β-dinitropropionic acid (IX) was obtained as a dipotassium salt (IXa) by the condensation of potassium glyoxylate hydrate with potassium dinitromethane in water. Acidification gave the free acid IX.

In contrast to the behavior of the butyric acid, we were unable to prepare esters of this nitro acid by direct esterification; instead, the α-alkoxy esters were obtained. Thus, methyl α-methoxy-β,β-dinitropropionate (X) resulted from the reaction of methanol on α-hydroxy-β,β-dinitropropionic acid (IX) in the presence of sulfuric acid. Ethyl α-ethoxy-β,β-dinitropropionate (XII) was prepared in a similar manner from the α-hydroxy ester XI. While the α-hydroxy esters could not be obtained by direct esterification, potassium ethyl α-hydroxy-β,β-dinitropropionate (XIa) was obtained by the condensation of ethyl glyoxylate hemiacetal and potassium dinitromethane. Upon acidification the free hydroxy ester XI was formed.

This difference in behavior of the butyric and propionic acids suggests the possible intermediate formation of the β,β-dinitroacrylate system in the latter case; however, efforts to prepare this intermediate were unsuccessful. Extensive decomposition, with elimination of oxides of nitrogen, was observed when the hydroxy ester XI was treated with dehydrating agents. The alkoxy esters were distilled unchanged from phosphorus pentoxide. Pyrolysis of ethyl α-acetoxy-β,β-dinitropropionate (XIII) resulted in the elimination of acetic acid and oxides of nitrogen, the residue being a mixture of organic compounds from which a pure component could not be isolated. Treatment of the acetoxy esters with base or urea again led to a mixture of products resulting from elimination of acetic and nitrous acids. Indeed it was observed in a qualitative way that nitrous acid was eliminated more readily from these compounds than was acetic acid.

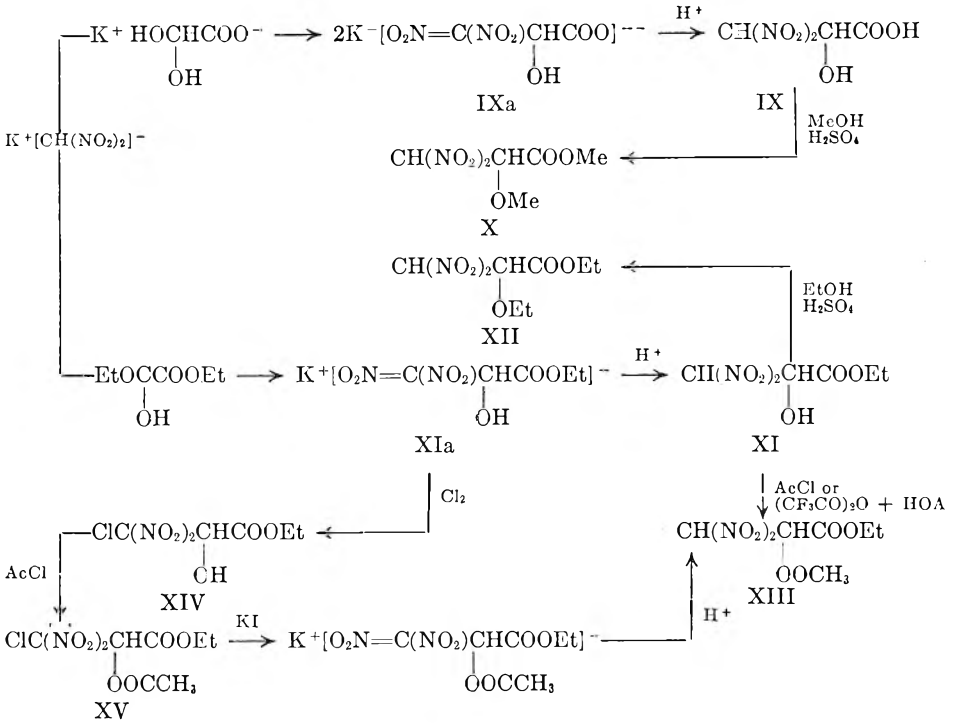
Ethyl α-acetoxy-β,β-dinitropropionate (XIII) was prepared directly by acetylation of the corresponding hydroxy ester XI and alternatively by the potassium iodide dehalogenation[7-9] of ethyl α-acetoxy-β-chloro-β,β-dinitropropionate (XV); the latter was obtained by acetylation of ethyl α-hydroxy-β-chloro-β,β-dinitropropionate (XIV) which in turn arose by chlorination of ethyl α-hydroxy-β,β-dinitropropionate potassium salt (XIa).

The potassium dinitromethane used in this work was prepared from 2,2-dinitropropanediol-1,3 by reaction with aqueous potassium hydroxide and treatment of the resulting potassium salt of 2,2-dinitroethanol with hot alkaline peroxide solution. It is of interest to note that use of strong aqueous alkali alone failed to convert the diol beyond the dinitroethanol stage.

EXPERIMENTAL[10]

α-Hydroxy-β,β-dinitrobutyric acid (I). A. *From glyoxylic acid.* A suspension of 20 g. (0.17 mole) of 1,1-dinitroethane in 50 ml. of water containing 2 drops of concentrated sulfuric acid and 0.15 mole of glyoxylic acid[11] was heated on a steam bath with stirring for 6 hr. On cooling to room temperature the solution remained homogeneous. The crude acid was isolated from the reaction mixture by five ether extractions. After drying, the ether and excess 1,1-dinitroethane were

(7) J. Meisenheimer, *Ber.*, **36**, 438 (1903).
(8) E. P. Kohler, *J. Am. Chem. Soc.*, **38**, 887 (1916).
(9) K. Klager, *Anal. Chem.*, **23**, 534 (1951).
(10) Microanalyses by M. J. Naranjo and C. A. Esquibel. All temperatures are uncorrected.
(11) The sirupy aqueous solution of glyoxylic acid, prepared by the method of O. Doebner, *Ann.*, **311**, 129 (1900), was assayed by titration with standard base prior to use.



removed under reduced pressure and the residue was crystallized from a mixture of 2-nitropropane and chloroform giving 11.5 g. (40%) of α-hydroxy-β,β-dinitrobutyric acid, m.p. 98–100°. An analytical sample, m.p. 101–102°, was obtained by recrystallization from chloroform.

Anal. Calcd. for $C_4H_6N_2O_7$: C, 24.75; H, 3.12; N, 14.43; neut. equiv. 97.05. Found: C, 24.92; H, 3.10; N, 13.97; neut. equiv. 94.

Weak to moderate absorption in the 2.9 to 3.2μ (OH) region, and strong absorption at 5.74μ (C=O) and 6.34μ (NO_2) were observed in the infrared in chloroform and acetonitrile solution.

B. *From glyoxal.* A suspension of 9 g. (0.075 mole) of 1,1-dinitroethane and 9 g. (0.05 mole) of 30% aqueous glyoxal in 15 ml. of water was warmed to 70–75° for 8 hr. The reaction mixture was extracted with ether, the ether solution dried with anhydrous magnesium sulfate, and the crude product isolated by evaporation of the ether. One recrystallization from a mixture of nitromethane and trichloroethylene gave 3.1 g. (32%) of α-hydroxy-β,β-dinitrobutyric acid (I), m.p. 98–100°.

Anal. Calcd. for $C_4H_6N_2O_7$: C, 24.75; H, 3.12; neut. equiv. 97.05. Found: C, 24.85; H, 3.09; neut. equiv. 94.7.

Methyl α-hydroxy-β,β-dinitrobutyrate (III). A solution of 17.7 g. (0.09 mole) of α-hydroxy-β,β-dinitrobutyric acid in 100 ml. of methanol containing 1.5 g. of concentrated sulfuric acid was heated under reflux for 7 hr. After removal of the excess methanol under reduced pressure, the residue was dissolved in chloroform, washed free of acid with water, and dried. Removal of the solvent and crystallization of the residue from an isopropyl ether–hexane mixture gave 15.4 g. (82%) of methyl α-hydroxy-β,β-dinitrobutyrate, m.p. 40–42°.

Anal. Calcd. for $C_5H_8N_2O_7$: C, 28.85; H, 3.87; N, 13.46. Found: C, 28.87; H, 3.50; N, 13.13.

Medium absorption at 2.87μ (OH), and strong absorptions at 5.70μ (C=O) and at 6.32μ (NO_2) were observed in the infrared in chloroform solution.

Ethyl α-hydroxy-β,β-dinitrobutyrate (II). Ethyl ethoxyhydroxyacetate[12] (5.2 g., 0.035 mole) and 4.5 g. (0.038 mole) of 1,1-dinitroethane suspended in 25 ml. of water containing 1 drop of concentrated sulfuric acid were stirred at 50° for 3 hr. After ether extraction and drying, removal of the solvent gave a yellow oil which was crystallized from a carbon tetrachloride-hexane mixture. Ethyl α-hydroxy-β,β-dinitrobutyrate, m.p. 35–37°, was obtained in 61% yield. An analytical sample, m.p. 44–45°, was obtained by another recrystallization from the same solvent mixture.

Anal. Calcd. for $C_6H_{10}N_2O_7$: C, 32.44; H, 4.54; N, 12.61. Found: C, 31.79; H, 4.64; N, 12.64.

Medium absorption at 2.84μ (OH), and strong absorptions at 5.70μ (C=O) and at 6.33μ (NO_2) were observed in the infrared in chloroform solution. The ester was distilled without decomposition at 90–92° (1 mm.).

α-Acetoxy-β,β-dinitrobutyric acid (IV). A suspension of 2 g. (0.01 mole) of α-hydroxy-β,β-dinitrobutyric acid in 5 ml. of chloroform containing 3 g. (0.04 mole) of acetyl chloride was heated under reflux for 2 hr., the solvent removed by distillation, and the residue crystallized from chloroform giving 2.03 g. (96%) of α-acetoxy-β,β-dinitrobutyric acid, m.p. 128–128.5°.

Anal. Calcd. for $C_6H_8N_2O_8$: C, 30.52; H, 3.41; N, 11.86; neut. equiv. 236. Found: C, 30.34; H, 3.55; N, 11.52; neut. equiv. 233.

Strong absorptions at 5.65μ and 5.68μ (C=O) and 6.30μ (NO_2) were observed in the infrared in chloroform solution. A broad band of moderate intensity was observed at 3.45 to 3.7μ (OH) in acetonitrile solution.

α-Trifluoroacetoxy-β,β-dinitrobutyric acid (VIII). A suspension of 2 g. (0.01 mole) of α-hydroxy-β,β-dinitrobutyric acid in 10 ml. of trifluoroacetic anhydride was heated under reflux for 1 hr. Removal of the solvent under reduced pressure at 50° gave a quantitative yield of α-trifluoroacetoxy-β,β-dinitrobutyric acid, m.p. 131–131.5°.

Anal. Calcd. for $C_6H_3F_3N_2O_8$: N, 9.66; neut. equiv. 96.7. Found: N, 9.93; neut. equiv. 97.

Attempts at crystallization from carbon tetrachloride or chloroform led to slow decomposition to the original hydroxy acid. Strong carbonyl absorptions at 5.50μ and 5.65μ, and nitro at 6.30μ, as well as three strong fluorine bands in the 8–9μ region, were observed in the infrared on freshly prepared samples.

Methyl α-aceloxy-β,β-dinitrobutyrate (VI). A solution of

(12) C. Weygand, *Organic Preparations*, Interscience Publishers, Inc., New York, 1945, page 455.

15.5 g. (0.062 mole) of methyl α-hydroxy-β,β-dinitrobutyrate and 100 ml. of acetyl chloride was heated under reflux for 6 hr. The excess acetyl chloride was removed by distillation and the residue fractionated giving methyl α-acetoxy-β,β-dinitrobutyrate, b.p. 89–91°/0.3 mm., n_D^{25} 1.4480, in 64% yield.

Anal. Calcd. for $C_7H_{10}N_2O_8$: C, 33.61; H, 4.03; N, 11.20. Found: C, 33.13; H, 3.93; N, 11.40.

Strong absorptions at 5.65μ (C=O), 6.31 and 7.62μ (NO_2) were observed in the infrared in chloroform solution.

Ethyl α-acetoxy-β,β-dinitrobutyrate (V). The ethyl ester, b.p. 106–107°/0.05 mm., n_D^{25} 1.4435, was prepared in 75% yield by the same procedure as described for the methyl ester VI.

Anal. Calcd. for $C_8H_{12}N_2O_8$: C, 36.37; H, 4.58; N, 10.60. Found: C, 36.47; H, 4.54; N, 10.24.

Reaction of α-hydroxy-β,β-dinitrobutyric acid (I) *with phosphorus tribromide.* To a solution of 0.95 g. (0.005 mole) of the hydroxy acid I in 5 ml. of toluene was added 1.4 g. of phosphorus tribromide with shaking and warming. After cooling the reaction mixture to room temperature a white crystalline product was collected by filtration and dried in a vacuum desiccator under reduced pressure giving 1.2 g., m.p. 169° (rapid dec.). The compound was free of bromine on fusion with sodium and contained 12.16% N and 10.83% P. It was not further characterized.

Reaction of ethyl α-hydroxy-β,β-dinitrobutyrate (II) *with hydrazine and ammonia.* Ethyl α-hydroxy-β,β-dinitrobutyrate (2.2 g., 0.01 mole) in 15 ml. of 95% ethanol was treated with 0.46 g. (0.01 mole) of hydrazine hydrate at 10°. A yellow salt crystallized in plates almost immediately. After about 1 hr. the suspension was filtered and dried giving 0.98 g. (69%) of 1,1-dinitroethane hydrazine salt (VII), m.p. 135–136° (dec.).

Anal. Calcd. for $C_2H_8N_4O_4$: C, 15.79; H, 5.30; N, 36.84. Found: C, 15.89; H, 5.32; N, 36.68.

An aqueous solution of this salt was acidified with hydrochloric acid and extracted with methylene chloride giving, after drying, a solution which had an infrared spectrum identical to that of a solution of 1,1-dinitroethane.

In a similar way dry ammonia cleaved the α-hydroxy ester in benzene solution to 1,1-dinitroethane ammonium salt, m.p. 117–119° (dec.), in 63% yield.

α-Hydroxy-β,β-dinitropropionic acid (IX). A solution equivalent to 5.3 g. (0.072 mole) of glyoxylic acid[11] in 10 ml. of water was neutralized to phenolphthalein with 20% potassium hydroxide solution. This was added dropwise during 15 min. to a stirred suspension of 10.5 g. (0.072 mole) of the potassium salt of dinitromethane in 40 ml. of water at room temperature. After all of the yellow crystalline potassium salt had disappeared (2 hr.) the solution was acidified with 20% sulfuric acid and extracted seven times with ether. The combined extracts were dried over magnesium sulfate. Removal of the solvent under reduced pressure yielded a crystalline residue which, upon recrystallization from a 2-nitropropane-chloroform mixture, yielded 8.7 g. of α-hydroxy-β,β-dinitropropionic acid (66%), m.p. 124–127° (dec.). Two more recrystallizations raised the melting point to 131.5–132° (dec.).

Anal. Calcd. for $C_3H_4N_2O_7$: C, 20.01; H, 2.24; N, 15.56; neut. equiv., 90. Found: C, 19.27, 19.35; H, 1.86, 2.03; N, 15.22, 15.27; neut. equiv., 90.

Weak to moderate absorption in the 2.9 to 3.2μ region (OH), and strong absorptions at 5.68μ (C=O), 6.33 and 7.53μ (NO_2) were observed in the infrared in acetonitrile solution.

Methyl α-methoxy-β,β-dinitropropionate (X). A solution of 5 g. (0.028 mole) of α-hydroxy-β,β-dinitropropionic acid in 50 ml. of methanol containing 5 drops of concentrated sulfuric acid was refluxed 16 hr. After removal of the excess methanol by distillation under reduced pressure, a chloroform solution of the residue was washed with water, dried, and the chloroform removed, giving a 55% yield of crude methyl α-methoxy-β,β-dinitropropionate. On crystallization from an isopropyl ether–hexane mixture an analytical sample, m.p. 60–61°, was obtained.

Anal. Calcd. for $C_5H_8N_2O_7$: C, 28.85; H, 3.87; N, 13.46. Found: C, 28.72; H, 3.94; N, 13.20.

Ethyl α-hydroxy-β,β-dinitropropionate (XI). Ethyl ethoxyhydroxyacetate[12] (5.92 g., 0.04 mole) was added dropwise to a stirred suspension of 5.76 g. (0.04 mole) of the potassium salt of dinitromethane in 20 ml. of water. After a few minutes the suspension was warmed on a steam bath until solution was complete, and then allowed to cool to room temperature with stirring. The potassium salt of ethyl α-hydroxy-β,β-dinitropropionate (8.85 g., 90%) was filtered from the ice-cold reaction mixture. After washing with methanol and one recrystallization from water, the salt melted with decomposition at 144°.

Anal. Calcd. for $C_5H_7KN_2O_7$: C, 24.39; H, 2.87; K, 15.38; N, 11.38. Found: C, 23.00; H, 2.97; K, 15.75; N, 11.36.

Ethyl α-hydroxy-β,β-dinitropropionate was freed from its potassium salt by acidification of 28.4 g. (0.12 mole) of the latter in 200 ml. of water with 20% sulfuric acid below 10° and extraction with ether. The combined ether extracts were dried over magnesium sulfate, treated with Norit, and the ether removed under reduced pressure giving 23.6 g. (94%) of ethyl α-hydroxy-β,β-dinitropropionate, n_D^{25} 1.4573.

Anal. Calcd. for $C_5H_8N_2O_7$: C, 28.85; H, 3.87; N, 13.46. Found: C, 29.46; H, 4.11; N, 13.39.

Moderate absorption at 2.87μ (OH), and strong absorption at 5.70μ (C=O) and 6.33μ (NO_2) were observed in chloroform solution in the infrared.

Ethyl α-ethoxy-β,β-dinitropropionate (XII). A suspension of 9.84 g. (0.04 mole) of the potassium salt of ethyl α-hydroxy-β,β-dinitropropionate in 100 ml. of ethanol was cooled to 5° while 2.8 g. (0.028 mole) of concentrated sulfuric acid was added with stirring. The mixture was refluxed for 7 hr. and then allowed to cool to room temperature. After removal of the potassium sulfate by filtration, the alcohol was distilled from the filtrate under reduced pressure. The residue was dissolved in 75 ml. of chloroform and treated with Norit and magnesium sulfate. After removal of the chloroform by distillation, the residue yielded 7.0 g. (74%) of product, b.p. 84–86.5°/0.3 mm. An analytical sample of ethyl α-ethoxy-β,β-dinitropropionate, b.p. 89–91.5°/0.7 mm., n_D^{25} 1.4397 was obtained by redistillation from phosphorus pentoxide.

Anal. Calcd. for $C_7H_{12}N_2O_7$: C, 35.60; H, 5.12; N, 11.86. Found: C, 35.46; H, 5.09; N, 11.46.

Strong absorptions at 5.72μ (C=O) and 6.32μ (NO_2) were observed in the infrared in chloroform solution; no absorption in the OH stretching region was observed.

Ethyl α-acetoxy-β,β-dinitropropionate (XIII). A. *By acetylation of ethyl α-hydroxy-β,β-dinitropropionate* (XI). To a solution of 5.1 g. (0.024 mole) of ethyl α-hydroxy-β,β-dinitropropionate in 1.7 g. (0.028 mole) of acetic acid cooled in an ice bath was added 15 ml. of trifluoroacetic anhydride.[13] The solution was allowed to warm to room temperature with stirring during 1 hr. After removal of the volatile components by distillation under reduced pressure the residue crystallized giving, after recrystallization from a benzene-hexane mixture, 5.3 g. (89%) of ethyl α-acetoxy-β,β-dinitropropionate, m.p. 54–54.5°. Strong absorptions at 5.65 and 5.72μ (C=O) and 6.32μ (NO_2) were observed in the infrared in chloroform solution.

Anal. Calcd. for $C_7H_{10}N_2O_8$: C, 33.61; H, 4.03; N, 11.20. Found: C, 34.55; H, 4.22; N, 11.38.

Acetylation with acetyl chloride gave the same compound in lower yields.

B. *From ethyl α-acetoxy-β-chloro-β,β-dinitropropionate* (XV). A solution of 1.4 g. (0.005 mole) of ethyl α-acetoxy-β-chloro-β,β-dinitropropionate in 3 ml. of methanol was treated with 1.7 g. (0.01 mole) of potassium iodide in 6 ml. of 50% methanol at 0 to 5°. After about 10 min. 1.0 g.

(13) E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Chem. Soc.*, 2976 (1949).

(70%) of the potassium salt of ethyl α-acetoxy-β,β-dinitropropionate precipitated. The crude salt was suspended in water, acidified with 20% sulfuric acid, chilled, and the solid removed by filtration. Extraction of the solid with benzene, evaporation of the benzene, and recrystallization of the residue from hexane yielded ethyl α-acetoxy-β,β-dinitropropionate, m.p. 54–55°.

Anal. Calcd. for $C_7H_{10}N_2O_8$: C, 33.61; H, 4.03; N, 11.20. Found: C, 32.98; H, 3.87; N, 11.16.

A sample of the purified potassium salt melted at 122° with decomposition.

Anal. Calcd. for $C_7H_9KN_2O_8$: K, 13.56. Found: K, 13.58.

Ethyl α-acetoxy-β-chloro-β,β-dinitropropionate (XV). A solution of crude ethyl α-hydroxy-β-chloro-β,β-dinitropropionate (XIV) in excess acetyl chloride was heated under reflux for 4 hr. After removal of the excess acetyl chloride, the residue was fractionated giving ethyl α-acetoxy-β-chloro-β,β-dinitropropionate, b.p. 67–69°/0.01 mm., n_D^{25} 1.4484 in about 30% yield.

Anal. Calcd. for $C_7H_9ClN_2O_8$: C, 29.54; H, 3.19; N, 9.84. Found: C, 29.78; H, 3.29; N, 9.53.

Strong absorptions at 5.64, 5.71μ (C=O) and 6.22μ (NO_2) were observed in the infrared in chloroform solution.

Ethyl α-hydroxy-β-chloro-β,β-dinitropropionate (XIV). A suspension of 12.3 g. (0.05 mole) of the potassium salt of ethyl α-hydroxy-β,β-dinitropropionate in 50 ml. of methylene chloride was cooled in an ice bath while 5 g. (0.07 mole) of chlorine in 50 ml. of cold methylene chloride was added with stirring. After 15 min. the yellow salt had been replaced by potassium chloride which was removed by filtration. Crude ethyl α-hydroxy-β-chloro-β,β-dinitropropionate suitable for conversion to the α-acetoxy ester XV was obtained in 94% yield by removing the solvent under reduced pressure. An analytical sample, b.p. 70°/0.2 mm., n_D^{25} 1.4419, was obtained by fractional distillation under reduced pressure. Weak to moderate absorption at 2.80μ (OH), and strong absorption at 5.71μ (C=O) and 6.30μ (NO_2) were observed in the infrared in chloroform solution.

Anal. Calcd. for $C_5H_7ClN_2O_7$: C, 24.75; H, 2.91; N, 11.55. Found: C, 24.90; H, 3.04; N, 11.80.

Potassium dinitromethane. An aqueous solution of 2,2-dinitropropanediol-1,3 was treated with excess cold 35% potassium hydroxide solution and, after chilling, the resulting potassium salt of 2,2-dinitroethanol was filtered and air dried. This salt (15.1 g., 0.087 mole) was suspended in 80 ml. of water containing 6.6 g. (0.1 mole) of 85% potassium hydroxide. During a 5-min. period, 20 g. (0.18 mole) of 30% hydrogen peroxide was added with stirring. The temperature of the reaction mixture rose to 45° during the addition. After warming on a steam bath for 40 min., a second portion of hydrogen peroxide equal to the first was added during 15 min. and heating was continued for another 15 min. The reaction mixture was allowed to cool to room temperature, chilled, and the potassium salt filtered, washed with methanol, and air dried (11.3 g., 90%).

Anal. Calcd. for $CHKN_2O_4$: K, 27.13. Found: K, 26.91.

As a safety precaution, all potassium salts were stored *only* for short periods of time and were handled while moist with water or alcohol.

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[CONTRIBUTION FROM THE LOS ALAMOS SCIENTIFIC LABORATORY]

Derivatives of Nitromethylamines. I. Nitromethyl Isocyanates

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Nitromethyl isocyanate, α-nitroethyl isocyanate, and α-nitroisopropyl isocyanate have been prepared by thermal rearrangement of the corresponding acid azides. The compounds are unstable and only α-nitroethyl isocyanate could be distilled. Infrared absorption spectra and other properties of these isocyanates are described.

While nitromethylamine is apparently unknown, two types of related compounds have been described. The nitromethylurethan I was believed to be obtained when the azide of nitrocyanoacetic acid (II) was refluxed with ethanol. The urethan I has not been isolated and its structure is based on the products of hydrolysis of crude material which

$$CH(NO_2)(CN)NHCOOEt$$
I

$$CH(NO_2)(CN)CON_3$$
II

include one mole of carbon dioxide, one mole of hydrogen cyanide, ethanol, and ammonium chloride.[1] The stable crystalline compounds IIIa have been prepared by coupling aryl diazonium salts with active methylene compounds and IIIb result from the analogous coupling reaction with secondary nitroparaffins or their methylol derivatives.[2,2a] COOMe, CN, $CONH_2$, SO_2Ar, SOAr, NO_2. R = H or alkyl.

$$ArNHN{=}C(NO_2)X$$
IIIa

X = H, COOMe, CN, $CONH_2$, SO_2Ar, SOAr, NO_2

$$ArN{=}NC(NO_2)R_2$$
IIIb

R = H or alkyl

(1) A. Darapsky and D. Hillers, *J. prakt. Chem.*, 92, 305 (1925).

(2) S. Hünig and O. Boes, *Ann.*, 579, 28 (1953); E. Bamberger, O. Schmidt, and H. Levenstein, *Ber.*, 33, 2059 (1900); H. E. Baumgarten and M. R. DeBrunner, *J. Am. Chem. Soc.*, 76, 3489 (1954); C. F. Feasly and E. F. Degering, *J. Org. Chem.*, 8, 13 (1943); Z. Eckstein and T. Urbanski, *Bull. acad. polon. Sci., Classe III*, 3, 433 (1955).

(2a) Other analogs of nitromethylamine which are reported in the literature, probably owe their stability to special structural features, as for instance, the α-nitropyrroles [H. Fischer and W. Zerweck, *Ber.*, 55, 1949 (1922)] and the 3-nitrocinnolines [H. E. Baumgarten and M. R. DeBrunner, *J. Am. Chem. Soc.*, 76, 3490 (1954)].

In the present investigation the Curtius reaction of nitro-substituted acid azides has been studied in some detail for the preparation of other derivatives of nitromethylamine.

$$CRR'(NO_2)CON_3 \longrightarrow CRR'(NO_2)N{=}C{=}O$$

R, R′ = H or alkyl

The required hydrazides can be prepared from α-nitro esters by the action of hydrazine. Thus methyl nitroacetate gives a solvated hydrazine salt of nitroacethydrazide (IV, R = H) with hydrazine hydrate in methanol. The intermediate hydrazine salt of the methyl ester cannot be isolated but the corresponding salt of the ethyl ester is formed in good yield from molar equivalents of ester and hydrazine hydrate in ethanol. It is converted to IV (R = H) by reaction with aqueous hydrazine hydrate at 25°. When this salt (IV, R = H) is treated with dry hydrogen chloride in ethanol, it is converted to the hydrazide hydrochloride (V, R = H) in 58% yield.

$$\underset{\text{IV}}{H_2N\overset{+}{N}H_3NO_2\overset{-}{C}RCONHNH_2} + HCl \longrightarrow \underset{\text{V}}{NO_2CHRCONH\overset{+}{N}H_3\ Cl^-}$$

R = H or Me

Ethyl α-nitropropionate yields a crystalline hydrazine salt which is converted to the salt of the hydrazide (IV, R = Me) by heating with excess hydrazine hydrate. Cold aqueous hydrochloric acid converts the salt to a product devoid of nitro groups as evidenced by its infrared spectrum. The hydrochloride V (R = Me) is obtained by using dry hydrogen chloride. Ethyl α-nitroisobutyrate is converted to the hydrazide by reaction with an equimolar amount of hydrazine hydrate at 5°, while heating with an excess of hydrazine hydrate causes the nitro group to be eliminated.

The nitroacid hydrazides (or their hydrochlorides) are completely converted to acid azides by nitrous acid at 0°. The solutions of the acid azides in chloroform or carbon tetrachloride show characteristic bands for N_3, C=O, and NO_2 in the infrared (Table I). After refluxing of the solutions, the first two bands disappear and a new intense band (N=C=O) occurs in the 4.4-μ region. Some slight decomposition occurs during the rearrangement of all the nitroacid azides. Nitromethyl and α-nitroethyl isocyanate have been obtained free from solvent and the latter has been distilled under reduced pressure. The rearrangement product of α-nitroisobutyrazide, on the other hand, is formed only at the higher temperatures of boiling carbon tetrachloride and decomposes when the solvent is removed.

All three nitromethyl isocyanates are extraordinarily reactive toward water and alcohols, and polymerize to unstable solids even below room temperature and, in part, during their formation. A chloroform solution of α-nitroethyl isocyanate (VI) reacts exothermically with methanol. The oil, obtained after removing the solvents, has an infrared spectrum corresponding to VII.

TABLE I

CHARACTERISTIC INFRARED ABSORPTION BANDS FOR AZIDES AND ISOCYANATES IN CHLOROFORM

	N_3	C=O	N=C=O	NO_2 as	NO_2 sym
$NO_2CH_2CON_3$	4.64	5.78	—	6.36	7.25
$NO_2CHMeCON_3$	4.64	5.78	—	6.36	7.36
$NO_2CMe_2CON_3$	4.66	5.81	—	6.44	7.47
$NO_2CH_2N{=}C{=}O$	—	—	4.41	6.33	7.30
$NO_2CHMeN{=}C{=}O$	—	—	4.42	6.36	7.37
$NO_2CMe_2N{=}C{=}O$	—	—	4.44	6.45	7.45

$$CH_3CH(NO_2)N{=}C{=}O$$
VI

$$CH_3CH{=}NCOOMe$$
VII

Its structure is established by hydrolysis with cold water, which gives an excellent yield of acetaldehyde (based on acetaldimethone). By analogy, the alcoholysis product of nitrocyanoacetazide is probably also an imine (CNCH=NCOOEt) rather than the urethan I.[1] The reported hydrolysis products[1] allow for either structure. The loss of nitrous acid seems to be characteristic for nitromethylamines with a hydrogen on the nitrogen.

EXPERIMENTAL[3]

Hydrazine salt of ethyl nitroacetate. Hydrazine hydrate (1.64 g., 0.032 mole) was added to a solution of ethyl nitroacetate (4.36 g., 0.032 mole) in 20 ml. of 95% ethanol. The warm solution was cooled immediately and kept at 5° for 15 hr. The crystalline precipitate was filtered, washed with benzene and petroleum ether, and dried at 60°; total yield (2 crops) 4.41 g. (81%). Recrystallization from 95% ethanol and then from methanol gave pale yellow plates, m.p. 104–105° (dec.).

Anal. Calcd. for $C_4H_{11}N_3O_4$: C, 29.09; H, 6.71; N, 25.45. Found: C, 28.95; H, 6.90; N, 25.60.

Hydrazine salt of nitroacethydrazide. The hydrazine salt of ethyl nitroacetate (1.65 g., 0.01 mole) was dissolved in 10 ml. of cold water. To this solution was added hydrazine hydrate (0.5 g., 0.01 mole) and the mixture was allowed to stand at 25° for 3.5 hr. The aqueous solution was evaporated at 25° (50 mm.) giving 1.5 g. of a yellow solid which was crystallized from 95% ethanol. The first crop (0.76 g.) was recrystallized from the same solvent; yield 0.73 g., m.p. 115–116° (dec.). The second crop of slightly less pure crystals melted at 113–114° (dec.). The over-all yield was 1.04 g. (60%). After several recrystallizations from 95% ethanol the salt melted at 117–118° (dec.).

Anal. Calcd. for $C_2H_9N_5O_3 \cdot {}^1/_2C_2H_5OH$: C, 20.69; H, 7.59; N, 40.23. Found: C, 19.78; H, 5.91; N, 40.93.

A solvate[4] with nearly identical infrared spectrum was obtained by adding hydrazine hydrate (2.0 g., 0.04 mole) with shaking to a solution of methyl nitroacetate (4.76 g., 0.04 mole, n_D^{25} 1.4238) in 25 ml. of methanol. The solution

(3) All temperatures uncorrected. Analyses by M. Naranjo and C. Esquibel.

(4) The composition of these solvates varied on crystallization. Analyses are reported for representative solvates which do not necessarily correspond to definite compounds.

was cooled to 5° and the colorless salt was filtered with suction, yield 5.73 g., m.p. 131–132° (dec.). Recrystallization from methanol gave colorless needles, m.p. 125° (dec.), yield 2.76 g. (70%).

Anal. Calcd. for $C_2H_9N_6O_3 \cdot 1^1/_2CH_3OH$: C, 21.09; H, 7.59; N, 35.17. Found: C, 21.25; H, 7.05; N, 35.99.

On recrystallization from 95% ethanol, the methanol solvate (m.p. 125°, dec.) was converted to the ethanol solvate, m.p. 117–118° (dec.).

Nitroacethydrazide hydrochloride. The hydrazine salt of nitroacethydrazide (1.51 g., 0.0087 mole, ethanol solvate, m.p. 117–118°), suspended in 25 ml. of 95% ethanol, was treated with a slow stream of hydrogen chloride while cooled in an ice bath. The colorless precipitate weighed 2.0 g. and the ethanol filtrate furnished an additional 0.2 g. The combined solids were digested with hot acetonitrile from which the sparingly soluble hydrochloride crystallized on cooling in colorless needles. Repeated digestions gave a total of 0.90 g. (66%) of hydrochloride, m.p. 124° (dec.), λ(C=O) 5.85 μ, λ(NO_2) 6.39, 7.26 μ.

Anal. Calcd. for $C_2H_6ClN_3O_3$: C, 15.45; H, 3.89; Cl, 22.79. Found: C, 15.24; H, 3.39; Cl, 24.36.

Nitromethyl isocyanate. A solution of 0.345 g. (0.005 mole) of sodium nitrite in 7.5 ml. of water was added dropwise with stirring to a mixture of 5 ml. of alcohol-free chloroform and a solution of 0.775 g. (0.005 mole) of nitroacethydrazide hydrochloride and 0.5 ml. of concentrated hydrochloric acid in 12.5 ml. of water at 0°. After completed addition the mixture was stirred at 0° for 0.5 hr. The chloroform layer was separated, the aqueous layer was extracted with 5 ml. of alcohol-free chloroform, and the combined extracts were dried over sodium sulfate.

The dry chloroform solution of nitroacetazide with infrared characteristics given in Table I was refluxed from a steam bath for 5 hr. The solution was filtered from 0.015 g. of unidentified tan solid. The isocyanate remained as pale yellow oil (0.08 g.) when the solvent was removed under reduced pressure.

Anal. Calcd. for $C_2H_2N_2O_3$: N, 27.46. Found: N, 27.52.

It started to decompose at room temperature within 10 min., forming a tan solid which also decomposed at room temperature.

The remaining oil (0.060 g.) was quickly dissolved in carbon tetrachloride and allowed to stand at room temperature. Infrared spectra, taken at intervals during 28 hr., showed that the isocyanate band at 4.41 μ disappeared and a new one appeared at 4.30 μ, while the nitro band was greatly diminished in intensity.

Hydrazine salt of ethyl α-nitropropionate. A colorless precipitate formed immediately when 0.5 g. (0.01 mole) of 65% hydrazine hydrate was added to 1.5 g. (0.01 mole) of ethyl α-nitropropionate (b.p. 75°/6 mm., n_D^{25} 1.4190) in 5 ml. of 95% ethanol. The mixture was brought to boiling, diluted with sufficient ethanol (5 ml.) to bring the salt into solution, and allowed to cool. The colorless salt which crystallized weighed 1.2 g. (75%). On recrystallization from 20 ml. of 95% ethanol, it was obtained in colorless needles, m.p. 131–133° (dec.), (lit. m.p. 120°),[5] yield 0.6 g. (33%).

Anal. Calcd. for $C_5H_{13}N_3O_4$: C, 33.52; H, 7.31; N, 23.46. Found: C, 33.21; H, 7.19; N, 23.87.

The salt burned slowly in a flame and was insensitive to impact.

Hydrazine salt of α-nitropropionhydrazide. The hydrazine salt of ethyl α-nitropropionate (4.0 g., 0.022 mole) was heated on a steam bath with 1.5 g. (0.03 mole) of hydrazine hydrate for 20 min. The clear yellow liquid solidified on cooling. It was stirred with 95% ethanol, filtered, and washed with ethanol. The dry salt weighed 3.5 g. (95%). After recrystallization from ethanol it melted at 139–140°.

Anal. Calcd. for $C_3H_{11}N_5O_3$: C, 21.82; H, 6.70; N, 42.40. Found: C, 21.77; H, 6.53; N, 41.42.

(5) A. K. Macbeth and D. Traill, *J. Chem. Soc.*, 897 (1925).

An over-all yield of 85% was obtained from ethyl α-nitropropionate when its crude moist hydrazine salt was heated with a slight excess of hydrazine hydrate. The compound melted and burned in a flame and was not sensitive to impact.

α-Nitropropionhydrazide hydrochloride. Dry hydrogen chloride reacted with a suspension of 12.8 g. (0.077 mole) of the above hydrazine salt in 75 ml. of methanol at 0° to give a colorless precipitate of hydrazine dihydrochloride, which was filtered with suction. The filtrate was heated on a steam bath under reduced pressure to remove the solvent. The glassy residue was dissolved in 100 ml. of boiling acetonitrile, the solution was filtered from a trace of hydrochloride, and allowed to cool. The crystalline hydrazide hydrochloride was filtered with suction; yield 8.0 g. (61%), m.p. 120–121° (dec.). A second crop of slightly less pure material weighed 4.0 g. (30%).

Anal. Calcd. for $C_3H_8ClN_3O_3$: C, 21.25; H, 4.75; Cl, 20.91; N, 24.78. Found: C, 21.49; H, 4.88; Cl, 20.83; N, 24.88.

α-Nitroethyl isocyanate. α-Nitropropionhydrazide hydrochloride (1.69 g., 0.01 mole) was converted to the azide as described for the lower homolog. The chloroform layer was separated and the aqueous layer was extracted with 5 ml. of chloroform. The combined chloroform solutions of α-nitropropionazide (15 ml.) were dried over sodium sulfate, filtered, and refluxed for 3 hr.

A part of the chloroform solution (5 ml.) was diluted with 5 ml. of methanol. The mixture warmed exothermically and then was refluxed from a steam bath for 30 min. The solvents were removed under reduced pressure leaving a yellow oil, λ(C—O) 8.1–8.25 μ, λ(C=O) 5.80, λ(C=N) 5.92, λ(CON=) 6.60 μ. The oil, mixed with 5 ml. of water, was allowed to stand at 25° for 12 hr. The aqueous solution was filtered from traces of insoluble material, treated with a solution of 1.4 g. of dimethyldihydroresorcinol in 5 ml. of acetic acid and 50 ml. of water, and allowed to stand for 3 hr. The precipitated acetaldehyde dimethone was filtered and dried to constant weight at 60°; yield 1.01 g. (91%), m.p. 140–141° (lit. value 140.2°).[6] It was converted to the anhydride, m.p. 176–177° (lit. value 175°),[6] by refluxing with acetic anhydride.

The remaining chloroform solution of the isocyanate (10 ml.) was distilled at 40 mm. to remove the solvent. The products from a number of runs, obtained in the same way, were distilled at pressures between 1 and 32 mm. The distillate, b.p. 69° (32 mm.), n_D^{25} 1.4317, was obtained in yields of 45% as a colorless oil accompanied by a yellow amorphous solid and nitrogen oxides. It reacted vigorously with water, ethanol, and methanol, and was unstable even when refrigerated in the dark. Under these conditions, as well as on heating or exposure to light and air, it was converted to a yellow solid which decomposed between 25 and 90° with evolution of gas on slow heating. On one occasion it decomposed explosively at room temperature. In view of this instability of the compound it was not possible to obtain good analytical data. It was established, however, that the yellow solid still had the approximate composition of the isocyanate. It was insoluble in chloroform, benzene, and ether, unlike the isocyanate, initially dissolved in acetonitrile but precipitated on standing. Its infrared spectrum was devoid of nitro absorption.

Ethyl α-nitroisobutyrate. The reaction of ethyl α-bromoisobutyrate (58.5 g., 0.3 mole) with sodium nitrite (41.4 g., 0.6 mole) and urea (40 g.) in dimethylformamide (500 ml.) at room temperature[7] gave 32.8 g. (68%) of ethyl α-nitro-

(6) D. Vorlander, *Z. anal. Chem.*, **77**, 321 (1929); *Ann.*, **309**, 370 (1899); W. Stepp and R. Feulgen, *Z. physiol. Chem.*, **114**, 301 (1921).

(7) N. Kornblum, H. O. Larsen, D. D. Mooberry, R. K. Blackwood, E. R. Oliveto, and C. E. Graham, *Chemistry & Industry*, 443 (1955); N. Kornblum and J. H. Eicher, *J. Am. Chem. Soc.*, **78**, 1496 (1956).

isobutyrate, b.p. 87° (16 mm.), n_D^{25} 1.4179, λ(C=O) 5.71 μ, λ(NO_2) 6.46, 7.43 μ.

α-Nitroisobutyrhydrazide. Hydrazine (64% in water, 5.0 g., 0.1 mole) was added to a solution of ethyl α-nitroisobutyrate (16.1 g., 0.1 mole) in 20 ml. of methanol. The mixture was allowed to stand at 5° for 168 hr. The pale yellow solution was then evaporated to dryness at 50 mm. and below room temperature. The hydrazide separated in crystalline form. This crude material (15.5 g.) was crystallized from benzene from which it was obtained in colorless plates, m.p. 96.5–97.5°, yield 7.5 g. (51%), λ(NH) 3.00 μ, λ(C=O) 5.90 μ, λ(NO_2) 6.42, 7.41 μ. The melting point was unchanged after vacuum sublimation at 0.1 mm.

Anal. Calcd. for $C_4H_9N_3O_3$: C, 32.65; H, 6.16; N, 28.57. Found: C, 32.36; H, 6.63; N, 28.44.

α-Nitroisopropyl isocyanate. A solution of 0.69 g. (0.01 mole) of sodium nitrite in 15 ml. of water was added slowly with stirring to a mixture of 1.47 g. (0.01 mole) of sublimed α-nitroisobutyrhydrazide in 25 ml. of water, 2 ml. of concentrated hydrochloric acid, and 10 ml. of chloroform contained in an ice bath. The mixture was stirred for 0.5 hr., the organic layer was separated, and the aqueous layer was extracted with 5 ml. of chloroform. The combined extracts were dried over sodium sulfate and filtered.

When a 10% solution of α-nitroisobutyrazide in chloroform was refluxed,[8] it turned yellow, a yellow solid precipitated, and NO_2 was evolved, but even after 21 hr. of refluxing there was considerable azide left in the mixture. The precipitated solid weighed 0.25 g. after refluxing for 10 hr. and 0.35 g. at the end of 21 hr. of boiling. It did not contain a band in the nitro region but had strong bands for NH (3.10) and C=O (5.80 μ) absorption.

Anal. Calcd. for $C_4H_6N_2O_3$: C, 36.92; H, 4.65; N, 21.53. Found: C, 36.96; H, 5.28; N, 21.50.

A fresh batch of α-nitroisobutyrazide (0.005 mole) in 15 ml. of chloroform was unchanged after refluxing for 3 hr. with 5 ml. of methanol.

α-Nitroisobutyrazide (0.01 mole) was successfully rearranged by refluxing in 30 ml. of carbon tetrachloride (b.p. 68°/580 mm.) protected from light and moisture. The solution turned pink after 30 min. The azide band had largely disappeared after 4 hr. and was completely absent after 12.5 hr. Some NO_2 was evolved during the process and the polymer which was filtered at the end of the heating period weighed 0.16 g. The yellow filtrate was concentrated at 50 mm. and below room temperature. On warming the residual liquid at 1 mm. it polymerized with evolution of gas to a glassy solid which was characterized by very weak absorption in the NO_2 stretching region (6.37 μ).

Infrared absorption spectra were determined with a Perkin-Elmer Model 21 spectrophotometer, liquids as capillary films, solutions in matched cells of 0.1-mm. thickness, and solids as potassium bromide disks in 0.5% concentration, 0.5 mm. thick.

LOS ALAMOS, N. M.

(8) The boiling point of chloroform at this altitude is 53° (580 mm.).

[CONTRIBUTION FROM RESEARCH LABORATORY OF THE AEROJET-GENERAL CORP.]

Preparation and Characterization of 2,2-Dinitroethanol[1]

MARVIN H. GOLD, EDWARD E. HAMEL, AND KARL KLAGER

Received April 1, 1957

A new synthesis is described for the preparation of potassium *aci*-2,2-dinitroethanol. At elevated temperatures in the presence of cyclopentadiene, 2,2-dinitroethanol is apparently dehydrated and yields the Diels-Alder addition product expected from the reaction of 1,1-dinitroethylene with cyclopentadiene. Potassium *aci*-2,2-dinitroethanol, upon condensation with formaldehyde in acid medium, yields 2,2-dinitro-1,3-propanediol. This compound, upon further condensation with formaldehyde, forms the cyclic product, 5,5-dinitro-1,3-dioxan.

The first reported synthesis of 2,2-dinitroethanol was made by Duden and Pondorff[2] who prepared it by acidification of the potassium salt with sulfuric acid. Because of the interest of these laboratories in compounds containing multiple nitro groups a reinvestigation of this work was made. In doing so several improvements were made in the synthetic methods. In Duden and Pondorff's original synthesis[2] the potassium *aci*-2,2-dinitroethanol was made by the condensation of formaldehyde with potassium *aci* dinitromethane. This latter compound was normally produced by a laborious nitration of tribromoaniline[3] in very poor yield. In this laboratory a new synthesis of 2,2-dinitroethanol was developed which is an adaptation of the method of ter Meer[4] for the synthesis of 1,1-dinitroethane. This involves the replacement of bromine in 2-bromo-2-nitroethanol by a nitro group, using a mixture of potassium nitrite and potassium hydroxide.

The 2-bromo-2-nitroethanol was most conveniently prepared by bromination of sodium *aci*-2-nitroethanol. The mode of addition of the reagents is very important because the alpha hydrogen is more acidic in the bromonitroethanol than in nitroethanol. Therefore, when bromine is added to the sodium enolate, an equilibrium mixture results:

$$Br_2 + NaO_2N = CH_2CH_2OH \longrightarrow NO_2CHBrCH_2OH + NaBr$$

$$NO_2CHBrCH_2OH + NaO_2N = CHCH_2OH \longrightarrow NaO_2N = CBrCH_2OH + NO_2CH_2CH_2OH$$

The sodium *aci*-2-bromo-2-nitroethanol then competes with the sodium *aci*-2-nitroethanol for additional bromine and consequently produces an appreciable quantity of dibromonitroethanol. In order to avoid the secondary reaction, it is necessary to

(1) This work was performed under contract with the Office of Naval Research.

(2) P. Duden and G. Pondorff, *Ber.*, **38**, 2031 (1905).

(3) M. A. Villiers, *Bull. soc. chim. France*, [2] **41**, 281 (1884); **43**, 322 (1885); P. Duden, *Ber.*, **26**, 3003 (1893); R. A. Gotts and L. Hunter, *J. Chem. Soc.*, **125**, 442 (1924).

(4) E. ter Meer, *Ann.* **181**, 4 (1876).

add a slurry of sodium *aci*-2-nitroethanol to an excess of bromine. This procedure gives 2-bromo-2-nitroethanol in good yield and with a small amount of side reaction products. Previously, 2-bromo-2-nitroethanol was prepared by the condensation of formaldehyde with bromonitromethane[5] and by the deformylation of 2-bromo-2-nitro-1,3-propanediol.[6]

Although 2,2-dinitroethanol has been reported as an unstable liquid,[2] it was found in this laboratory to be far more stable than was previously believed. The dinitroethanol is liberated from the salt by strong acids, such as sulfuric or hydrochloric acids. It can be distilled from high boiling carrier solvents, such as the higher phthalates or sebacates, in a cyclic molecular still. This distillate upon low-temperature crystallization from ethyl chloride gives white crystals, m.p. 2–3°. The liquid alcohol may be stored for several weeks at −20°.

2,2-Dinitroethanol is apparently easily dehydrated at elevated temperatures. However, all attempts to isolate free 1,1-dinitroethylene were fruitless. Evidence of its intermediate formation was obtained by heating a mixture of cyclopentadiene with 2,2-dinitroethanol in chlorobenzene. At 100–110° the reaction proceeded rapidly to give 6,6-dinitrobicyclo[2.2.1]-2-heptene, the product expected from the Diels-Alder reaction of 1,1-dinitroethylene with cyclopentadiene. Thus it appears likely that the reaction followed the course:

$$HOCH_2CH(NO_2)_2 \longrightarrow CH_2C(NO_2)_2 + H_2O$$

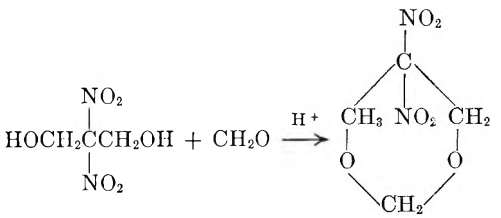
$$CH_2{=}C(NO_2)_2 + \begin{matrix} CH{=}CH \\ | \\ CH{=}CH \end{matrix}\!\!>CH_2 \longrightarrow \text{(NO}_2\text{)}_2\text{-bicyclo[2.2.1]-2-heptene, CH}_2\text{ bridge}$$

Potassium *aci*-2,2-dinitroethanol will react with aqueous formaldehyde in the presence of acetic acid to produce 2,2-dinitro-1,3-propanediol:[7]

$$KO_2N{=}\overset{NO_2}{\overset{|}{C}}CH_2OH + CH_2O \underset{OH^-}{\overset{H^+}{\rightleftharpoons}} HOCH_2\overset{NO_2}{\overset{|}{C}}CH_2OH + K^+$$

As indicated by the above equilibrium, the salt of 2,2-dinitroethanol can be regenerated in good yield from the dinitropropanediol by heating the diol with an aqueous-alcoholic solution of potassium hydroxide. This is similar to the equilibrium between potassium *aci*-dinitromethane and potassium *aci*-2,2-dinitroethanol described by Duden and Pondorff.[2]

The hydroxy groups of 2,2-dinitro-1,3-propanediol are difficult to replace in substitution reactions due to their proximity to the nitro groups.[8] However, the glycol does undergo some of the reactions attributed to the hydroxyl group. With formaldehyde in equimolecular quantities, it forms the corresponding 1,3-dioxan:



and the Schotten-Bauman reaction with benzoyl chloride produces the dibenzoate.

EXPERIMENTAL

2-Bromo-2-nitroethanol. 2-Nitroethanol[6] (637 g.) and 1500 ml. of methanol were placed in a 5-liter, three-necked flask fitted with a thermometer, stirrer, dropping funnel, and a bottom drain. The solution was cooled to −10° and a solution of 290 g. of U.S.P. sodium hydroxide in 2100 ml. of methanol was added slowly with stirring, maintaining the temperature between −10 and 0°.

In another 5-liter, three-necked flask placed below the first reaction flask and fitted with stirrer, dropping funnel, thermometer, and connection to the bottom drain of the upper flask, was placed 300 ml. of methanol. The methanol was cooled to −10°, and while being stirred, 350 ml. of bromine and the slurry of sodium *aci*-2-nitroethanol were added simultaneously. An excess of bromine was maintained at all times and the temperature was maintained below 0°. After the addition, the reaction mixture was allowed to warm to room temperature, then filtered to remove sodium bromide. The sodium bromide was washed with 200 ml. of methanol, and the combined filtrates concentrated under reduced pressure. The resulting concentrate was treated with 1 liter of ether, the precipitated salt washed with 200 ml. of ether, and the combined filtrates again concentrated under reduced pressure. The residue was vacuum distilled and the fraction boiling at 83°/2 mm. collected. The yields averaged 1083 g. (91%) based on 2-nitroethanol with a purity of 87–95%. The product thus obtained was found to be satisfactory for use in the next step of the synthesis.

Potassium aci-2,2-dinitroethanol. A solution of 1020 g. of 2-bromo-2-nitroethanol and 1500 ml. of methanol was maintained at 0° by means of a Dry Ice–acetone bath and with stirring, a solution of 620 g. of 96% potassium nitrite in 900 ml. of water was added in a fine stream. When the addition was complete, a solution of 492 g. of 85% potassium hydroxide was added, also in a fine stream. The temperature was maintained at 0° until crystallization began, then it was allowed to rise slowly to 7–10°. When this addition was complete, the solution was again cooled to 0° and filtered. The yellow salt was washed with 100 ml. of methanol and then suspended in 900 ml. of water and stirred at 25° for 15 min. to remove inorganic material. The purified salt was again filtered, washed twice with 100-ml. portions of methanol, and partially dried by means of an aspirator. The yield of moist salt (77–87% solids) from several preparations weighed 423–450 g. It was stored at −20° in brown bottles without further drying.

This salt was easily converted into the corresponding bromo-derivative, *2-bromo-2,2-dinitroethanol*, by dropping bromine into a cooled suspension of the salt in ether. It is a solid when dry, m.p. 63–65°, and is extremely hygroscopic,

(5) M. J. Maas, *Chem. Zentr.*, 1899 I, 179; *Rec. trav. chim.*, **17**, 386 (1898).

(6) R. Wilkendorf and M. Trenel, *Ber.*, **56B** 611 (1923).

(7) H. Feuer, G. B. Bachman, and J. P. Kispesrky, *J. Am. Chem. Soc.*, **73**, 1360 (1951).

(8) To be reported in subsequent publications.

liquefying when exposed to the atmosphere. It can be distilled, having a boiling point of 85–90° at 2 mm.

Anal. Calcd. for $C_2H_3BrN_2O_5$: Br, 37.23. Found: Br, 36.85.

The acetate, b.p. 59–60°/1 mm., and the *p*-nitrobenzoate, m.p. 76°, of the bromo compound were prepared in the usual manner.

Anal. Calcd. for $C_4H_5BrN_2O_6$: N, 10.90. Found: N, 10.59.

Anal. Calcd. for $C_9H_6BrN_3O_8$: C, 29.67; H, 1.65; Br, 21.98; N, 11.54. Found: C, 30.20; H, 1.74; Br, 21.75; N, 10.85.

2,2-Dinitroethanol. To 1 liter of ice water at 3° was added 300 g. of damp potassium *aci*-2,2-dinitroethanol. The slurry was stirred and cooled by means of an ice bath while a solution of 33 ml. of concentrated sulfuric acid in 320 ml. of water was added. The reaction mixture was maintained below 3° during the addition. After the addition was complete, the aqueous solution was extracted five times with ice-cold 20-ml. portions of ether. The ether solutions were combined and dried over sodium sulfate while being stored at −20°. Then, after filtering to remove the hydrated salts, the ether was removed from the solution under vacuum, leaving a light yellow liquid residue weighing 65 g. To this residue were added 2 drops of sulfuric acid and 75 ml. of dibutyl sebacate. This mixture was then further evacuated to remove the last traces of volatiles, after which it was transferred to a Distillation Products CMS-5 cyclic molecular still, degassed, and distilled at 50–60°/0.2 mm. Two fractions were obtained weighing 11 g. and 2 g., respectively. The first fraction had n_D^{20} 1.4717 while the second fraction had n_D^{20} 1.4710. Fraction 1 was extracted with petroleum ether (b.p. 30–60°) and then crystallized from ethyl chloride at Dry-Ice temperature. The white crystalline solid was collected on a precooled Buchner funnel and then quickly transferred to a cooled flask. The residual solvent was removed at a vacuum of 0.5 micron while maintaining the flask at −15°. A sample which was thus crystallized twice, melted at 2–3° and was analyzed on the same day.

Anal. Calcd. for $C_2H_4N_2O_5$: C, 17.64; H, 2.94; N, 20.59. Found: C, 17.98; H, 2.97; N, 21.08.

6,6-Dinitrobicyclo[2.2.1]-2-heptene. A solution of 4 g. (0.05 mole) distilled cyclopentadiene in 15 ml. of chlorobenzene was heated to reflux (100–110°) and a mixture of 3 g. of distilled 2,2-dinitroethanol in 15 ml. of chlorobenzene was added dropwise over a period of 10 min. Reflux was continued for an additional 20 min., and during this time the reaction mixture darkened and some polymer was deposited on the walls of the flask. The reaction mixture was clarified with charcoal and the solvent and excess cyclopentadiene were removed under reduced pressure. The residue was transferred to a small cold-finger distillation apparatus and distilled under vacuum. This operation was conducted behind a safety glass shield, as an earlier preparation had decomposed violently, spraying hot oil in all directions. The product sublimed at 145°/2 mm. and solidified on the cold-finger as a crystalline compound. The waxy crystals after recrystallization from ether melted at 117–118°.

Anal. Calcd. for $C_7H_8N_2O_4$: C, 45.6; H, 4.35; N, 15.21. Found: C, 44.93; H, 4.38; N, 15.21.

2,2-Dinitro-1,3-propanediol. A solution of 37% formaldehyde (460 g.) was added during a 1-hr. period to a suspension of 870 g. of pure potassium *aci*-2,2-dinitroethanol in 2 liters of water. When the addition was complete, 333 g. of glacial acetic acid was added dropwise during a 2.5-hr. period, and the resulting mixture stirred for an additional 2 hr. It was then extracted five times with 1-liter portions of ether and the extracts dried over sodium sulfate. The ether was removed under reduced pressure and the concentrate dissolved in 1 liter of 1-chloro-1-nitroethane and subsequently cooled to induce crystallization. The white crystals of 2,2-dinitro-1,3-propanediol which separated were filtered and washed with two 100-ml. portions of chloroform, and finally dried in a vacuum oven at 50°/30 mm. for 4 hr. There was obtained 630 g. (76%) of product melting at 139–140°.

Anal. Calcd. for $C_3H_6N_2O_6$: C, 21.69; H, 3.64; N, 16.89. Found: C, 21.97; N, 3.90; N, 17.09.

The dibenzoate was prepared in the usual manner, m.p. 79°.

Anal. Calcd. for $C_{17}H_{14}N_2O_8$: N, 7.49. Found: N, 7.64.

5,5-Dinitro-1,3-dioxan. A mixture of 10 g. of 2,2-dinitro-1,3-propanediol, 2.0 g. of paraformaldehyde, 10 ml. of acetic acid, and 0.1 ml. of sulfuric acid was heated on a steam bath for nearly 8 hr. The mixture was filtered and then concentrated under reduced pressure. The sirup that remained was distilled in a micro distillation apparatus. At an oil-bath temperature of 140° and a pressure of 2–3 mm., 8 g. of clear distillate was obtained which partially crystallized in the receiver. About 2 g. of liquid was decanted and then the solid residue was dissolved in chloroform. To this solution was added petroleum ether (b.p. 30–60°) and a crystalline product was recovered which, after several recrystallizations from the same solvent, melted at 53–53.5°. According to the analysis the compound is the 1,3-dioxan.

Anal. Calcd. for $C_4H_6N_2O_6$: N, 15.73; Found: N, 15.90.

AZUSA, CALIF.

[CONTRIBUTION FROM THE LABORATORY FOR THE STUDY OF HEREDITARY AND METABOLIC DISORDERS, AND THE DEPARTMENTS OF BIOLOGICAL CHEMISTRY AND MEDICINE, UNIVERSITY OF UTAH]

Improved Preparation of Diethyl Oximino-, Formamido- and Acetamidomalonates[1]

KENNETH N. F. SHAW AND CHRIS NOLAN

Received April 8, 1957

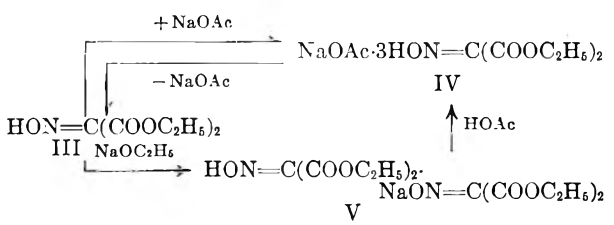
Diethyl malonate was converted by the action of sodium nitrite and acetic acid to diethyl oximinomalonate, which was isolated in 93% yield as a crystalline 3:1 addition compound with sodium acetate. The properties of this new compound are described. The addition compound was reduced with zinc and formic acid to diethyl formamidomalonate in 87% yield, and with zinc, acetic acid, and acetic anhydride to diethyl acetamidomalonate in 100% yield.

Diethyl formamidomalonate (I)[2] and diethyl acetamidomalonate (II)[3,4] have been known for many years, but only recently were introduced as intermediates for the synthesis of various amino acids.[5–9] These and other acylamidomalonates have usually been obtained by reductive acylation of diethyl oximinomalonate (III). Improvements in the preparation of these compounds are presented in this paper.

The oxime III has been synthesized from diethyl sodiomalonate and "nitrous gases",[10,11] or methyl nitrite,[12,13] or *n*-butyl nitrite,[5,14] and from diethyl malonate, sodium nitrite and acetic acid.[5,6,15–21] The last method is convenient, but has been criticized[14] on the grounds that the original yield (80–90%)[15,16] cannot be reproduced. High yields of crude oxime III of uncertain purity have been reported by some investigators[5,17] using this method, but the yield of pure oxime III recorded by others[18,21] has not exceeded 63%. The reaction of diethyl malonate with sodium nitrite and acetic acid was used in the present work, and III was isolated in 93% yield as a crystalline 3:1 addition compound (IV) with sodium acetate, which melts at 87–88°. It is probable that a crystalline substance, m.p. 86.5–88°, which was designated as the oxime III in a recent patent,[20] may actually have been IV.

The addition compound IV is purified more readily than the oily oxime III, and is thus more suitable as an intermediate for other syntheses. IV is stable under normal storage conditions and crystallizes readily from dichloromethane, chloroform, benzene, or toluene. IV undergoes partial dissociation into the oxime III and sodium acetate in ethyl acetate, or in organic solutions in contact with water. In diethyl ether, however, dissociation is complete. This behavior in ether was used to establish the nature of the addition compound IV; quantitative recovery of sodium acetate was effected, and the resulting oxime III was then combined with authentic sodium acetate to reconstitute IV.

The acid sodium salt (V) of the oxime III, which had been encountered in an earlier synthesis of III,[12] was obtained as a minor (2%) contaminant of the addition compound IV. The nature of V was established by its alternate preparation from the oxime III by the action of sodium ethoxide, and by its conversion to the addition compound IV upon treatment with acetic acid. Varying small amounts of the acid salt V are produced when the addition compound IV is heated *in vacuo* and are responsible



for the color of organic solutions of IV (almost colorless to yellow). The acid salt V is of potential inter-

(1) Supported by research grants from the National Institutes of Health, U. S. Public Health Service.

(2) M. Conrad and A. Schulze, *Ber.*, **42**, 729 (1909).

(3) R. Locquin and V. Cerchez, *Bull. soc. chim. France*, [4], **43**, 932 (1928); [4], **49**, 42 (1931).

(4) V. Cerchez, *Bull. soc. chim. France*, [4], **49**, 45 (1931).

(5) A. Galat, *J. Am. Chem. Soc.*, **69**, 965 (1947).

(6) H. R. Snyder and C. W. Smith, *J. Am. Chem. Soc.*, **66**, 350 (1944).

(7) H. R. Snyder, J. F. Shekleton, and C. D. Lewis, *J. Am. Chem. Soc.*, **67**, 310 (1945).

(8) N. F. Albertson, S. Archer, and C. M. Suter, *J. Am. Chem. Soc.*, **66**, 500 (1944).

(9) N. F. Albertson and S. Archer, *J. Am. Chem. Soc.*, **67**, 308 (1945).

(10) M. Conrad and C. A. Bischoff, *Ber.*, **13**, 595 (1880); *Ann.*, **209**, 211 (1881).

(11) F. Ratz, *Monatsh.*, **25**, 55 (1904).

(12) L. Bouveault and A. Wahl, *Compt. rend.*, **137**, 196 (1903); *Bull. soc. chim. France*, [3], **29**, 628, 960 (1903).

(13) N. J. Putochkin, *Ber.*, **56**, 2213 (1923).

(14) C. E. Redemann and M. S. Dunn, *J. Biol. Chem.*, **130**, 341 (1939).

(15) R. Locquin and V. Cerchez, *Compt. rend.*, **186**, 1360 (1928); *Bull. soc. chim. France*, [4], **47**, 1274 (1930).

(16) V. Cerchez, *Bull. soc. chim. France*, [4], **47**, 1279 (1930).

(17) Z. J. Vejdělek, *Chem. Listy*, **44**, 73 (1950) [*Chem. Abstr.*, **45**, 8004 (1951)].

(18) J. A. Spring, U. S. Patent **2,635,960** [*Chem. Abstr.*, **47**, 8565 (1953)].

(19) M. Vignau, *Bull. soc. chim. France*, 638 (1952).

(20) J. C. Vander Weele, E. C. Britton, and H. C. White, U. S. Patent **2,649,474** [*Chem. Abstr.*, **48**, 8818 (1954)]; Brit. Patent **713,144** [*Chem. Abstr.*, **49**, 2492 (1955)].

(21) A. Ek and B. Witkop, *J. Am. Chem. Soc.*, **76**, 5579 (1954).

est as an intermediate in syntheses where the addition compound IV may be unsuitable because of its sodium acetate component. The unusual solubility of IV and V in benzene and dichloromethane indicates covalent bonding and probable chelation of sodium in these compounds; other similar examples of chelated sodium compounds are well known.

Diethyl formamidomalonate (I) has been prepared from the oxime III by the action of zinc and formic acid[2,5,15,17]; a 55–70% yield of impure I was reported. "Very poor results"[21] have been indicated more recently with this reaction, and may have been related to partial decomposition of I during vacuum distillation and to incomplete recovery because of its low melting point and tendency to form oils.[22] These difficulties have been circumvented by use of catalytic hydrogenation,[21,23,24] or by use of the higher melting methyl esters.[22] In the present work, the reaction of zinc and formic acid with the addition compound IV, rather than impure oxime III, and avoidance of vacuum distillation have given pure I in 87% yield. A lower yield of I was obtained upon prolonged exposure to boiling formic acid, possibly because of transesterification, and also when I was separated from zinc formate at room temperature, probably because of occlusion.

Diethyl acetamidomalonate (II) has been obtained from the oxime III by reductive acetylation, usually without isolation of the intermediate diethyl aminomalonate; the reducing agents included aluminum amalgam,[3,4,13,15,25,26] zinc and acetic acid,[27–29] hydrogen (catalytic),[6,13,14,19,20,24,30–33] or hydrogen sulfide.[34,35] The use of impure III may have been partly responsible for the wide variation in the reported yields of II (40–90%). In the present work, treatment of the addition compound IV in a mixture of acetic acid and acetic anhydride with zinc has consistently provided II in quantitative yield.

The addition compound IV should prove suitable as an intermediate in the preparation of other diethyl acylamidomalonates.

EXPERIMENTAL

Diethyl oximinomalonate-sodium acetate complex (IV). A solution of 160.2 g. (1.0 mole) of redistilled diethyl malonate (b.p.$_{11}$ 87°, uncorrected) in 175 ml. (3.0 moles) of glacial acetic acid was stirred *vigorously* at 0–5° while a solution of 207.0 g. (3.0 moles) of sodium nitrite in 250 ml. of water was added dropwise during 3–4 hr. The ice bath was removed and the mixture was stirred vigorously for 20 hr. more. The nitrosation was carried out in a three-necked flask with appropriate fittings and a small vent to permit escape of nitric oxide; the system was otherwise sealed to prevent ingress of air. The reaction mixture was extracted with a 400-ml., and then three 100-ml. portions of dichloromethane. The combined dichloromethane extracts were dried over anhydrous sodium sulfate and treated with charcoal; the filtrate was concentrated *in vacuo* at 60° or less until the residual yellow oil crystallized. The residue was dissolved in 500 ml. of warm dichloromethane; the solution was shaken with Celite and 40 g. of anhydrous sodium acetate for 15 min. and filtered. Sodium acetate reacts with any free oxime III in the solution and ensures maximum recovery of the addition compound IV. Sodium acetate also eliminates residual acetic acid, which impedes crystallization of IV, as solvates which are insoluble in dichloromethane. The filtrate was concentrated *in vacuo* at 60° or less to 400 ml. and petroleum ether (b.p. 30–60°) was added until the solution was faintly cloudy (500–600 ml.). The mixture was allowed to stand at room temperature for an hour and, after thorough mixing to promote crystallization, was refrigerated overnight. IV (194.2 g., 90% yield) was recovered as colorless blunt needles, m.p. 87–88°.[36] A second crop of 7.08 g. (3% yield), m.p. 83–85°, was obtained by concentrating the filtrate and crystallizing the residue from dichloromethane–petroleum ether.

The total yield of IV decreased to 80% when the reaction mixture was stirred for only 4 hr. after addition of the sodium nitrite solution. The total yield was 85–87% when practical grade diethyl malonate was used without redistillation and with stirring for 18–24 hr. When the reaction mixture was extracted with diethyl ether instead of dichloromethane, the oxime III containing acetic acid and small amounts of unreacted diethyl malonate was obtained in place of IV.

For analysis, IV was recrystallized from dichloromethane–petroleum ether (b.p. 30–60°), m.p. 87–88°.

Anal.[37] Calcd. for $C_{23}H_{36}N_3O_{17}Na$: C, 42.53; H, 5.59; N, 6.47; Na, 3.55. Found: C, 42.95; H, 5.45; N, 6.27; Na, 3.45.

Characterization of diethyl oximinomalonate-sodium acetate complex (IV). *A. Recovery of sodium acetate.* A suspension of 40.00 g. (0.0616 mole) of IV in 800 ml. of anhydrous ether was simmered for 10 min., cooled, and filtered. The filter cake was washed thoroughly with anhydrous ether and dried at 0.1 mm. and 60° over phosphorus pentoxide and potassium hydroxide to yield 6.01 g. of impure sodium acetate, m.p. 324–326° (darkened above 310°). This material was simmered with 50 ml. of dichloromethane, the suspension was filtered, and the filter cake was washed thoroughly with dichloromethane. The resulting white powder was dried *in vacuo;* 5.03 g. (99% yield), m.p. 327–329°

(22) H. Hellmann and F. Lingens, *Z. physiol. Chem.*, **297**, 283 (1954).

(23) A. Cohen and J. A. Silk, Brit. Patent **611,600** [*Chem. Abstr.*, **43**, 3445 (1949)].

(24) A referee has commented that III is hydrogenated readily in the presence of Raney nickel at room temperature and atmospheric pressure.

(25) O. Piloty and J. Neresheimer, *Ber.*, **39**, 514 (1906).

(26) V. Cerchez, *Bull. soc. chim. France*, [4], **47**, 1282 (1930).

(27) H. J. F. Weiss, Brit. Patent **583,307** [*Chem. Abstr.*, **41**, 2747 (1947)].

(28) M. Tishler and E. E. Howe, U. S. Patent **2,521,809** [*Chem. Abstr.*, **45**, 644 (1951)].

(29) S. Tatsuoka, T. Kinoshita, and R. Nakamori, *J. Pharm. Soc. Japan*, **71**, 702 (1951) [*Chem. Abstr.*, **46**, 1978 (1952)]; Japan Patent **4472** (1952) [*Chem. Abstr.*, **48**, 8256 (1954)].

(30) P. A. Levene and A. Schormüller, *J. Biol. Chem.*, **106**, 595 (1934).

(31) P. Mastagli and M. Métayer, *Bull. soc. chim. France*, 1091 (1948) [*Chem. Abstr.*, **43**, 5738 (1949)].

(32) S. I. Lur'e, G. A. Ravdel, and E. S. Chaman, *Zhur. Obshcheĭ Khim.*, **22**, 2011 (1952) [*Chem. Abstr.*, **47**, 8649 (1953)].

(33) S. Murahashi and S. Horie, Japan Patent **4871** (1952) [*Chem. Abstr.*, **48**, 8818 (1954)].

(34) T. B. Johnson and B. H. Nicolet, *J. Am. Chem. Soc.*, **36**, 345 (1914).

(35) R. Schwarz and K. Capek, *Monatsh.*, **84**, 595 (1953).

(36) Melting points are corrected and were taken in open capillary tubes.

(37) Analyses were performed by the Weiler and Strauss Microanalytical Laboratory, Oxford, England.

(colorless melt), not depressed upon admixture with authentic sodium acetate (m.p. 328–330°).

B. Recovery of diethyl sodio-oximinomalonate (acid salt) (V). The dichloromethane filtrate and wash from the sodium acetate (section *A*) was concentrated to dryness *in vacuo*. The residue (0.90 g.) was crystallized from 10 ml. of dichloromethane by addition of 20 ml. of petroleum ether (b.p. 30–60°) to give 0.82 g. of cream-colored powder, m.p. 141° (dec.). Following recrystallization from dichloromethane–petroleum ether, faintly yellow rosettes of stout needles were obtained, m.p. 141° (dec.), not depressed upon admixture with authentic V (section E).

Anal. Calcd. for $C_{14}H_{21}N_2O_{10}Na$: C, 42.00; H, 5.29; N, 7.00; Na, 5.75. Found: C, 42.55; H, 4.88; N, 6.80; Na, 5.62.

C. Recovery of diethyl oximinomalonate (III). The ether filtrate and wash from the sodium acetate (section A) was washed successively with 50 ml. of 1*N* sodium bicarbonate and three 50-ml. portions of water, treated with charcoal, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to dryness *in vacuo* at 60° or less to give 34.00 g. (97% yield) of III as a pale yellow, thick oil. III was colorless when concentration was effected without external heating, but darkened to orange-brown if heated at 100° *in vacuo* for 15 min.

D. Reconstitution of addition compound IV *from oxime* III. To a solution of 33.30 g. (0.1760 mole) of III (section C) in 200 ml. of dichloromethane was added 10.00 g. of anhydrous sodium acetate. The mixture was simmered for 10 min., cooled, and filtered. The filter cake was washed thoroughly with dichloromethane and dried *in vacuo* at 60° and 0.1 mm.; 5.08 g. of sodium acetate was recovered, m.p. 328–330°. The filtrate was concentrated to dryness *in vacuo* to give 37.97 g. of IV as a yellow oil which crystallized on cooling. The weight of the combined sodium acetate, averaged from the weight increase sustained in converting III to IV and from the weight of sodium acetate recovered, is 4.80 g.; the calculated value for IV is 4.82 g. The residue was crystallized from dichloromethane–petroleum ether to give two crops of IV; 36.37 g., m.p. 87–88°, and 0.89 g., m.p. 85–86° (total yield 98%).

E. Diethyl sodio-oximinomalonate (acid salt) (V) *from oxime* III. To a solution of 18.57 g. (0.098 mole) of III (section C) in 100 ml. of absolute ethanol was added 98 ml. of 0.5*N* sodium ethoxide in absolute ethanol. The yellow solution was concentrated to dryness *in vacuo*. The residue was concentrated to dryness with two successive 100-ml. volumes of dichloromethane, and then crystallized from dichloromethane–petroleum ether (1:2) to give 18.35 g. (97% yield) of V, m.p. 143° (dec.). Faintly yellow rosettes of stout needles were obtained by recrystallization from the same solvent mixture, m.p. 141° (dec.).

F. Conversion of acid salt V *to addition compound* IV. To a solution of 6.01 g. (0.015 mole) of V in 100 ml. of dichloromethane was added 0.90 ml. (0.015 mole) of glacial acetic acid; the yellow color of V disappeared and sodium acetate precipitated. The mixture was treated with charcoal and Celite, and the filtrate was concentrated to dryness *in vacuo*. The residual oil was crystallized from dichloromethane–petroleum ether to give 6.05 g. (93% yield) of IV, m.p. 87–88°.

Diethyl formamidomalonate (I). A solution of 90.94 g. (0.140 mole) of addition compound IV in 600 ml. of 88% formic acid, initially at 80°, was stirred vigorously, and 80 g. of zinc dust was added in small portions during 30 min. at such a rate that the temperature was maintained at 95–103°. The reaction was not easily controlled if carried out below 95°. The mixture was filtered through a preheated sintered glass filter immediately after addition of the final portion of zinc, and the filter cake was washed thoroughly with boiling formic acid. The filtrate was concentrated *in vacuo* at 70° or less until distillation of formic acid ceased. The residual oily crystals were shaken with a mixture of 300 ml. of dichloromethane and 300 ml. of water containing 75 g. of sodium chloride; the aqueous phase was reextracted with three successive 50-ml. volumes of dichloromethane. The combined dichloromethane extracts were shaken with increasing increments (50–100 ml.) of 1*N* sodium bicarbonate until the *p*H of the bicarbonate phase was 7.0–7.2; 12–25 g. of sodium chloride was then added and the bicarbonate phase was reextracted with three more 50-ml. volumes of dichloromethane. The combined dichloromethane extracts were treated with charcoal, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residual oil was dissolved in 250 ml. of anhydrous ether and petroleum ether (b.p. 30–60°) was added until the solution was faintly cloudy (100–125 ml.). Following refrigeration, 69.56 g. (82% yield) of I was recovered as long colorless needles, m.p. 51–53° (lit.[21] m.p. 50–52°). A second crop of 4.46 g. (5% yield), m.p. 50–52°, was obtained by concentrating the filtrate and crystallizing the residual oil from ether–petroleum ether. I was also obtained as dense prismoids, m.p. 52–53°, when an ether solution was shaken immediately after addition of petroleum ether. The melting point of each form was raised to 53–54° by recrystallization from ether–petroleum ether.

Diethyl acetamidomalonate (II). A solution of 90.94 g. (0.140 mole) of addition compound IV in a mixture of 200 ml. of glacial acetic acid and 300 ml. of acetic anhydride, initially at 80°, was stirred vigorously, and 80 g. of zinc dust was added in small portions during 40 min. at such a rate that the temperature was maintained at 110–115°. The reaction was not readily controlled if carried out below 110°. The mixture was filtered through a preheated sintered glass funnel, and the filter cake was washed thoroughly with boiling acetic acid. The filtrate was concentrated *in vacuo* until distillation of acetic acid ceased. The crystalline residue[38] was treated with dichloromethane, sodium chloride solution, and sodium bicarbonate solution, and the combined dichloromethane extracts were treated with charcoal, dried, and concentrated in the manner described for I (preceding section). The residual solid was dissolved in 100 ml. of boiling ethyl acetate and 400 ml. of hot cyclohexane was added. Following refrigeration, 89.00 g. (98% yield) of II was recovered as large colorless dendritic crystals, m.p. 96–97°, unchanged by recrystallization from ethyl acetate–cyclohexane (lit.[28] m.p. 95–97°). A second crop of 1.71 g. (2% yield), m.p. 93–95°, was obtained by concentrating the filtrate and crystallizing the residue from ethyl acetate–cyclohexane.

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(38) The direct recovery of II by recrystallization of a similar residue from isopropyl alcohol has been reported in a recent patent.[30] The presence of a substantial amount of zinc acetate in II prepared in this manner can be demonstrated by dissolving the material in dichloromethane or benzene.

[CONTRIBUTION FROM THE CHEMICAL CORPS, CHEMICAL RESEARCH DIVISION, U. S. A. CHEMICAL WARFARE LABORATORIES]

Synthesis of Phosphinic Acids, Chlorides, and Fluorides[1]

THOMAS P. DAWSON AND KENNETH C. KENNARD[2]

Received May 1, 1957

A simple procedure has been developed for obtaining phosphinic acids by treating alkylphosphonic difluorides, $RP(O)F_2$, with appropriate Grignard reagents R'MgX; the alkyl groups may be alike or different depending upon the Grignard reagent and the $RP(O)F_2$ selected. A series of phosphinic acids and their corresponding chlorides and fluorides has been prepared.

The reaction of Grignard reagents with phosphoryl chloride to produce phosphine oxides and phosphinic acids has been described by several authors.[3] Symmetrically substituted tertiary phosphine oxides are produced in high yield by this reaction (Equation 1).

$$3\ RMgX + POCl_3 \longrightarrow R_3PO + 3\ MgClX \quad (1)$$

However, the facile reaction of Grignard reagents with phosphorus halides, which accounts for the success of the above reaction, makes it very difficult to replace selectively only two of the chlorine atoms (Equation 2).

$$POCl_3 \xrightarrow[(2)\ H_2O]{(1)\ RMgX} R_2P(O)OH + R_3PO + MgXCl \quad (2)$$

With improved procedures,[4,5] useful yields of phosphinic acids have been obtained. Variations, including the blocking of one position on the phosphorus atom, have been investigated but generally require added synthetic steps.[3,6]

Attempts were made in these laboratories to substitute phosphonic dichlorides for phosphoryl chloride in order to prepare unsymmetrical phosphinic acids by a reaction (Equation 3) directly analogous to Equation 2 discussed above.

$$R'P(O)Cl_2 \xrightarrow[(2)\ H_2O]{(1)\ RMgX} RR'P(O)OH + MgXCl \quad (3)$$

It is interesting to note that the reaction between phenylphosphonic dichloride and one mole of phenylmagnesium bromide furnished diphenylphosphinic acid in 53% yield[7] or practically the same yield reported for the reaction of phosphoryl chloride with phenylmagnesium bromide.[4] Also di-*t*-butylphosphinic acid has been prepared in 16% yield from *t*-butylphosphonic dichloride and one mole of *t*-butylmagnesium bromide.[8] However, when methylphosphonic dichloride, which is generally much more reactive toward nucleophilic reagents than the phenyl homolog, was reacted with one mole of an alkyl Grignard reagent only minute amounts, if any, of the desired phosphinic acid were obtained.

The less reactive methylphosphonic difluoride, on the other hand, reacted with Grignard reagents at low temperatures to furnish gray, solid complexes which may be represented by $RCH_3POF \cdot MgXF$ (Equation 4). These compounds, which separated in nearly quantitative yield from the ethereal reaction mixture, were readily hydrolyzed to furnish unsymmetrical phosphinic acids (Equation 5).

$$CH_3POF_2 + RMgX \longrightarrow RCH_3POF \cdot MgXF \quad (4)$$

$$RCH_3POF \cdot MgXF + NaOH \longrightarrow RCH_3P(O)OH + NaF + MgXF \quad (5)$$

The yield of phosphinic acid seems to increase with increasing size of the R group. The final isolation step involves a methylene chloride extraction of the acid from an aqueous mixture of salts. The acids which have a low carbon-containing moiety are very soluble in water and thus are not readily removed by methylene chloride extraction.

It is believed that this method is susceptible to more extensive development than is afforded it here. The availability of the requisite phosphonic difluorides from the corresponding chlorides, which are in turn available *via* the convenient aluminum chloride method,[9] makes this method a straightforward path to unsymmetrical phosphinic acids.

The phosphinic chlorides and fluorides prepared from the corresponding phosphinic acids are summarized in Table I.

EXPERIMENTAL

Methylphosphonic difluoride. Methylphosphonic dichloride[9] (300 g., 2.26 moles) was melted and placed in a 500-ml.

(1) The experimental work described herein was completed in 1950–51. Recent declassification has made publication possible.

(2) Present address: Research Laboratories, Eastman Kodak Co., Rochester 4, N. Y.

(3) G. M. Kosolapoff, *Organophosphorus Compounds*, John Wiley and Sons, Inc., New York, 1950, pp. 107 and 132.

(4) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **64**, 2983 (1942).

(5) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **73**, 5466 (1951).

(6) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **71**, 369 (1949); **72**, 5508 (1950).

(7) Work done at the University of Nebraska by K. C. K.

(8) P. C. Crofts and G. M. Kosolapoff, *J. Am. Chem. Soc.*, **75**, 3379 (1953).

(9) A. M. Kinnear and E. A. Perren, *J. Chem Soc.*, 3437 (1952).

TABLE I

PREPARATION OF PHOSPHINIC CHLORIDES AND FLUORIDES, RCH_3POX

R	X	Yield, %	B.P., °C.	Mm.	Formula	Analyses, % P Calcd.	P Found	Cl Calcd.	Cl Found
$(CH_3)_2CHCH_2$	Cl	68	61–62	1–2	$C_5H_{12}ClOP$	20.04	19.95	—	—
$CH_3(CH_2)_4$	Cl	61	95–105	3	$C_6H_{14}ClOP$	18.37	18.35	21.03	21.43
C_6H_{11}	Cl	83	93–95[a]	1	$C_7H_{14}ClOP$	17.15	17.00	19.63	19.55
$(CH_3)_2CHCH_2$	F	68	71–72	3.5	$C_5H_{12}FOP$	22.43	22.30	—	—
$CH_3(CH_2)_4$	F	85	74–75	2	$C_6H_{14}FOP$	20.36	20.09	—	—
C_6H_{11}	F	83	77	1–1.5	$C_7H_{14}FOP$	18.87	18.89	11.58[b]	11.45

[a] L. Z. Soborovskiĭ and Yu. M. Zinovev, *Zhur. Obshcheĭ Khim.*, 24, 516–19 (1954) report this as b.p. 101–102°/3 mm. [b] Fluorine analysis.

three necked flask equipped with stirrer, thermometer, and Y-adapter for gas inlet tube and reflux condenser which was protected from outside atmosphere with a calcium chloride drying tube. Anhydrous hydrogen fluoride (92.2 g., 4.52 moles plus 2% excess) was condensed from a stock cylinder into a small Monel vessel fitted with Monel tubing and connections. The cooling bath was then removed from the vessel and gaseous HF allowed to flow into the reaction mixture at such a rate that the reaction temperature could be maintained at 40–45° with tap-water cooling. About 4 hr. was required to complete the addition. The reaction mixture was then warmed to 80° for 45 min., and a stream of nitrogen was introduced to remove dissolved gases. The product was distilled through a short helix-packed column to give 185 g. (82%) of methylphosphonic difluoride; colorless liquid, b.p. 98–99°; d_4^{25} 1.3609; n_D^{25} 1.3148.

Anal. Calcd. for CH_3OF_2P: F, 38.0; P, 30.98. Found: F, 38.46; P, 31.18.

Diphenylphosphinic acid. The Grignard reagent prepared from 5 g. of magnesium and 31.4 g. of bromobenzene in 500 ml. of ether was added dropwise with stirring to 39 g. of phenylphosphonic dichloride in 500 ml. of ether at such a rate as to maintain the solvent at reflux temperature. After the addition was completed, the reaction mixture was further stirred at reflux temperature for 15 min. The ether was decanted and the solid was broken up and added in portions to 300 ml. of ice water. The mixture was thoroughly stirred and the lumps were again broken. The undissolved solid was collected on a filter and treated with a minimum of dilute aqueous alkali. The insoluble triphenylphosphine oxide was removed by filtration and the filtrate was acidified and cooled. The diphenylphosphinic acid was collected on a filter and recrystallized from dilute ethanol to yield 23 g. (53%) of crystals, m.p. 189–192° (lit. m.p. 190–192[4]).

Phosphinic acids—general procedure. The Grignard reagent, prepared in the usual way, was transferred from the reaction flask to a dropping funnel using a positive pressure of dry nitrogen. One arm of the siphon reached nearly to the bottom of the Grignard flask and thus removed all but the final traces of the ether solution so that the solid particles and excess magnesium remained behind. The ethereal solution was added dropwise with stirring to an equivalent amount of methylphosphonic difluoride in ether. The reaction flask was protected from moisture by drying tubes and cooled to Dry Ice–acetone temperature. The precipitation of a gray solid began immediately and continued throughout the addition. The cooling bath was removed and stirring was continued for 15 min. after completion of the addition. The ether was decanted and the solid, generally 98–99% of theoretical, was dried *in vacuo* in a desiccator. The solid was then treated with a 3*M* equivalent of dilute aqueous sodium hydroxide solution. The basic magnesium salts were collected on a filter and washed well with water. The filtrate and washings were combined, acidified, and evaporated on the steam bath to a small volume. The residual mixture of product and inorganic salts were extracted with several portions of hot methylene chloride and the extract was treated with charcoal and filtered. The phosphinic acids, obtained by evaporation of the solvent, were viscous light yellow oils which could be further purified by additional charcoal treatment in methylene chloride. Three phosphinic acids were prepared. One of them, methyl amyl phosphinic acid, was given additional treatments with charcoal and methylene chloride and analyzed for phosphorus.

Anal. Calcd. for $C_6H_{15}O_2P$: P, 20.63. Found: P, 20.58.

The remaining two acids, after one treatment with charcoal in methylene chloride, were chlorinated directly to the corresponding chlorides which were more readily purified by distillation.

Phosphinic chlorides—general procedure. The phosphinic acid was treated with about 100% excess of thionyl chloride and the mixture was heated under reflux for 2–3 hr. The excess thionyl chloride was removed by distillation at atmospheric pressure and the crude residue was distilled under reduced pressure. The material thus obtained was fractionated through a 6-in. column packed with $^3/_{16}$-in. glass helices to obtain a pure product. The acid chlorides were clear mobile oils of sharp odor which hydrolyzed easily in the presence of moisture.

Phosphinic fluorides—general procedure. Anhydrous hydrogen fluoride from a stock cylinder was condensed in a weighed Monel vessel fitted with Monel tubing and connections until an excess of 10–15% of the stoichiometric amount was obtained. Gaseous hydrogen fluoride, generated by warming the vessel, was then bubbled into the stirred phosphinic chloride in a glass vessel protected from moisture with drying tubes. For 0.2–0.3 mole of chloride the introduction of hydrogen fluoride required approximately 1 hr. The reaction temperature was maintained at 40–45° by cooling with tap water. The solution was stirred for 1 hr. after the addition was completed. The mixture was then subjected to reduced pressure to remove the hydrogen chloride. The residue was distilled under reduced pressure followed by fractionation to obtain a pure product.

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ARMY CHEMICAL CENTER, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Derivatives of Sulfenic Acids. XXIX.[1,2] The Characterization of Certain Hydroxysteroids with 2,4-Dinitrobenzenesulfenyl Chloride

ROBERT B. LANGFORD AND NORMAN KHARASCH

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The pyridine-catalyzed reactions of 2,4-dinitrobenzenesulfenyl chloride (I) with testosterone, 19-nortestosterone, 17-α-methyltestosterone, and 11-α-hydroxyprogesterone are described. Evidence is presented for the conclusion that the products are sulfenate esters, formed by the reactions of I with the alcohol functions. It is suggested that these reactions, coupled with chromatographic separations of mixtures of the derivatives and regeneration of the hydroxysteroids from the esters, which has been achieved, may prove of value in isolation studies in this field of work. The synthesis of octadecyl 2,4-dinitrobenzenesulfenate is also reported.

In a previous paper,[3] it was shown that 2,4-dinitrobenzenesulfenyl chloride (I) reacts rapidly and in good yield with cholesterol to form the sulfenate ester, II. Because of the considerable interest in the isolation and characterization of compounds related to the corticosteroids, it was desired to extend this study to representative members of this class of substances. The reactions of I with testosterone, 19-nortestosterone, 17-α-methyltestosterone, and 11-α-hydroxyprogesterone, all of which contain an alcohol function, were therefore examined.

$$\underset{\text{I}}{(NO_2)_2C_6H_3SCl} + C_{27}H_{45}OH + C_5H_5N \longrightarrow \underset{\text{II}}{(NO_2)_2C_6H_3SOC_{27}H_{45}} + C_5H_5N{:}HCl$$

The principal products (Table I) from the reactions of I with the above hydroxysteroids were the sulfenate esters, rather than those which might result by reaction of I at the 4,5-olefin position or at the α-methylene group of the ketone functions present in some of these molecules.[4] The conclusions as to the structures of the products are based on (1) elementary analyses, (2) previously reported results with simpler alcohols, (3) cleavage of certain of the present products to regenerate the hydroxysteroids, (4) comparisons of the spectra of the products with those of the original hydroxysteroids, and (5) the consideration that the reactions of I and the hydroxysteroids would occur much more rapidly at the alcohol function than at the 4,5-olefin position or the methylene group alpha to the carbonyl function.

The products obtained are listed in Table I. The yields from testosterone, 19-nortestosterone, and cholesterol were reasonably good, considering that the runs were made on a small scale and that the products were subjected to thorough purification. With 17-α-methyltestosterone and 11-α-hydroxyprogesterone, however, the yields were decidedly lower (45% and 22%). Some side reactions, especially with the former, and the known fact that tertiary alcohols give lower yields than primary or secondary ones, in the reaction with I, are the most likely reasons for the lower yields in these cases.[5] Although such complications in the reactions of I with the hydroxysteroids can thus arise, it is nevertheless believed that 2,4-dinitrobenzenesulfenyl chloride may have considerable utility in the characterization of hydroxysteroids. The facts that the products are colored, that they lend themselves well to chromatographic procedures, and that they have definite spectral characteristics are positive features toward the use of I for the characterization of hydroxysteroids. For example, it was shown, in the present study, that mixtures of the hydroxysteroid derivatives can be separated simply by chromatography on alumina, and that the sulfenate esters can be cleaved to regenerate the alcohol component. Such separations, followed by regeneration of the hydroxysteroids, by cleavage of the esters, suggests a potentially valuable technique for separation of hydroxysteroids from complex mixtures.

In the course of this work the octadecyl ester of 2,4-dinitrobenzenesulfenic acid was also prepared, characterized, and cleaved to regenerate the alcohol. This was done to conserve the somewhat limited supplies of the hydroxysteroids while developing the procedure. The octadecyl alcohol derivative was convenient for exploratory work in the chromatographic purifications and for finding suitable conditions for the regeneration of the alcohol by cleavage of the sulfenate ester.

(1) This study was conducted under auspices of the Office of Scientific Research, Air Research and Development Command.

(2) For preceding papers, *cf. J. Org. Chem.*, **21**, 590 (1956); *J. Am. Chem. Soc.*, **78**, 2728 (1956) and *J. Chem. Ed.*, **33**, 585 (1956); **34**, 510 (1957).

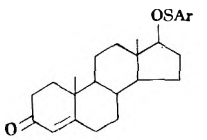
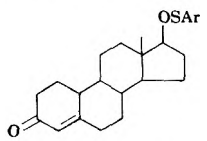
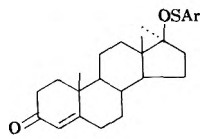
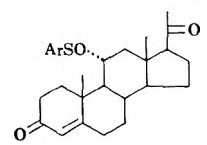
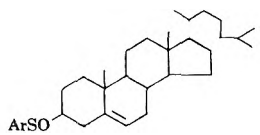
(3) N. Kharasch, D. P. McQuarrie, and C. M. Buess, *J. Am. Chem. Soc.*, **75**, 2658 (1953); *cf.* also, L. Goodman and N. Kharasch, *J. Am. Chem. Soc.*, **77**, 6541 (1955).

(4) For references to the reaction of I with olefins and ketones, *cf.*, *J. Chem. Ed.*, **33**, 585 (1956); **34**, 510 (1957).

(5) In the tertiary alcohols, competition by water is more serious and leads to the formation of bis(2,4-dinitrophenyl) disulfide and other hydrolysis products; cf., N. Kharasch, W. King, and T. C. Bruice, *J. Am. Chem. Soc.*, **77**, 931 (1955).

TABLE I

PRODUCTS FROM THE REACTION OF 2,4-DINITROBENZENESULFENYL CHLORIDE WITH CERTAIN HYDROXYSTEROIDS

Hydroxysteroid	Product Ar = 2,4-Dinitrophenyl	Yield, %	M.P., °C.	Analyses Calcd. C	H	S	Found C	H	S
Testosterone		70	204–205	61.71	6.21	6.59	61.91	5.84	6.70
19-Nortestosterone		60	199–200	61.00	5.95	6.79	60.71	5.78	7.01
17-α-Methyltestosterone		45	170–171	62.38	6.44	6.40	62.65	6.56	6.15
11-α-Hydroxyprogesterone		32	198–199	61.34	6.10	6.07	61.08	6.21	5.74
Cholesterol[a]		80	190–191						
Octadecanol[b]	$CH_3—(CH_2)_{17}—O—S—Ar$	80	88.0–88.5				Footnote[c]		

[a] Reported in reference (3); m.p., 188–190°C. [b] Not a steroid. [c] N: Calcd. 5.74, found, 6.03.

EXPERIMENTAL

Starting materials. 2,4-Dinitrobenzenesulfenyl chloride (I), m.p. 95–96°, was prepared by the catalytic chlorinolysis of bis-(2,4-dinitrophenyl) disulfide or obtained from Cyclo Chemical Corp.,[6] m.p. 95–96°. Benzene was A.C.S. grade Baker and Adamson reagent, dried by distillation. Pyridine was also A.C.S. grade Baker and Adamson reagent, distilled from barium oxide and stored over calcium hydride. The hydroxysteroids were supplied by the Upjohn Co., in purities from 95% to 100%.

General Procedure for characterizing hydroxysteroids. To 1.00 g. of the hydroxysteroid, dissolved in 5 ml. of dry benzene, was added 0.5 ml. of dry pyridine, an excess. A solution containing the calculated equivalent amount of I, in 5 ml. of dry benzene, was added to the hydroxysteroid-pyridine mixture at room temperature, with stirring. Completion of the reaction was indicated by a negative starch-iodide test, when I was not used in excess. In most cases the reaction was complete after a few minutes.

The reaction mixture was filtered and the precipitate was extracted with several small portions of hot benzene. To the combined filtrates, at the boiling point, was added twice their volume of hot ethanol. This solution was refrigerated overnight to induce the formation of crystals, which were collected by filtration and air or vacuum dried. The products are listed in Table I. Some variation of the solvent ratios and volumes was necessary to obtain the optimum yields of the various sulfenates.

(6) 1930 E. 64th Street, Los Angeles 1, Calif.

Further purification of the products was obtained by adding them, in benzene solution, to an alumina chromatographic column, prewet with petroleum ether, developing the chromatogram with benzene, and eluting with benzene-methanol (9:1). The purified material was then crystallized as before.

Chromatographic separation of sulfenate esters of hydroxysteroids. A solution of 50 mg. each of cholesteryl 2,4-dinitrobenzenesulfenate and testosteronyl 2,4-dinitrobenzenesulfenate in 1.0 ml. of benzene was added to an alumina chromatographic column, prewet with petroleum ether. Additional benzene was used to develop the chromatogram, followed by benzene-methanol (9:1) for elution. Two distinct bands formed and were readily separated on elution. The melting points of the materials, thus obtained, identified the first fraction as the testosterone derivative, and the other as the cholesterol product.

Recovery of a hydroxysteroid from its sulfenate ester. The recovery of testosterone exemplifies the procedure used. To a solution of about 100 mg. of testosteronyl 2,4-dinitrobenzenesulfenate in 25 ml. of ethanol was added 2.0 ml. of concentrated hydrochloric acid. This mixture was boiled for 5 min. and filtered. The filtrate was refrigerated overnight, yielding a crop of fine, cream colored crystals, m.p. 156–158°. In comparison, the testosterone used to prepare the sulfenate had a melting point of 152–153°, but was rated only 95% pure. On mixing these materials, a melting point of 152–154° was obtained.

Determination and evaluation of spectra. Infrared absorption spectra were obtained from carbon disulfide solutions of testosterone, 19-nortestosterone, testosteronyl 2,4-dinitrobenzenesulfenate, and 19-nortestosteronyl 2,4-dinitro-

benzenesulfenate. Both hydroxysteroids had absorption bands in the hydroxyl region, near 3625 cm.$^{-1}$ These absorption bands were not present in the spectra of either derivative, indicating that the reaction occurred at the hydroxyl group, rather than at some other point in the hydroxysteroid molecule.

Acknowledgment. We are indebted to the Upjohn Co., Kalamazoo, Mich., for a generous supply of the hydroxysteroids and to Mr. D. M. Frankel of the Stauffer Chemical Co., Torrance, Calif., for assistance with the infrared spectra.

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Thiocarboxylic Esters and Related Compounds[1]

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The reaction of unsaturated acid chlorides with lead mercaptides gave the corresponding thiolesters. Polymerization of thiolacrylates and thiolmethacrylates yielded glasslike materials, comparable in properties to the corresponding ester polymers. Attempts to prepare thionoacrylates by dehydrohalogenation of halothionopropionates failed. The stability of the intermediate halo- and dihalopropionimidates to decomposition was found to decrease markedly with increasing halogen substitution. The reaction of unsaturated acid chlorides with sodium sulfhydrate yielded polymeric material, equivalent in analytical composition to the corresponding thioacids.

In spite of the abundant literature published in recent years on lower unsaturated acids and esters, unsaturated thioacid derivatives received remarkably little attention. Previous work in this field was in fact limited to the investigations of Reppe[3] and Jacobs.[4]

In the present study, a number of new thiolesters and thionoesters were prepared, and their physical and chemical properties determined and evaluated. Since this work was completed, Jacobs[4] made a series of thiolacrylates by debromination of dibromothiolpropionates. His attempts to obtain thiolacrylates directly from acrylyl chloride and a mercaptan in presence of sodium carbonate were not successful, due presumably to the addition of the mercaptan to the double bond and the formation of a mercapto thiolpropionate.

In the present work, thiolesters of unsaturated carboxylic acids were prepared directly from the corresponding acid chloride and lead mercaptide, by a modification of the method first described by Obermeyer,[5] which is based on the reaction:

$$2\ RCOCl + Pb(SR')_2 \longrightarrow 2\ RCOSR' + PbCl_2$$

Attempts to prepare ethyl thiolmethacrylate from methacrylyl chloride and lead ethyl mercaptide by Obermeyer's method without a solvent resulted in a violet, exothermic reaction and the formation of a dark, polymerized product. This difficulty was overcome by using anhydrous ether, in which the lead mercaptide was slurried up initially, and by adding the acid chloride gradually with good agitation and cooling. An excess of lead mercaptide (10%) was used to avoid the troublesome separation of unreacted acid chloride.

Properties and analyses of a number of unsaturated thiolesters made by this procedure are listed in Table I.

Samples of the thiolesters were heated in bulk, or in a solvent, or irradiated with ultraviolet light to obtain polymers. As could be expected by analogy with the corresponding esters, only thiolacrylates and thiolmethacrylates were found to polymerize under the conditions employed, yielding transparent, colorless materials.

Saturated thionoesters have been made by Matsui[6] and by Sacurada[7] from an iminoester and hydrogen sulfide:

$$RC(OR')NH + 2\ H_2S \longrightarrow RCSOR' + NH_3$$

Unsaturated thionoesters have not been described before, and it was an object of this work to attempt their preparation by dehydrohalogenation of halothionopropionates.

A modification of Matsui's method was used for the preparation of a series of halothionopropionates from the corresponding halopropionimidates. The analyses and physical properties of these new compounds are listed in Table II.

Dichloro- and dibromothionopropionates intended for dehalogenation trials, could not be prepared from the corresponding iminoesters, as dihalopropionimidates are not sufficiently stable for reaction with hydrogen sulfide.

(1) Includes some data from "Unsaturated Thioacids and Derivatives" by G. Braude and T. Lieser (Doctoral Dissertation), University of Halle.

(2) Present address: Grace Research & Development Co., Curtis Bay, Baltimore, Md.

(3) W. Reppe, *Ann.*, **582**, 1 (1939). German Patent **856,293**, July 8, 1949.

(4) L. Jacobs, "Thioacrylic Esters," Doctoral Dissertation, University of Illinois, 1955.

(5) J. Obermeyer, *Ber.*, **20**, 2920 (1887).

(6) M. Matsui, *Mem. Coll. Sci. Kyoto*, **1**, 285 (1908); **3**, 247 (1912).

(7) Y. Sacurada, *Mem. Coll. Sci. Kyoto*, **9**, 237 (1925/26).

TABLE I

UNSATURATED THIOLESTERS

Compound	Boiling Point °C.	Mm. Hg	Spec. Grav., d_D^{20}	Analyses Calculated C	H	S	Found C	H	S
Methyl thiolacrylate[a] $CH_2{=}CHCOSCH_3$	65	110	1.052	46.8	5.90	31.2	46.9	5.93	30.8
Ethyl thiolacrylate $CH_2{=}CHCOSC_2H_5$	58	30	1.012	51.7	6.93	27.6	51.2	7.23	27.4
Methyl thiolmethacrylate[b] $CH_2{=}C(CH_3)COSCH_3$	58	36	1.032	51.7	6.93	27.6	51.2	7.40	27.1
Ethyl thiolmethacrylate[b] $CH_2{=}C(CH_3)COSC_2H_5$	50–51	13	0.973	55.3	7.77	24.6	55.1	7.75	24.8
Ethyl thiolcrotonate[b,c] $CH_3CH{=}CHCOSC_2H_5$	74–75	20	1.003	55.3	7.77	24.6	55.3	7.78	24.6
Ethyl thiocinnamate $C_6H_5CH{=}CHCOSC_2H_5$	66–67	13							
	290	752	1.098	68.7	6.30	16.65	68.1	6.13	16.49
	171–173	21							
	128–130	0.5							

[a] Yield: 53%. Irritating white liquid, horseradish odor. [b] Not described before. [c] Oily, slightly yellowish liquid.

TABLE II

THIONOESTERS

Compound	Boiling Point, °C./mm.	Analyses Calculated C	H	Cl	S	Found C	H	Cl	S
Methyl β-chlorothionopropionate $CH_2ClCH_2CSOCH_3$	63–65/13	34.7	5.06	25.6	23.1	34.7	4.94	26.4	23.8
Ethyl β-chlorothionopropionate[a] $CH_2ClCH_2CSOC_2H_5$	81–83/20 55–56/3	39.4	5.94	23.3	21.0	40.3	6.19	23.2	20.2
				Br				Br	
Ethyl β-bromothionopropionate $CH_2BrCH_2CSOC_2H_5$	121–124/15	30.5	4.57	40.6	16.25	30.2	4.76	39.8	15.71

[a] Specific Gravity d_4^{20} 1.133.

Attempts to dehydrohalogenate the halothionopropionates by treatment with alkali or amines resulted in hydrolysis and decomposition with the formation of dark, tarry materials. Thionoacrylates could not be isolated and identified in any of these reaction products.

In the course of this work, a number of new β-halopropionimidates and dihalopropionimidate hydrohalides were synthesized as intermediates.

Attempts to prepare the free iminoesters from the hydrohalides revealed interesting differences in their stability. Unsubstituted propionimidates are reported as quite stable at room temperature, but β-chloropropionimidates decompose within a few minutes on storage above 0°. Ethyl β-bromopropionimidate had to be prepared with the utmost care below 0° from the hydrohalide, and ethyl dichloropropionimidate decomposed on formation immediately. It is evident that the stability of propionimidates is adversely affected by an increasing halogen substitution.

A number of trials were carried out in the course of this study with the object of preparing unsaturated thioacids.

Hydrolysis of unsaturated thiolesters with sodium hydroxide or sodium sulfhydrate did not yield any thioacid, but an acid and a mercaptan instead, or only polymeric material. In another series of trials, acrylyl or methacrylyl chloride were reacted at room temperature with anhydrous sodium sulfhydrate in ether solution. However, monomeric thioacid or thioacid salt could not be isolated even from reactions run in presence of hydroquinone as an inhibitor.

After the elimination of ether and inorganic salts from the reaction products of acrylyl chloride and sodium sulfhydrate, a water-insoluble solid residue remained. This was separated into several fractions of increasing molecular weight and melting point by extraction with a series of hot solvents and crystallization. Elemental analyses of these fractions gave nearly identical values, which were close to theory for thioacrylic acid.

This material can therefore be considered a mixture of polymers of a molecular weight of over about 400, formed under milder conditions than required for the polymerization of acrylic acid.

This raises the question as to structure, and the following may be a possible explanation. Sherlin,[8] in attempts to polymerize acrylic acid in furan at

(8) Sherlin, *J. Gen. Chem.* (*U.S.S.R.*), **8**, 7–15 (1938).

160°, obtained a dimer of the structure:

$$CH_2{=}CHCOOCH_2CH_2COOH$$

A trimer and higher polymers were formed under similar conditions in benzene.

Sulfhydryl groups, on the other hand, are known to be very reactive. Holmberg,[9] for instance, reported a very exothermic reaction between thioacidic acid and acrylic acid at room temperature, yielding a thiolester structure:

$$CH_3COSH + CH_2{=}CHCOOH \longrightarrow CH_3COSCH_2CH_2COOH$$

By analogy, it was considered conceivable that thioacrylic acid, formed initially, polymerized in the following way:

$$CH_2{=}CHCOSH + CH_2{=}CHCOSH \longrightarrow CH_2{=}CHCOSCH_2CH_2COSH$$

and finally to:

$$CH_2{=}CHCOS(CH_2CH_2COS)_nCH_2CH_2COSH$$

Titration of samples of this material with an alcoholic caustic solution gave values equivalent to one acid group for 5–7 moles, or n = 5–7. This is roughly equivalent to apparent molecular weights obtained, and confirms the structure concept expressed.

Further attempts to clarify the identity of these compounds were not conclusive. A more complete structure determination could not be carried out in the course of this work, but would certainly be of interest.

EXPERIMENTAL

Ethyl thiolmethacrylate. The preparation of ethyl thiolmethacrylate is typical for all the reactions in this series.

Lead ethyl mercaptide was prepared by adding ethyl mercaptan to an excess of lead acetate solution under stirring, then filtering off the yellow precipitate, which was washed successively with water, alcohol, and ether. Samples of the mercaptide were made immediately before use to avoid decomposition on storage. Methacrylyl chloride was prepared from methacrylic acid and thionyl chloride and purified by vacuum-distillation.

Lead ethyl mercaptide (36.2 g., 0.11 mole) was slurried in 200 ml. of anhydrous ether, and 21 g. (0.2 mole) of methacrylyl chloride was added over a period of 2–3 hr., stirring continuously. The temperature was maintained between 10° and 20° by cooling and agitation was continued for 1 hr. after the reaction was completed. The salts, consisting of lead chloride and some unreacted lead mercaptide, were then filtered off and washed with ether. All filtrates were combined and the ether was distilled off, leaving a yellow liquid.

Hydroquinone (1%) was then added to prevent polymerization, and the product was distilled under vacuum. The bulk of the material distilled at 50–51° under 13 mm., and weighed 14.8 g., corresponding to a yield of 57% (based on methacrylyl chloride).

All thiolesters listed in Table I were prepared in an analogous manner from the acid chlorides and lead mercaptides in ether solution, using the corresponding molar ratios of starting materials.

Bromination. Methyl thiolacrylate (10 g.) was dissolved in carbon tetrachloride and 15.5 g. of bromine was added gradually under agitation. The solution, which became light yellow a few minutes after the end of the bromine addition, was distilled under vacuum. Methyl dibromothiolpropionate distilled at 92° (13 mm.) as a light yellow oil, which turned red on storage.

Anal. Calcd. for $C_4H_6Br_2OS$: C, 18.32; H, 2.29; Br, 61.0; S, 12.22. Found: C, 18.08; H, 2.29; Br, 58.8; S, 11.31.

Hydrolysis. Ethyl thiolacrylate was refluxed for 3 hr. with an excess of 30% sodium hydroxide solution. The ethyl mercaptan liberated was passed into lead acetate solution and identified as lead ethyl mercaptide.

Anal. Calcd. for $C_4H_{10}PbS_2$: for Pb: 62.8. Found 62.0.

The remaining solution was acidified cautiously with dilute sulfuric acid and extracted with ether. The residue remaining after evaporation of the ether was free of sulfur and was identified as acrylic acid by the silver salt method, according to Biilman.[10]

Ethyl thiolcrotonate could not be saponified readily with caustic solution and was identified by a method described by Sachs.[11] Mercuric acetate was reacted with the thiolester in alcoholic solution at room temperature to form ethyl mercapto mercuric chloride, which crystallized readily.

Anal. Calcd. for C_2H_5ClHgS: for S, 10.75. Found: 10.60.

Polymerization. Samples of the distilled thiolesters were heated in test tubes to 60° or 130° with or without benzoyl peroxide (1%) as a catalyst. Another series of samples was irradiated with ultraviolet light.

Ethyl thiolcrotonate and ethyl thiolcinnamate did not polymerize under any of the conditions employed. Hard to rubbery, transparent materials were obtained from all thiolacrylates and thiolmethacrylates with the exception of methyl thiolmethacrylate, which yielded a very hard, glasslike polymer.

Methyl β-chloropropionimidate hydrochloride. This compound was prepared in 88% yield by the general method described by Clemo[12] from acrylonitrile, anhydrous methanol, and hydrogen chloride, and purified by recrystallization from a warm acidic acid, ether mixture.

Anal. Calcd. for $C_4H_9Cl_2NO$: C, 30.4; H, 5.74; Cl, 44.9; N, 8.87. Found: C, 30.7; H, 5.62; Cl, 45.8; N, 8.61.

Ethyl β-chloropropionimidate hydrochloride was prepared in an analogous way from acrylonitrile, ethanol, and hydrogen chloride.

Ethyl β-bromopropionimidate hydrobromide. Acrylonitrile (53 g., 1 mole) was dissolved in 250 g. of anhydrous ether and dried hydrogen bromide was passed through the solution. The crystalline material which precipitated was filtered off and washed with ether. It was then reprecipitated from warm glacial acetic acid by the addition of ether. This new compound crystallized in the form of needles and melted at 110° (dec.). The yield was 72%.

Anal. Calcd. for $C_5H_{11}Br_2NO$: C, 23.1; H, 4.27; Br, 61.2; N, 5.40. Found: C, 23.5; H, 4.17; Br, 62.1; N, 5.49.

Ethyl dichloropropionimidate hydrochloride was prepared by saturating a solution of α,β-dichloropropionitrile in anhydrous ethanol with dry hydrogen chloride, and separating the resulting crystalline iminoester hydrochloride. This new compound could not be recrystallized from glacial acetic acid due to a lack of solubility. Analyses gave consistently high chlorine values, a fact reported previously for other iminoester hydrochlorides.

Anal. Calcd. for $C_5H_{10}BrClNO$: C, 20.3; H, 3.41; Br, 54.2; Cl, 12.02; N, 4.74. Found: C, 19.74; H, 3.15, Br, 54.8; Cl, 16.24; N, 4.91.

Methyl β-bromopropionimidate. Preparation of free iminoesters. Due to the ease with which halopropioniminoesters hydrolyze in solution, it was found necessary to cool all reagents and glass equipment to below −10° before use.

One hundred twenty-four grams (0.5 mole) of ground

(9) B. Holmberg, *Arkiv Kemi*, **14A**, No. 7 (1940); **15A**, No. 20 (1942).

(10) Biilman, *J. prakt. Chem.*, (2), 61, 493 (1900).

(11) G. Sachs, *Ber.*, 54, 1851 (1921).

(12) G. R. Clemo, *J. Chem. Soc.*, 729 (1928).

methyl β-bromopropionimidate hydrobromide was suspended in 500 ml. of anhydrous ether and cooled to −10°. This suspension was then treated in portions with a cold, aqueous solution of potassium carbonate (40%) in a jacketed, brine-cooled separatory funnel. The ether solution of free iminoester obtained was then dried with anhydrous sodium sulfate and used for the preparation of the thionoester without delay. The identity of this iminoester was established by its conversion to the thionoester, as all attempts to eliminate the ether under vacuum led to decomposition. All other iminoesters were prepared in an analogous manner from the corresponding hydrogen halide salts.

Methyl β-chlorothionopropionate. An ether solution of methyl β-chloropropionimidate was prepared from 79 g. (0.5 mole) of methyl β-chloropropionimidate hydrochloride by the general method described, and saturated with hydrogen sulfide. The solution turned yellow, and a white precipitate separated, which was filtered off and washed with ether. It consisted of ammonium hydrogen sulfide and was discarded. The filtrates were combined, dried with sodium sulfate, and distilled under vacuum to yield 42 g. (61%) of a yellow liquid, b.p. 63–65° (13 mm.).

Ethyl β-chlorothionopropionate and ethyl β-bromothionopropionate were prepared in an analogous manner from the corresponding propionimidates. In Table II analyses and boiling points are listed.

Reaction of acrylyl chloride with sodium sulfhydrate. Anhydrous sodium sulfhydrate (62 g., 1.1 moles), prepared from sodium ethoxide and hydrogen sulfide in alcoholic solution and separated by addition of ether, was suspended in 250 ml. of ether, and 90 g. (1.0 mole) of acrylyl chloride was added gradually, stirring and cooling continuously. The temperature was kept below 20°. Stirring was continued for 1 hr. after the end of the reaction, and the solid precipitate obtained was separated from the ether solution by filtration. The latter was discarded, as it was found to contain only traces of material.

Treating of a part of the yellow solid obtained with dilute hydrochloric acid, followed by ether extraction did not yield any ether soluble material. The main portion was extracted repeatedly with water to dissolve inorganic salts. An ash-free residue remained after filtration and drying, which was extracted successively with hot methanol, benzene, and toluene. Much remained undissolved. Cooling of the solutions yielded white powders, which were analyzed.

Starting with 10 g. of dried crude material, extraction with boiling benzene yielded 3 g. of purified product.

Anal. Calcd. for C_3H_4OS (thioacrylic acid): C, 40.9; H, 4.57; S, 36.3. Found: C, 41.0; H, 4.90; S, 35.2.

Molecular weights (Rast) and melting points were determined for the different fractions separated from solvents:

Methanol extract:	Mol. Wt. 316	m.p. 87–88°
Toluene extract:	Mol. Wt. 542	m.p. 118–120°
Benzene extract:	Mol. Wt. 698	m. p. —
Residue:	(insoluble)	m.p. 130–135°

Methacrylyl chloride and sodium sulfhydrate. Methacrylyl chloride (52 g., 0.5 mole) was reacted with 34 g. (0.6 mole) of sodium sulfhydrate in 250 ml. of ether at room temperature. The resulting material was separated into a salt residue and an ether solution, which contained the organic part of the reaction products. After evaporation of the ether, a yellow semisolid material was obtained, which solidified on standing. Soluble in ether and benzene when freshly prepared, it became partly insoluble after 1 to 2 days. The residue remaining after extraction with benzene was analyzed:

Anal. Calcd. for C_4H_6OS (thiomethacrylic acid): C, 47.1; H, 5.93; S, 31.4. Found: C, 46.9; H, 5.91; S, 30.2.

LINTHICUM, MD.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF WICHITA AND THE RESEARCH LABORATORY OF THE VETERANS ADMINISTRATION, WICHITA, KANSAS]

Reaction of *N*-Bromosuccinimide with Secondary Alcohols

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When aliphatic secondary alcohols are oxidized with *N*-bromosuccinimide under anhydrous conditions, subsequent bromination occurs *via* debromination of *N*-bromosuccinimide by hydrogen bromide, followed by bromination of the ketone by free bromine. This bromination can be suppressed by addition of a proton acceptor such as pyridine or calcium carbonate.

N-bromosuccinimide has been used as an oxidizing agent for the conversion of secondary aliphatic alcohols to the corresponding ketones.[3,4] *N*-bromosuccinimide[5] and *N*-chlorosuccinimide[6] have been shown to react with the aromatic secondary alcohol, benzhydrol, to give benzophenone. When Kruse *et al.*[7] attempted to oxidize ethyl lactate to ethyl pyruvate, they obtained a mixture of ethyl pyruvate and ethyl bromopyruvate from equimolecular quantities of *N*-bromosuccinimide and ethyl lactate, whereas twice the quantity of *N*-bromosuccinimide gave a 64% yield of ethyl bromopyruvate. The latter result was obtained with several other secondary alcohols. Ethyl mandelate was oxidized to ethyl phenylglyoxylate in satisfactory yields.

Our interest in the preparation of α-ketoesters and their halogenated derivatives prompted us to investigate the mode of formation of α-brominated ketones from secondary aliphatic alcohols, with a view to finding a method for repressing the bromi-

(1) Abstracted in part from the Master's Thesis of Gary G. Hammer, University of Wichita.

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(3) L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, **71**, 3935 (1949); **71**, 3938 (1949).

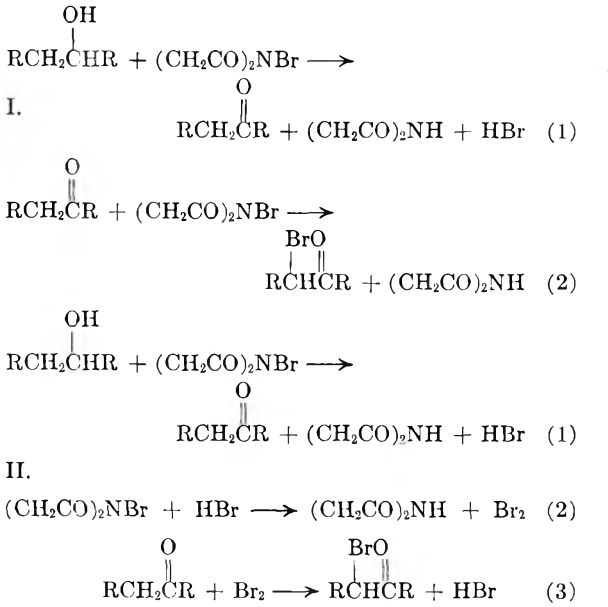
(4) M. Z. Barakat and G. M. Mousa, *J. Pharm. Pharmacol.*, **4**, 115 (1952).

(5) M. Z. Barakat, M. F. A. El-Wahab, and M. M. El-Sadr, *J. Am. Chem. Soc.*, **77**, 1670 (1955).

(6) Hebbelynck and R. M. Martin, *Experientia*, **5**, 69 (1949).

(7) P. F. Kruse, N. Geurkink, and K. L. Grist, *J. Am. Chem. Soc.*, **76**, 5796 (1954).

nation reaction. We visualized two possible routes to the brominated ketones:



I.

$$RCH_2\underset{OH}{\underset{|}{C}}HR + (CH_2CO)_2NBr \longrightarrow RCH_2\overset{O}{\overset{\|}{C}}R + (CH_2CO)_2NH + HBr \quad (1)$$

$$RCH_2\overset{O}{\overset{\|}{C}}R + (CH_2CO)_2NBr \longrightarrow RC\underset{BrO}{\underset{|}{\overset{\|}{C}}}R + (CH_2CO)_2NH \quad (2)$$

II.

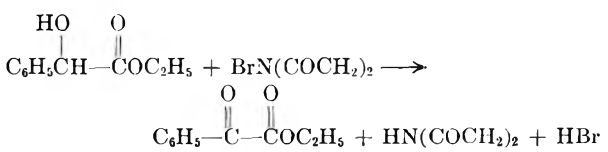
$$RCH_2\underset{OH}{\underset{|}{C}}HR + (CH_2CO)_2NBr \longrightarrow RCH_2\overset{O}{\overset{\|}{C}}R + (CH_2CO)_2NH + HBr \quad (1)$$

$$(CH_2CO)_2NBr + HBr \longrightarrow (CH_2CO)_2NH + Br_2 \quad (2)$$

$$RCH_2\overset{O}{\overset{\|}{C}}R + Br_2 \longrightarrow RC\underset{BrO}{\underset{|}{\overset{\|}{C}}}R + HBr \quad (3)$$

Ketones have been brominated alpha to the carbonyl function with *N*-bromosuccinimide in the absence of both light and peroxides.[8] We were unable to brominate either ethyl pyruvate or acetone with *N*-bromosuccinimide in refluxing carbon tetrachloride. On the other hand, 2-propanol, like ethyl lactate, yields a brominated ketone when reacted with *N*-bromosuccinimide. Barakat and Mousa[4] did not report the formation of bromoacetone in the latter reaction. Their results are not necessarily at variance with ours since they used a ten-to-one molar ratio of 2-propanol to *N*-bromosuccinimide.

The following evidence is offered in support of route II. Ethyl bromopyruvate was obtained in 40% yield from equimolar amounts of ethyl pyruvate and *N*-bromosuccinimide in the presence of HBr. A mixture of ethyl mandelate, *N*-bromosuccinimide and ethyl pyruvate gave ethyl phenylglyoxylate (89%), and ethyl bromopyruvate (55%):



$$C_6H_5\underset{HO}{\underset{|}{C}}H\text{—}\overset{O}{\overset{\|}{C}}OC_2H_5 + BrN(COCH_2)_2 \longrightarrow C_6H_5\text{—}\overset{O}{\overset{\|}{C}}\text{—}\overset{O}{\overset{\|}{C}}OC_2H_5 + HN(COCH_2)_2 + HBr$$

followed by reactions II (2) and II (3). Preferential reaction of pyridine or calcium carbonate with the hydrogen bromide liberated in the oxidation suppresses or eliminates the production of brominated ketones. Bromine vapor, present in copious amounts in the upper part of the reaction flask and lower part of the reflux condenser when a proton acceptor is absent, still persists, though to a lesser extent when calcium carbonate is present. Pyridine eliminates the bromine vapor. From Table I it can be seen that pyridine is more effective than calcium carbonate in preventing bromination. However, in the case of ethyl lactate better yields of ethyl pyruvate are obtained with calcium carbonate as a proton acceptor. Pyridine or pyridinium bromide apparently catalyzes the formation of high boiling non-brominated products.

The reaction appears to be general for secondary alcohols, provided the alcohol contains no functional groups that are sensitive to *N*-bromosuccinimide. For example, β-hydroxyisovaleronitrile yields a variety of products when reacted with *N*-bromosuccinimide despite the presence of a proton acceptor.

It is of interest to note that the oxidation of ethyl 3-chlorolactate to ethyl chloropyruvate with *N*-bromosuccinimide is not accompanied by bromination, though not admixed with pyridine or calcium carbonate.

EXPERIMENTAL

Attempted bromination of ethyl pyruvate with N-bromosuccinimide. A mixture of 5.8 g. (0.05 mole) of ethyl pyruvate, 8.9 g. (0.05 mole) of *N*-bromosuccinimide, and 75 ml. of carbon tetrachloride was refluxed for 48 hr. Filtration and distillation of the filtrate yielded an 85% recovery of unreacted ethyl pyruvate.

Bromination of ethyl pyruvate with N-bromosuccinimide and hydrogen bromide. Hydrogen bromide was slowly bubbled through a refluxing mixture of 5.8 g. (0.05 mole) of ethyl pyruvate, 8.9 g. (0.05 mole) of *N*-bromosuccinimide, and 75 ml. of dry carbon tetrachloride until the reddish brown bromine color disappeared (16 hr.). The mixture was filtered and the filtrate was dried over anhydrous sodium sulfate and distilled. The yield of ethyl bromopyruvate was 4.8 g. (40%) b.p. 71–73° (5 mm.), n_D^{25} 1.464.

Bromination of ethyl pyruvate with N-bromosuccinimide in the presence of ethyl mandelate. A mixture of 4.64 g. (0.04 mole) of ethyl pyruvate, 7.21 g. (0.04 mole) of ethyl mandelate, 7.21 g. (0.04 mole) of *N*-bromosuccinimide, and 75 ml. of dry carbon tetrachloride was refluxed for 10 hr. The succinimide was filtered off and the filtrate was dried over sodium sulfate and distilled at 5 mm. There was obtained 0.53 g. (10%) of unreacted ethyl pyruvate (b.p. 51–53°, n_D^{25} 1.403), 3.9 g. (55%) of ethyl bromopyruvate (b.p. 71–73°), and 6.3 g. (89%) of ethyl phenylglyoxylate (b.p. 108–112°).

Synthesis of ethyl pyruvate from ethyl lactate and N-bromosuccinimide. To a solution of 10 g. (0.084 mole) of ethyl lactate in 75 ml. of dry carbon tetrachloride were added 14.24 g. (0.08 mole) of *N*-bromosuccinimide and 8.4 g. of calcium carbonate. After four hours refluxing, the mixture was filtered, the filtrate dried over anhydrous sodium sulfate and fractionated. The yield of ethyl pyruvate was 5.67 g. (58%) and ethyl bromopyruvate, 2.57 g. (19%).

In another experiment calcium carbonate was replaced by an equivalent amount of pyridine and the reaction mixture was held between 60 and 70° for 4 hr. The carbon tetrachloride was decanted and the residue washed with dry carbon tetrachloride. After removal of the carbon tetra-

(8) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **29**, 573 (1946). For additional references see, C. Djerassi, *Chem. Revs.*, **43**, 271 (1948). Djerassi points out that the claim for the bromination of the methyl ketone group in 3-pentene-2-one and mesityl oxide by NBS [N. P. Buu-Hoï, *Experientia*, **2**, 310 (1946)] is equivocal since the possibility of allylic rearrangement was not considered in the purported evidence for the structure of the brominated products. Furthermore, Southwick, *J. Am. Chem. Soc.*, **72**, 1600 (1950), has shown that benzalacetone is not brominated in the methyl group by NBS.

TABLE I

REACTION OF N-BROMOSUCCINIMIDE WITH VARIOUS SECONDARY ALCOHOLS[a]

Alcohol	Moles of Alcohol: Moles of NBS[b]	Proton Acceptor	Products			
			Ketone	%	Brominated ketone	%
2-Propanol	1:1	None	None		Bromoacetone	30
2-Propanol	1:1	$CaCO_3$	Acetone[c]	Trace	Bromoacetone	30
2-Propanol	1:1	Pyridine	Acetone	60	None	
Cyclohexanol	1:1	Pyridine	Cyclohexanone	61	None[d]	
Phenyl methyl carbinol[e]	1:1	Pyridine	Acetophenone	65	None	
Phenyl methyl carbinol	1:2	None	None		Phenacyl bromide	45
Ethyl lactate	1:1	None	Ethyl pyruvate	10	Ethyl bromopyruvate	20
Ethyl lactate	1:1	$CaCO_3$	Ethyl pyruvate	58	Ethyl bromopyruvate	19
Ethyl lactate	1:1	Pyridine	Ethyl pyruvate	42	None	
Ethyl 2-hydroxybutyrate[e]	1:1	Pyridine	Ethyl 2-ketobutyrate[f]	50	None	

[a] Carbon tetrachloride was the solvent in all reactions. When pyridine was used as the proton acceptor the temperature was held between 60–70°; the reactions with 2-propanol are exothermic; the others were refluxed from 4–8 hr. [b] *N*-Bromosuccinimide. [c] Isolated as the 2,4-dinitrophenylhydrazone; m.p. 126°. [d] H. Schmid and P. Karrer[8] reported the direct bromination of cyclohexanone with *N*-bromosuccinimide. The oxidation in this case is extremely rapid. [e] Ref. 7. [f] B.p. 66–67° (16 mm.); m.p. of phenylhydrazone 191°. Van der Sleen, G., *Rec. trav. chim.*, **21**, 234 (1902).

chloride on a steam bath the residue was diluted with ether, washed successively with saturated aqueous calcium chloride and 5% hydrochloric acid, dried over anhydrous magnesium sulfate, and fractionated. The yield of ethyl pyruvate was 42%. No ethyl bromopyruvate was formed.

Oxidation of cyclohexanol. A mixture of 5 g. (0.05 mole) of cyclohexanol, 8.9 g. (0.05 mole) of *N*-bromosuccinimide, and 3.9 g. (0.05 mole) of pyridine in 50 ml. of dry carbon tetrachloride was heated on a steam bath at 60–70° for 4 hr. The mixture was allowed to stand overnight at room temperature, filtered, and the filtrate fractionated through a short column. The yield of cyclohexanone, b.p. 148–150°, was 3 g. or 61%. The melting point of its 2,4-dinitrophenylhydrazone was 162°.

Oxidation of ethyl 3-chlorolactate. A mixture of 7.67 g. (0.05 mole) of ethyl 3-chlorolactate, 8.9 g. (0.05 mole) of *N*-bromosuccinimide, and 75 ml. of carbon tetrachloride was refluxed for 3 hr. The mixture was filtered, the filtrate dried over anhydrous sodium sulfate, and distilled. The yield of ethyl chloropyruvate[9] boiling at 74–75° (8 mm.) was 5.5 g. (72%).

Attempted oxidation of β-hydroxyisovaleronitrile. A mixture of 9.9 g. (0.1 mole) of β-hydroxyisovaleronitrile, 17.8 g. (0.1 mole) of *N*-bromosuccinimide, 7.9 g. (0.1 mole) of pyridine in 100 ml. of carbon tetrachloride reacted spontaneously as evidenced by the rise in temperature of the reaction mixture. After the initial temperature increase had abated the mixture was kept at 60 to 70° for 2 hr. The mixture was then treated as described for ethyl lactate. Distillation yielded isobutyraldehyde, a small amount of 2-oxo-*iso*-valeric acid and a larger fraction which, judged by its boiling point (217–218°), may have been the dimer of β-oxoisovaleronitrile described by Moritz.[10]

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(9) J. Parrod, *Compt. rend.*, **218**, 599 (1944).
(10) E. Moritz, *J. Chem. Soc.*, **39**, 23 (1881).

[CONTRIBUTION FROM THE SHELL DEVELOPMENT CO.]

Reactions of Hydrogen Peroxide. II. A Novel Use of Selenium Dioxide as Catalyst for the Ring Contraction of Cycloalkanones to Cycloalkanecarboxylic Acids[1]

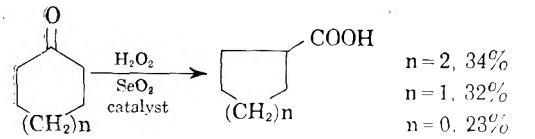
GEORGE B. PAYNE AND CURTIS W. SMITH

Received June 10, 1957

Oxidative ring contractions of cycloheptanone, cyclohexanone, and cyclopentanone to cyclohexane-, cyclopentane-, and cyclobutanecarboxylic acids in 34, 32, and 23% yields, respectively, have been obtained with hydrogen peroxide and selenium dioxide as catalyst.

The use of selenium dioxide as catalyst for the oxidation of acrolein to acrylic acid has recently been described.[1] In a further investigation of the action of selenium dioxide in the presence of hydrogen peroxide, the oxidation of cycloheptanone, cyclohexanone, and cyclopentanone was investigated. It was anticipated that the cyclic ketones might undergo the well-known reaction with selenium dioxide giving alpha-diketones, with hydrogen peroxide serving merely to oxidize selenium metal back to the dioxide. It was found, however, that along with other competing reactions, all three ketones underwent oxidative ring contraction to cyclohexane-, cyclopentane- and cyclobutanecarboxylic acids in 34, 32, and 23% yields, respectively. Adipic acid was identified as another prod-

(1) For the preceding article in this series see C. W. Smith and R. T. Holm, *J. Org. Chem.* **22**, 746 (1957).



uct of the reaction of cyclohexanone by esterification of the non-volatile acids formed. No investigation was made of the other higher boiling products from cyclopentanone or cycloheptanone, however.

The reactions were best carried out in tertiary butyl alcohol solution at 80° for about 2 hr. using equimolar quantities of ketone and hydrogen peroxide and about 2 mole % of selenium dioxide catalyst. In the case of cyclohexanone, the solvent-free mixture of products was separated into neutral and acidic fractions which were distilled separately. About 15% of starting ketone was recovered, along with just a trace of higher boiling neutral material. Distillation of the acidic portion gave cyclopentanecarboxylic acid as the only volatile product. Similar results were obtained with cycloheptanone.

No attempt was made to separate the mixture from cyclopentanone oxidation into acidic and neutral portions. Instead, direct distillation gave cyclobutanecarboxylic acid as the only volatile product.

The ring contraction of a 6-membered ring cyclic ketone to a cyclopentanecarboxylic acid has been observed before[2] in a β-diketone system that was incorporated in a dispiro compound; the Faworskii rearrangement of α-chlorocyclohexanone to cyclopentanecarboxylic acid is, of course, well known.[3] The contraction of a 5-membered ring to a 4, however, as in the case of cyclopentanone, appears to be rather unusual. For example, the Faworskii rearrangement of α-chlorocyclopentanone to cyclobutanecarboxylic acid was not observed.[3]

That the α-diketone is probably not an intermediate in the rearrangement was indicated by the failure of 1,2-cyclohexanedione to give any cyclopentanecarboxylic acid when subjected to the action of a catalytic amount of selenium dioxide and hydrogen peroxide. Aside from this evidence, little is known about the mechanism of the ring contraction. One can postulate, however, that selenium dioxide (selenious acid) is oxidized by hydrogen peroxide to selenic acid and that in some unknown manner the latter promotes the oxidative ring contraction.

EXPERIMENTAL[4]

Selenium dioxide catalyzed oxidation of cyclohexanone. To a stirred solution of 300 g. (3.0 moles) of 34% hydrogen peroxide and 5 g. (0.045 mole) of selenium dioxide in 1000 ml. of tertiary-butyl alcohol at 80° was added dropwise 294 g. (3.0 moles) of cyclohexanone. The reaction mixture was held at 80° by cooling with an ice bath during the hour required for addition. After completion of the addition, the reaction maintained temperature at 80° for 1.5 hr. with very little cooling being required. At that point, red selenium metal was deposited and the mixture was allowed to cool to room temperature overnight. After removal of selenium by filtration, distillation was carried out with a 40-tray Oldershaw column[4a] to remove the alcohol-water azeotrope. When the head temperature reached 85°, distillation was halted and the residue was cooled and poured into 750 ml. of ether. The ether solution was extracted successively with 20% potassium carbonate solution and water and dried over anhydrous sodium sulfate. Distillation of the ether solution gave 45 g. of recovered cyclohexanone, b.p. 153–155°, and only 5 g. of residual neutral product. The carbonate extract was acidified and extracted with ether. The ether solution was water-washed, dried over sodium sulfate, and concentrated to low volume on the steam bath. Distillation of the residue through a 1 × 50 cm. glass-helices packed column gave 77 g. (27% yield based on unrecovered cyclohexanone) of cyclopentanecarboxylic acid, b.p. 87–89° (2–3 mm.). n_D^{20} 1.4534; m.p. 3–4°; reported values: b.p. 215–216°[5]); n_D^{20} 1.4532;[6] m.p. 4–5°.[5]

Esterification of the 98 g. of residue from the above distillation with 1-butanol afforded 19 g. (5% yield based on unrecovered ketone) of butyl cyclopentanecarboxylate, b.p. 58–59° (1 mm.), n_D^{20} 1.4394; reported[7]) b.p. 95–97° (15 mm.). Thirteen grams of crude dibutyl adipate, b.p. 112–115° (1 mm.), n_D^{20} 1.4402, was also obtained.

Anal. Calcd. for butyl cyclopentanecarboxylate, $C_{10}H_{18}O_2$: C, 70.5; H, 10.6; saponification equiv., 170. Found: C, 70.3; H, 10.6; sapon. equiv., 172.

Anal. Calcd. for dibutyl adipate, $C_{14}H_{26}O_4$: C, 65.1; H, 10.1; sapon. equiv., 130. Found: C, 64.6; H, 9.9; sapon. equiv., 137.

The *acid chloride* of cyclopentanecarboxylic acid was prepared from 30 g. of the acid by refluxing with 50 ml. of thionyl chloride for 1 hr. The mixture was distilled to give 30 g. (86%) of product, b.p. 160–162°; reported[8] b.p. 160–162°.

The *amide* was prepared from a portion of the acid chloride by reaction with concentrated ammonium hydroxide. It was recrystallized from water and sublimed at 125° (2 mm.), m.p. 177–178°; reported[9] m.p. 178–179°.

Oxidation of cyclopentanone. The oxidation of 126 g. (1.5 moles) of cyclopentanone was carried out exactly as described above for cyclohexanone. The crude reaction mixture was filtered to remove selenium metal and distilled through the 50 cm. packed column to give 35 g. of cyclobutanecarboxylic acid (23% yield based on cyclopentanone charged; no attempt made to recover unreacted ketone), b.p. 74–76° (2.5 mm.); n_D^{20} 1.4446; reported[10], b.p. 195–196°, n_D^{20} 1.4434. The residue from the distillation amounted to 60 g. of dark viscous oil; it was not investigated.

The *amide* was prepared as above from crude acid chloride, m.p. 151–152°; reported[11]) m.p. 152–153°. The melt-

(2) C. Mannich, *Ber.*, **74B**, 1007 (1941).

(3) M. Mousseron, R. Jacquier, and A. Fontaine, *Compt. rend.*, **231**, 864 (1950); R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 4707 (1951).

(4) All melting points are corrected.

(4a) C. F. Oldershaw, *Ind. Eng. Chem., Anal. Ed.* **13**, 265 (1941).

(5) A Faworskii and V. Bozhovskii, *J. Russ. Phys. Chem. Soc.*, **46**, 1092 (1914).

(6) S. S. Nametkin and A. K. Ruzhentzova, *J. Russ. Phys. Chem. Soc.*, **46**, 1540, (1914).

(7) M. Mousseron and R. Jacquier, *Compt. rend.*, **229**, 374 (1949).

(8) E. Haworth, and H. W. Perkin, *J. Chem. Soc.*, 99 (1894).

(9) D. Venus-Danilova, *J. Gen. Chem. U.S.S.R.*, **6**, 697 (1936).

(10) G. J. Östling, *J. Chem. Soc.*, 473 (1912).

(11) W. H. Perkin, *J. Chem. Soc.*, 958 (1894).

ing point was not depressed when mixed with an authentic sample of cyclobutanecarboxamide, m.p. 151–152°.[12]

The *anilide* was prepared from crude acid chloride, m.p. 111–112° after recrystallization from benzene-petroleum ether; reported[13] m.p. 111°.

Oxidation of cycloheptanone. The oxidation of 100 g. (0.89 mole) of cycloheptanone (Aldrich Chemical Co. n_D^{20} 1.4608) was carried out exactly as above. After removal of solvent the crude product was separated into neutral and acidic fractions which were distilled separately through a 1 × 50 cm. packed column. The neutral portion afforded 18.5 g. of recovered ketone, b.p. 92° (50 mm.), n_D^{20} 1.4610, and 6 g. of non-volatile residue. The acidic fraction gave 32 g. (34% based on unrecovered cycloheptanone) of cyclohexanecarboxylic acid, b.p. 63–67° (<1 mm.), m.p. 25–29°; reported values: b.p. 223.5°, m.p. 29°.[14]

Anal. Calcd. for $C_7H_{12}O_2$: Neut. equiv., 128. Found: Neut. equiv., 128.

EMERYVILLE, CALIF.

(12) We are indebted to Prof. Henry Rapoport of the University of California for a generous sample of authentic acid chloride from which this amide was prepared.

(13) M. Freund and E. Gudeman, *Ber.*, **21**, 2692 (1888).

(14) J. S. Lumsden, *J. Chem. Soc.*, 90 (1905).

CONTRIBUTION FROM THE SHELL DEVELOPMENT CO.]

Reactions of Hydrogen Peroxide. III. Tungstic Acid Catalyzed Hydroxylation of Cyclohexene in Nonaqueous Media

GEORGE B. PAYNE AND CURTIS W. SMITH

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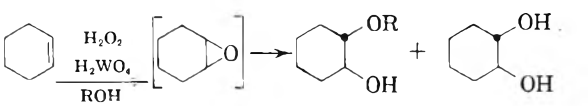
A novel conversion of an unsaturated linkage to its corresponding α-glycol monoether has been realized. Thus, tungstic acid catalyzed hydroxylations of cyclohexene with 90% hydrogen peroxide in methanol, ethanol, and 2-propanol have given the corresponding 2-alkoxycyclohexanols in 70, 41, and 21% yields, respectively. *Trans*-1,2-cyclohexanediol was also obtained in each case. With tertiary butyl alcohol as solvent no glycol monoether was found and the major product was the diol; also isolated in this case was 1-cyclopentenecarboxaldehyde, formed by the acid catalyzed rearrangement of the intermediate peroxide, 2-hydroperoxycyclohexanol. Isolation of the latter (as its cyclic ketal with acetone) represents a significant addition to the understanding of the cleavage of olefins to aldehydes with hydrogen peroxide.

The literature contains many reports on the use of osmium tetroxide, performic acid, and peracetic acid for the hydroxylation of a variety of unsaturated materials. Tungstic acid has also been described as an effective hydroxylation catalyst, particularly when employed in aqueous or acetic acid solution.[1]

Mugdan and Young[1] reported poor yields in the hydroxylation of cyclohexene in tertiary butyl alcohol solution, and also noted that loss of peroxide due to decomposition to water and oxygen was troublesome when such solvents as acetone, dioxane, or methanol were used.

In the present study, we have subjected cyclohexene to the action of hydrogen peroxide and tungstic acid catalyst in methanol, ethanol, 2-propanol, tertiary butyl alcohol, and acetone. Using 90% hydrogen peroxide with methanol as solvent, a 70% yield of 2-methoxycyclohexanol was realized along with a 16% yield of *trans*-1,2-cyclohexanediol.

This direct conversion by hydrogen peroxide of an unsaturated linkage to its corresponding α-glycol monoether has apparently not been reported before. Evidence that the reaction is a general one for lower molecular weight primary and secondary alcohols was obtained by the formation of 2-ethoxycyclohexanol and 2-isopropoxycyclohexanol, respectively, when ethanol and isopropyl alcohol were substituted for methanol.



R = CH_3:	70%	16%
R = C_2H_5:	41%	36%
R = *i*-C_3H_7:	21%	44%
R = *t*-C_4H_9:	0%	50%

The glycol monoethers are undoubtedly formed by the acid catalyzed action of alcohol, in competition with water (from the hydrogen peroxide), on the intermediate epoxide.[2] It was not surprising to find, therefore, that the most polar alcohol, methanol,[3] gave the highest yield of α-glycol monoether and the lowest yield of α-glycol.

While ethanol and isopropyl alcohol provided smaller, but nevertheless substantial amounts of hydroxy ether, none of the latter was observed when *tert*-butyl alcohol was employed as solvent. Either the tertiary alcohol failed to react with the intermediate epoxide, or any tertiary ether that might have been formed was unstable in the acidic medium and underwent conversion to α-glycol and isobutylene.[4] From the reaction in *tert*-butyl alcohol

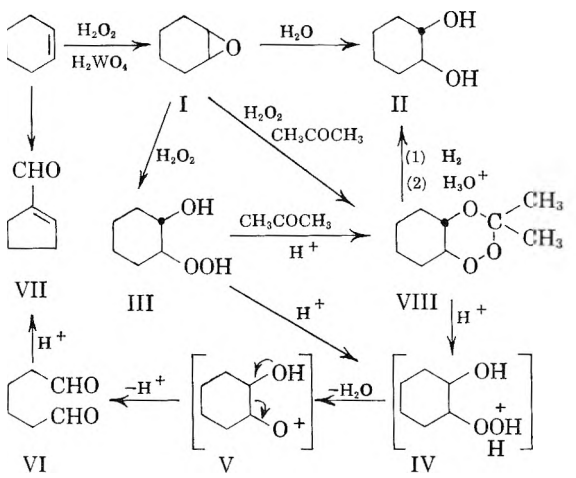
(1) I. Bergsteinson, U.S. Patent 2,373,942 (Apr. 17, 1945); M. Mugdan and D. P. Young, *J. Chem. Soc.* 2988 (1949).

(2) Epoxy compounds have been isolated as intermediates in the hydroxylation of other unsaturated materials with tungstic acid catalyst (unpublished results, Shell Development Co.).

(3) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Company, Inc., New York, N. Y., 1950, p. 256.

(4) T. W. Evans and K. R. Edlund, *Ind. Eng. Chem.*, **28**, 1186 (1936).

solution, *trans*-1,2-cyclohexanediol was obtained as the major product in 50% yield. Direct distillation of the reaction mixture without prior removal of tungstic acid catalyst also afforded a 9% yield of 1-cyclopentenecarboxaldehyde (VII). Isolation of the latter material indicated adipaldehyde (VI) as a probable intermediate, since VII is known to form from VI under acidic conditions.[5] Evidence that the diol II was not a precursor of either VII or adipaldehyde was obtained from a blank experiment in which pure diol was recovered in better than 95% yield following treatment with hydrogen peroxide and tungstic acid catalyst in *tert*-butyl alcohol solution.



This type of cleavage of an ethylenic linkage by hydrogen peroxide has been observed before. Mugdan and Young[1] isolated 4,4-dimethyl-2-pentanone as one of the products from the hydroxylation of 2,4,4-trimethyl-1-pentene using tungstic acid in acetic acid solution. The same by-product was also obtained by Byers and Hickinbottom[6] from their peracetic acid hydroxylation of 2,4,4-trimethyl-1-pentene.

A detailed investigation of the hydroxylation of cyclohexene in *tert*-butyl alcohol led to the discovery that even with 30% hydrogen peroxide, a significant amount of organic peroxide was being formed. This peroxide was postulated as *trans*-2-hydroperoxycyclohexanol (III), and was thought to arise from epoxide ring opening by hydrogen peroxide. It was felt that, during distillation, such a peroxide would readily undergo acid catalyzed rearrangement to adipaldehyde, by way of the postulated intermediates IV and V.

The presence of III was established by subjecting crude diol (from ether extraction of a water-flooded reaction mixture) to the action of acetone under acidic conditions. Distillation at reduced pressure afforded the peroxy cyclic ketal, VIII, 2,2-dimethyl-1,3,4-trioxa-*trans*-decalin, free of any cyclic ketal of the diol.[7] Structure VIII was confirmed by ultimate analysis, peroxide determination, molecular weight, and by the absorption of one molar equivalent of hydrogen to give *trans*-1,2-cyclohexanediol and acetone.[8]

As evidence that III could be the precursor of VII, the cyclic peroxide VIII was converted to the 2,4-dinitrophenylhydrazone of VII by heating with 2,4-dinitrophenylhydrazine in ethanolic hydrochloric acid solution for 0.5 hour. When the preparation was confined to a three-minute heating period, the bis-(2,4-dinitrophenylhydrazone) of adipaldehyde (VI) resulted.

When the hydroxylation of cyclohexene was carried out in acetone, cyclic peroxide VIII was obtained directly. With 34% hydrogen peroxide, the yields of crude VIII and diol were 23 and 49%, respectively. With 90% hydrogen peroxide, the yields were 40 and 48%, respectively, but VIII was contaminated with a solid explosive peroxide which co-distilled. The latter was tentatively identified as trimeric acetone peroxide by its melting point and explosive character. The crude VIII was not further investigated. *In view of the isolation of an explosive material from a reaction involving the use of 90% hydrogen peroxide in acetone solution, it is recommended that caution be exercised in the isolation of products prepared in this system.*

The cyclic peroxide VIII, itself, did not explode when warmed on a steel spatula; nevertheless, care was taken to carry out all concentrations and distillations at temperatures below 70°.

In an alternative route to VIII, 1,2-epoxycyclohexane (I) and 90% hydrogen peroxide were allowed to react in acetone solution in the presence of tungstic acid. The yields of diol and cyclic peroxide were 24 and 20%, respectively. Here again, VIII was contaminated with a substantial amount of explosive peroxide, and it was necessary to hydrogenate the crude product to the diol in order to calculate a firm yield.

EXPERIMENTAL[9]

2-Methoxycyclohexanol. To a 2-l., 3-neck, round-bottom flask equipped with mechanical stirrer, dropping funnel, and condenser were charged 123 g. (1.5 moles) of cyclohexene (Eastman, redistilled, b.p. 82°), 800 g. (25 moles) of methanol, and 10 g. of tungstic acid (North Metal and Chemical Co.). The mixture was warmed with stirring to 40° and 38 g. (1.0 mole) of 90% hydrogen peroxide was added dropwise[10]

(5) R. R. Read and R. M. Freer, *J. Am. Chem. Soc.*, **48**, 1401 (1926).

(6) A. Byers and W. J. Hickinbottom, *J. Chem. Soc.* 1328 (1948).

(7) *Trans*-1,2-cyclohexanediol is reported not to form an isopropylidene derivative. *Cf.* B. Rothstein, *Ann. chim.*, **14**, 461 (1930).

(8) In the present investigation there was detected none of the allylic type of oxidation found in the vanadium-catalyzed reaction; see W. Treibs, G. Franke, G. Leichsenring, and H. Roder, *Ber.*, **86**, 616 (1953).

(9) All melting points are corrected.

(10) See E. S. Shanley and F. P. Greenspan, *Ind. Eng. Chem.*, **39**, 1536 (1947) for a discussion of the potential hazards involved in the use of high strength hydrogen peroxide.

over a 1-hr. period at 45–50°. After completion of the addition, the mixture was warmed at the same temperature for 2 hr. longer. Iodometric titration then indicated the complete consumption of peroxide. After cooling, the precipitated catalyst was removed by filtration and the filtrate was distilled through a 1 × 50 cm. glass helices packed column. After removal of solvent and recovered cyclohexene (amount not determined), 2-methoxycyclohexanol, b.p. 122–124° (100 mm.), n_D^{20}, 1.4595 (reported[11] b.p. 181°, n_D^{20} 1.4605), was obtained in the amount of 91 g. (70% based on hydrogen peroxide). Bottoms from the distillation (27 g.) were triturated with 100 ml. of cold ether and the insoluble solid was collected by filtration. The yield of *trans*-1,2-cyclohexanediol thus obtained was 18 g. (16% based on hydrogen peroxide), m.p. 103–103.5° (reported[7] m.p. 104°).

Anal. Calcd. for $C_6H_{12}O_2$: α-glycol value, 0.86 equiv./100 g. Found: 0.85 equiv./100 g.

2-Ethoxycyclohexanol. The preparation was carried out exactly as above using ethanol in place of methanol. The yield of diol was 36% and the yield of 2-ethoxycyclohexanol was 41%, b.p. 65–67° (4 mm.), n_D^{20} 1.4562 (reported[11] b.p. 187°, n_D^{20} 1.4563).

2-Isopropoxycyclohexanol. Substitution of isopropanol in the above reaction afforded a 44% yield of diol and a 21% yield of 2-isopropoxycyclohexanol, b.p. 94–96° (20 mm.), n_D^{20} 1.4506.

Anal. Calcd. for $C_9H_{18}O_2$: C, 68.3; H, 11.5; hydroxyl value, 0.63 equiv./100 g. Found: C, 68.1; H, 11.4; hydroxyl value, 0.64 equiv./100 g.

Hydroxylation of cyclohexene in tert-butyl alcohol. To a stirred mixture of 123 g. (1.5 moles) of cyclohexene, 5 g. of tungstic acid, and 1850 g. (25 moles) of *tert*-butyl alcohol held at 40° was added dropwise[10] over 10 min. 38 g. (1.0 mole) of 90% hydrogen peroxide. The reaction maintained temperature at 46–47° for 20 min. and then slowly rose to 60°; it was held there by intermittent cooling. When the reaction was no longer exothermic, heat was applied to maintain 60°. After a total time of 2 hr. at 60°, iodometric titration indicated the presence of 20 mole % of an organic hydroperoxide (negative test with ammonium molybdate for free hydrogen peroxide[12]). After filtration to remove suspended catalyst, excess olefin (0.53 mole by bromine titration of total distillate), *tert*-butyl alcohol, and water were removed by Claisen distillation to a head temperature of 100°. The residual crude diol was distilled through a 1 × 50 cm. packed column to give 8 g. of volatile product, b.p. 58–68° (20 mm.), and 80 g. of residual crude *trans* 1,2-cyclohexanediol (70% purity by α-glycol value). The yield of diol (100% basis) was 50% based on unrecovered cyclohexene.

A sample of the volatile product was converted to a deep red 2,4-dinitrophenylhydrazone with a melting point constant at 202–204° (dec.) after 2 recrystallizations from ethyl acetate. An authentic sample of 1-cyclopentenecarboxaldehyde[13] was converted to its 2,4-dinitrophenylhydrazone, m.p. 206–208° (dec.).[14] The mixed melting point was 202–204° (dec.). In view of the slight disparity in melting points, the sample melting at 202–204° was analyzed.

Anal. Calcd. for $C_{12}H_{12}N_4O_4$: C, 52.2; H, 4.4; N, 20.3. Found: C, 51.8; H, 4.3; N, 20.0.

Hydroxylation of cyclohexene in acetone. (A) *with 34% hydrogen peroxide.* A mixture of 123 g. (1.5 moles) of cyclohexene, 5 g. of tungstic acid, and 100 g. (1.0 mole) of 34% hydrogen peroxide in 500 ml. in acetone was stirred under gentle reflux (50°) for 4 hr. The reaction maintained temperature for the first 2 hr. After removal of solvent and excess olefin, the residue was shaken with a mixture of 500 ml. of water (A) and 200 ml. of ether (B) and allowed to separate. The water layer (A) was concentrated under vacuo at 50° to a constant weight of 63 g. After a wash with cold ether there was obtained 57 g. of *trans*-1,2-cyclohexanediol, m.p. 100–103° (49% based on hydrogen peroxide). The original ether solution (B) was dried over magnesium sulfate and concentrated on the steam bath to an internal temperature of 50°. Claisen distillation afforded 20 g. (23%) of 2,2-dimethyl-1,3,4-trioxa-*trans*-decalin, b.p. 55–63° (2 mm.). Redistillation through a 1 × 50 cm. packed column afforded 15 g. of analytically pure peroxide, b.p. 42–44° (1 mm.), n_D^{20} 1.4624. It did not explode when heated on a steel spatula in a free flame.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.8; H, 9.4; O, 27.8; mol. wt. 172. Found: C, 62.6; H, 9.4; O, 27.4; mol. wt. 170 ± 3.

A 0.791-g. sample was shaken in the dark for 0.5 hr. with a mixture of 250 ml. of 30% sulfuric acid and 100 ml. of 20% potassium iodide. Titration with 89.3 ml. of 0.0966*N* sodium thiosulfate indicated a peroxide value of 1.12 equiv./100 g. (theory, 1.16 equiv./100 g.).

The *2,4-dinitrophenylhydrazone* of *1-cyclopentenecarboxaldehyde* (VII) was obtained by boiling for 0.5 hr. equimolar amounts of cyclic peroxide VIII and 2,4-dinitrophenylhydrazine in ethanolic hydrochloric acid; m.p. 204–206° (dec.), mixed m.p. not depressed.

The *bis-(2,4-dinitrophenylhydrazone)* of *adipaldehyde* was obtained by warming a sample of cyclic peroxide in ethanolic hydrochloric acid for 5 min. followed by a 3-min. boiling of that solution with 2.5 molar equivalents of added 2,4-dinitrophenylhydrazine; m.p. 229° (dec.) after trituration with hot ethyl acetate (reported[15] m.p. 227° with dec.); mixed m.p. not depressed.

(B) *With 90% hydrogen peroxide.* When the hydroxylation of cyclohexene was carried out as above using 90% hydrogen peroxide in place of the 34% reagent, there was obtained a 48% yield of diol and a 40% yield of crude cyclic peroxide, b.p. 44–59° (1 mm.), n_D^{20} 1.4582. The latter material, on attempted redistillation through a column afforded an initial cut which contained a substantial amount of an explosive solid peroxide, m.p. 95–98°, thought to be trimeric acetone peroxide.[16] The distillation was halted at that point in view of the hazard involved in handling such a material (it detonated when struck sharply with a hammer).

Hydrogenation of 2,2-dimethyl-1,3,4-trioxa-trans-decalin. A solution of 8.6 g. (0.05 mole) of the cyclic peroxide VIII in 100 ml. of methanol was treated with 1 g. of 10% palladium-on-charcoal and shaken at a starting pressure of 50 pounds of hydrogen. In 3 min. one molar equivalent of hydrogen was consumed as the reaction temperature rose from 25° to 50°. During another hour at 30° the hydrogen uptake remained unchanged. The catalyst was removed by filtration and the filtrate stirred for 1 hr. with 20 ml. of water and 10 g. of IR-120 ion exchange resin. After decantation from the resin, the solution was concentrated to a solid residue of *trans*-1,2-cyclohexanediol, m.p. 101–102°. Distillate from the concentration was converted to the 2,4-dinitrophenylhydrazone of acetone, m.p. 122–123°, mixed m.p. not depressed.

Cyclic peroxide VIII *from 1,2-epoxycyclohexane.* To a 1-l., 3-neck, round-bottom flask equipped with thermometer, stirrer, condenser, and dropping funnel were charged 500 ml. of acetone and 5 g. of tungstic acid catalyst. To the stirred suspension was added dropwise[10] 19 g. (0.50 mole) of 90% hydrogen peroxide over a 5-min. period. The mixture was warmed to 55° with stirring and 49 g. (0.50 mole) of 1,2-epoxycyclohexane[17] was added over a 20-min. period

(11) M. Mousseron and R. Granger, *Compt. rend.* **205**, 327 (1937).

(12) G. Chavanne and E. Bode, *J. Am. Chem. Soc.* **52**, 1609 (1930).

(13) J. B. Brown, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 3634 (1950).

(14) M. S. Kharasch and J. G. Burt, *J. Org. Chem.*, **16**, 150 (1951), report m.p. 210–211° for this derivative.

(15) F. Weygand, G. Eberhardt, H. Linden, F. Schaefer and I. Eigen, *Angew. Chem.* **65**, 525, (1953).

(16) R. Wolffenstein, *Ber.*, **28**, 2265 (1895) reported m.p. 97°.

(17) Prepared from cyclohexene and peracetic acid in chloroform by the procedure of B. A. Arbusow and B. M. Michailow, *J. prakt. Chem.*, **127**, 1 (1930).

with cooling to maintain the temperature at 55°. After completion of the addition, the mixture was allowed to stir for 4 hr. at 55–58°. One gram of 5% palladium-on-charcoal was then added to decompose any unreacted hydrogen peroxide, and the mixture was allowed to cool to room temperature overnight. After filtration to remove tungstic acid and palladium-on-charcoal catalysts, the bulk of the acetone was removed under vacuo at 50°. The concentration was halted when crystalline diol started to precipitate. The resultant crude product was shaken with a mixture of 250 ml. each of water (A) and ether (B). Concentration of the water layer (A) afforded 19 g. of crude *trans* diol from which 14 g. (24%) of pure product, m.p. 103–103.5°, was secured by washing with cold ether. Ether extract (B) was dried over magnesium sulfate and concentrated on the steam bath, taking care to hold the internal temperature below 50°. From this concentrate, after standing overnight at room temperature, was obtained by decantation 10 g. of moist crystalline peroxide. The latter was tentatively identified as trimeric acetone peroxide by its m.p. 94–98° and by its explosive behavior.[16] In view of the hazard involved in handling this peroxide, the moist 10 g. were discarded without further investigation. Another 3 g. of explosive peroxide were precipitated by dilution of the residual concentrate with Skellysolve B followed by chilling to 0°. Removal of solvent from the resulting filtrate, followed by Claisen distillation at 1 mm. afforded 27 g. of crude VIII, b.p. 40–48°. Since the latter still appeared to be contaminated with crystalline explosive peroxide, it was analyzed for VIII content by hydrogenation as described above. The 11 g. of *trans*-1,2-cyclohexanediol, m.p. 103–103.5°, thus obtained indicated a 20% yield of VIII.

Acknowledgment. The authors wish to acknowledge the original isolation of the peroxy cyclic ketal by Mr. E. R. Bell of these laboratories.

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Notes

A department for short papers of immediate interest.

Iodinated Benzamidotetrazoles

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Many iodinated benzoic acids have been prepared to be used as x-ray diagnostic agents. One of the main difficulties is to obtain a compound that is both soluble and non-toxic. In an attempt to accomplish this, several iodinated benzoic acids were converted to the corresponding iodinated benzamidotetrazoles *via* their acid chlorides.

Ettel and Nosek[1] have prepared several substituted benzamidotetrazoles by this method but none containing iodine.

EXPERIMENTAL[2]

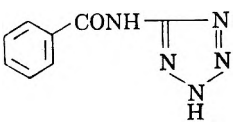
All of the iodinated benzoic acids were prepared as reported by Goldberg.[3]

Iodinated benzamidotetrazole. A mixture of iodinated benzoic acid (0.1 mole) and thionyl chloride (300 ml.) was heated under reflux for 1 hr. The resultant clear yellow solution was evaporated to dryness on a steam bath under vacuum. The residue was crystallized from *n*-heptane. Yields of the acid chloride were nearly quantitative.

Equimolar amounts of the acid chloride and 5-aminotetrazole were suspended in dry benzene (100 ml. benzene/0.01 mole tetrazole) and refluxed for 24 hr. During this time a fine white crystalline precipitate formed which was collected and washed well with water. It was dissolved by suspending in water and adding an equivalent of sodium hydroxide. After decolorizing with charcoal and filtering, the solution was acidified with acetic acid and the white product collected and dried in a vacuum oven at 110° C. Fifty to seventy-five percent yields were obtained.

The solubilities of the sodium salts of the tetrazoles were found to be equal to or greater than those of the corresponding sodium salts of the iodinated benzoic acids.

TABLE I
IODINATED BENZAMIDOTETRAZOLES



Substituents	M.P., °C.	Formula	Carbon		Hydrogen		Iodine		Toxicities[a] ALD$_{50}$	
			Calcd.	Found	Calcd.	Found	Calcd.	Found	T	B
3,4-Diiodo-	266.7–27[illegible].3	$C_8H_5I_2N_5O$	21.78	21.89	1.14	1.99	57.57	57.00	>200	225
3,5-Diiodo-	295.8–297.7	$C_8H_5I_2N_5O$	21.78	21.64	1.14	1.61	57.57	58.10	300	180
2,5-Diiodo-	>300	$C_8H_5I_2N_5O$	21.78	21.77	1.14	1.33	57.57	57.90	900	500
3,5-Diiodo-4-hydroxy-	252.0–258.0	$C_8H_5I_2N_5O_2$	21.02	21.13	1.10	1.11	55.54	55.20	950	750
3,5-Diiodo-2-hydroxy-	234.4–234.9	$C_8H_5I_2N_5O_2$	21.02	20.96	1.10	1.30	55.54	55.30	300	...
3,5-Diiodo-2-methoxy-	243.2–243.6	$C_9H_7I_2N_5O_2$	22.95	23.13	1.50	1.88	53.90	53.60	360	360
3,5-Diiodo-4-methoxy-	224.5–228.0	$C_9H_7I_2N_5O_2$	22.95	23.10	1.50	1.47	53.90	53.80	450	300
3,4,5-Triiodo-	>300	$C_8H_4I_3N_5O$	16.95	17.26	0.71	0.94	67.17	66.70	250	>160
2,3,5-Triiodo-	>300	$C_8H_4I_3N_5O$	16.95	16.74	0.71	0.84	67.17	66.30	250	>200

[a] Toxicities were run in mice intravenously. The column headed by T shows the toxicities of the tetrazoles and the column headed by B shows the toxicities of the corresponding iodinated benzoic acids.

When administered intravenously as the sodium salt to cats at dose levels of 200–400 mg./kg. of body weight, the gall bladder was outlined in x-ray photographs.

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(1) V. Ettel and J. Nosek, *Coll. Czechoslov. Chem. Communs.*, **15**, 335 (1950).

(2) All melting points are corrected. Analyses were carried out by Messrs. M. E. Auerbach, K. D. Fleischer, and staff.

(3) A. Goldberg *et al.*, *Quart. J. and Yearbook of Pharmacy*, **19**, 483 (1946).

N-Substitution Products of 2-Aminomethyl-1,4-benzodioxane

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Benzodioxane and phenyl alkylamine ethers are among the classes of compounds which have been shown to exhibit adrenergic blocking activity.[2–4] In the search for a more nearly perfect sympatholytic drug, an investigation was initiated on a series of compounds which link 2-methyl-1,4-benzodioxane with a phenyl alkylamine ether. Several *N*-substitution products of 2-aminomethyl-1,4-benzodioxane have been previously synthesized. *N*,*N*-Diethyl- and *N*-methyl-2-aminomethyl-1,4-benzodioxane have been prepared by heating diethylamine and methylamine respectively with 2-chloromethyl-1,4-

(1) Present address: The Dow Chemical Co., Midland, Mich.

(2) D. Bovet and A. Simon, *Compt. Rend. Biol.*, **116**, 842 (1934).

(3) D. Bovet and A. Simon, *Arch. Intern. Pharmacodynamic*, **55**, 15 (1937).

(4) R. B. Barlow, *Introduction to Chemical Pharmacology*. John Wiley and Sons, Inc., New York, N. Y., 1955, p. 242.

benzodioxane under pressure for 5 hr. at 140–150°.[5] These two compounds were also synthesized by heating the same reactants in a sealed tube at 175° for 2 hr.[6] 2-(1-Piperidyl)methyl-1,4-benzodioxane[7] was prepared by treating piperidine with 2-chloromethyl-1,4-benzodioxane. 2-(Tetrahydro-*p*-oxazinyl)methyl-1,4-benzodioxane[8] was prepared by heating 2-chloromethyl-1,4-benzodioxane with morpholine in an autoclave at 150° for 10–12 hr. Only a few preparations have been described for substitution products of 2-aminomethyl-1,4-benzodioxane which have two dissimilar groups attached to the nitrogen. Kerwin[9] prepared *N*-(2-hydroxyethyl)-*N*-ethyl-2-aminomethyl-1,4-benzodioxane by refluxing 2-ethylaminoethanol and 2-chloromethyl-1,4-benzodioxane in xylene for 13.5 hr. The chloro derivative was obtained by treating the reaction product with thionyl chloride. Kerwin also prepared *N*-benzyl, *N*-methylallyl, and *N*-cyclohexyl derivatives of *N*-(2-hydroxyethyl)-2-aminomethyl-1,4-benzodioxane by similar methods.

A tabulation of *N*-substitution products of 2-aminomethyl-1,4-benzodioxane reported in the literature to date reveals 31 such compounds of a secondary or tertiary type. All the compounds were prepared by the reaction of 2-chloromethyl-1,4-benzodioxane with an amine. Grum[10] has reported that the ester of an organic acid and 2-hydroxymethyl-1,4-benzodioxane will react with amines to form these products.

The preparation of reasonably pure secondary amines by the reaction of a halide and amine is subject to the disadvantage that some higher substitution inevitably occurs. Wheeler and Wilson[11] have outlined a procedure for *N*-phenylbenzylamine which minimizes disubstitution. This is accomplished by slowly adding the halide to a large excess of amine. In addition to inhibiting disubstitution, the excess primary amine ties up the hydrogen halide liberated by the reaction.

This study is concerned with the development of a procedure for the synthesis of a series of tertiary amines having a *N*-substituted alkyl aryl ether on *N*-benzyl-2-aminomethyl-1,4-benzodioxane. Specifically, the object was to synthesize and characterize *N*-benzyl-2-aminomethyl-1,4-benzodioxane, *N*-(2-phenoxyethyl)-*N*-benzyl-2-aminomethyl-1,4-benzodioxane, and *N*-(2-*o*-toloxyethyl)-*N*-benzyl-2-aminomethyl-1,4-benzodioxane. Suitable starting materials for these syntheses appeared to be 2-chloromethyl-1,4-benzodioxane,[6] 2-phenoxyethyl bromide,[12] 2-*o*-toloxyethyl bromide,[12] and benzyl amine, the first three of which were prepared by published methods and the fourth is readily available commercially. As a result *N*-benzyl-2-aminomethyl-1,4-benzodioxane has been synthesized and characterized for the first time. The formation and characterization of two derivatives of the same, namely the benzoyl and the benzenesulfonyl, further support the identification of the compound. Two corresponding tertiary amines, *i.e.*, the 2-phenoxyethyl and 2-*o*-toloxyethyl are also reported for the first time.

The preparation of *N*-benzyl-2-aminomethyl-1,4-benzodioxane was also attempted by the use of inert organic solvents, *i.e.*, ether and toluene, but results were less satisfactory. The reactant, benzylamine, was found to be the most satisfactory solvent for the reaction. The excess benzylamine combined with the hydrogen chloride liberated in the reaction, thus eliminating the need for an additional base in the reaction mixture, and greatly simplified the isolation of the desired compound. Separation of the excess primary and desired secondary amine was facilitated by the relative insolubility of the hydrochloride salt of *N*-benzyl-2-aminomethyl-1,4-benzodioxane in cold water. Little residue was left after distillation of the secondary amine, indicating that the formation of a tertiary amine was negligible under the conditions employed. *N*-Benzyl-2-aminomethyl-1,4-benzodioxane reacted, at room temperature, with benzoyl chloride and benzenesulfonyl chloride without the addition of another base. However, satisfactory yields were not obtained until the reaction mixtures were heated and an excess of the acid halides were used.

N-Benzyl-2-aminomethyl-1,4-benzodioxane was found to be a suitable intermediate for the synthesis of *N*-(2-phenoxyethyl)-*N*-benzyl-2-aminomethyl-1,4-benzodioxane and *N*-(2-*o*-toloxyethyl)-*N*-benzyl-2-aminomethyl-1,4-benzodioxane. When an excess of the parent secondary amine was stirred with phenoxyethyl bromide or *o*-toloxyethyl bromide, a reaction took place as soon as the temperature of the mixture reached 100°, and was complete after 6 hr. More drastic conditions produced some decomposition and less drastic resulted in incomplete reaction. The addition of another organic base to combine with the hydrogen bromide liberated in the reaction should increase the yield of tertiary amine in terms of the parent secondary amine. In the procedure employed, however, the hydrobromide salt of *N*-benzyl-2-aminomethyl-1,4-benzodioxane is easily recovered for reuse and the purification of the final tertiary amine is greatly simplified.

The viscous oil consistency of *N*-(2-phenoxyethyl)-*N*-benzyl-2-aminomethyl-1,4-benzodioxane and *N*-(2-*o*-toloxyethyl)-*N*-benzyl-2-aminomethyl-1,4-benzodioxane make final purification by recrys-

(5) E. Fourneau, Mm. de Lestrange, and P. Maderni, *J. Pharm. chim.*, 18, 185 (1933).

(6) J. Trefouel, Mme. J. Trefouel, and Y. Dunant, *Bull. Sci. Pharmacol*, 42, 459 (1935).

(7) E. Forneau, U. S. Patent, 2,056,046 (1936).

(8) A. Green, U. S. Patent 2,366,102 (1944).

(9) J. F. Kerwin, U. S. Patent 2,551,013 (1951).

(10) A. Grum, U. S. Patent 2,366,102 (1944).

(11) T. Wheeler and T. Wilson, *Org. Syntheses*, **Coll. Vol. I**, 102 (1941).

(12) C. S. Marvel and A. L. Tannenbaum, *Org. Syntheses*, **Coll. Vol. I**, 436 (1941).

tallization from common organic solvents impractical. Distillation of these compounds had to be performed below 1 mm. to prevent decomposition.

As a result of this study, five new secondary or tertiary amines and related derivatives have been prepared and characterized for the first time. The findings also indicate that other *N*-substituted alkyl-aryl ether derivatives of *N*-benzyl-2-aminomethyl-1,4-benzodioxane can be prepared by the method developed in the preparation of the original members of this series.

EXPERIMENTAL

N-Benzyl-2-aminomethyl-1,4-benzodioxane. A 36.8 g. (0.2 mole) portion of 2-chloromethyl-1,4-benzodioxane was added dropwise with stirring, under reflux, during 2.5 hr. to 85.6 g. (0.8 mole) of benzylamine; the mixture was refluxed an additional 1.5 hr., and then cooled to room temperature. Upon the addition of 200 g. of 6*N* hydrochloric acid, a precipitate of secondary amine hydrochloride was obtained. This precipitate was collected and washed with water and ether to remove the excess benzylamine hydrochloride and other impurities. The crude product was then recrystallized from hot water. The free secondary amine was obtained as a viscous oil by neutralization of the hydrochloride salt with sodium bicarbonate. The oil was extracted with ether and the ether then removed by evaporation. The residue was distilled at 180–200° in a Hickmann molecular still at 1 mm. pressure. The yield was 36 g. (70.5%) of a clear viscous liquid with d_4^{25} of 1.1448 and n_D^{25} of 1.5773. Upon prolonged cooling the compound solidified to a white crystalline product, melting at 41°.

Anal. Calcd. for $C_{16}H_{17}O_2N$: C, 75.3; H, 6.67; N, 5.59; M.R., 74.7; mol. wt. 255. Found: C, 75.6; H, 6.98; N, 5.49; M.R. 75.6; mol. wt. 253.

The hydrochloride salt melted at 185° and the hydrobromide salt melted at 214°.

The benzoyl and the benzenesulfonyl derivatives of *N*-benzyl-2-aminomethyl-1,4-benzodioxane, were prepared for further characterization of the above compound. A 5.1 g. (0.02 mole) portion of *N*-benzyl-2-aminomethyl-1,4-benzodioxane was stirred for 0.5 hr. with 5.2 g. (0.04 mole) of benzoyl chloride at 100°, 30 ml. of 10% aqueous sodium hydroxide was then added and the heating continued for an additional 1.5 hr. Upon cooling, the sodium hydroxide solution was decanted, and the remaining precipitate was washed three times with 30 ml. portions of 10% aqueous sodium hydroxide. The remaining product was dissolved in 30 ml. of ether, the solution washed first with 6*N* hydrochloric acid and then with water, and finally dried over anhydrous sodium sulfate. The resulting solution was filtered, the ether evaporated, and the residue distilled at 0.05 mm. in a Hickmann molecular still, at 250–60°, yielding a slightly yellow, extremely viscous oil that solidified below −5°, and had n_D^{25} of 1.5895.

Anal. Calcd. for $C_{23}H_{21}O_3N$: C, 76.88; H, 5.85; N, 3.90; mol. wt. 359. Found: C, 76.53; H, 5.56; N, 4.19; mol. wt. 353.

The benzenesulfonyl derivative was similarly prepared by stirring 5.1 g. (0.02 mole) of *N*-benzyl-2-aminomethyl-1,4-benzodioxane at 100° for 0.5 hr. with 7.1 g. (0.04 mole) of benzenesulfonyl chloride. Thirty ml. of 10% aqueous sodium hydroxide was then added and the heating continued for an additional 1.5 hr. Upon cooling, the sodium hydroxide solution was decanted, and the residue washed three times with 30 ml. portions of 10% aqueous sodium hydroxide. The remaining product was dissolved in 30 ml. of ether, the solution washed first with 6*N* hydrochloric acid, then with water, and finally the ether evaporated. The residue changed from a yellow oil to a white crystalline product when warmed with ethanol. The crystals were triturated several times with ethanol and water and dried, yielding a final derivative melting at 84°.

Anal. Calcd. for $C_{22}H_{21}O_4N$: C, 66.84; H, 5.32; N, 3.54; mol. wt. 395. Found: C, 66.86; H, 5.24; N, 3.73; mol. wt. 399.

N-(2-Phenoxyethyl)-N-benzyl-2-aminomethyl-1,4-benzodioxane. A 10.8 g. (0.04 mole) portion of *N*-benzyl-2-aminomethyl-1,4-benzodioxane and 6 g. (0.03 mole) of phenoxyethyl bromide was heated with stirring at 120° for 6 hr. The reaction mixture was then cooled and triturated with ether and the ether mixture filtered to remove the hydrobromide salt of *N*-benzyl-2-aminomethyl-1,4-benzodioxane. Upon the addition of 20 ml. of 6*N* hydrochloric acid, the hydrochloride salt of *N*-(2-phenoxyethyl)-*N*-benzyl-2-aminomethyl-1,4-benzodioxane separated from the ether as a slightly yellow, very viscous oil. After the salt had been washed with water and ether, it was heated in water and treated with sodium bicarbonate to release the free amine. The free amine was extracted from the mixture with ether, the ether solution washed with water, dried over anhydrous sodium sulfate and filtered. The ether was distilled off, and the residue distilled at 220–240°, in a Hickmann molecular still at 0.05 mm., yielding a pale yellow viscous liquid with n_D^{27} of 1.5820, and d_4^{27} of 1.1415 and which solidified to a white crystalline solid on prolonged standing and melted at 43°.

Anal. Calcd. for $C_{24}H_{25}O_3N$: C, 76.80; H, 6.67; N, 3.73; M.R. 108.9; mol. wt. 375. Found: C, 76.97; H, 6.87; N, 3.38; M.R. 108.76; mol. wt. 372.

N-(2-o-Toloxyethyl)-N-benzyl-2-aminomethyl-1,4-benzodioxane. This compound was prepared and purified by a procedure similar to that described immediately above for N-(2-phenoxyethyl)-N-benzyl-2-aminomethyl-1,4-benzodioxane, except *o*-toloxyethyl bromide was used in place of phenoxyethyl bromide. The product was a pale yellow viscous oil, with a n_D^{27} of 1.5790, and d_4^{27} of 1.1342.

Anal. Calcd. for $C_{25}H_{27}O_3N$: C, 77.12; H, 6.94; N, 3.60; M.R., 113.5; mol. wt. 389. Found: C, 77.47; H, 6.55; N, 3.32; M.R., 112.7; mol. wt. 384.

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Studies in the Pyrazole Series. IX.[1] Aminolytic and Substitution Reactions of 3,5-Dimethyl-1-(*N*,*N*-diphenylcarbamyl)-pyrazole

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While the solvolytic deacylation reactions of 1-guanyl- and related pyrazoles[1] have been ascribed to a so-called $B_{AC}2$ type[3] mechanism, no unequivocal evidence has been obtained to exclude from

(1) Part VIII: F. L. Scott, *J. Org. Chem.*, 22, 1568 (1957).

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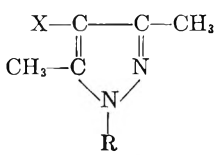
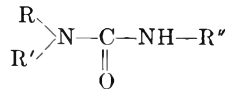
(3) See C. K. Ingold, *Structure and Mechanisms in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, pp. 752 *et seq.*, wherein the $B_{AC}2$ mechanism is defined as a base-induced bimolecular hydrolysis of esters with acyl scission.

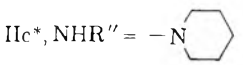
consideration mechanisms involving anionic intermediates such as Ia. The present work was an effort to demonstrate that at least such deacylations need not *necessarily* involve the formation of anionic intermediates, and that the $B_{AC}2$ type mechanism can be sufficiently effective therein. Accordingly, the prototype (Ib) of a new class of pyrazoles, *viz.*, the 1-(*N*,*N*-diphenylcarbamyl) type, wherein the formation of such intermediates as Ia is structurally prohibited, was synthesized and its solvolysis reactions were examined. It proved extremely resistant to ethanolysis,[4] to base-induced hydrolysis by either acetate or hydroxide ions, and to aminolysis by a variety of bases in ethanolic solution. However, use of certain bases as both solvents and reactants did effect decarbamylation of Ib. Thus, when Ib was refluxed for 1 hr. in a 20-molar proportion of either *n*-amylamine or *n*-butylamine, without further solvent, it afforded the corresponding 1,1-diphenyl-3-alkylureas (IIa and b) in 85 and 75% yields, respectively, as well as 3,5-dimethylpyrazole (Ic) in 80% yields. These successful aminolyses clearly demonstrate that the solvolytic deacylation of 1-acylpyrazoles can occur without the necessary intervention of an anionic intermediate.[5] Even under these forcing conditions, Ib remained relatively unreactive, however. Thus it was



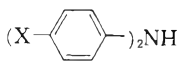
Ia*, R = C(=NH)—$\overset{\ominus}{N}$—R′
Ib*, R = C(=O)—N(C_6H_5)$_2$
Ic*, R = H
Id*, R = C(=O)—NHR′, where R′ = NH_2 or $CH_2C_6H_5$
Ie, X = Cl, R = C(=O)—N(C_6H_5)$_2$
If, X = Br, R = H
Ig, X = Br, R = C(=O)—N(C_6H_5)$_2$
Ih, X = I, R = C(=O)—N(C_6H_5)$_2$
Ij, X = I, R = H
Ik*, R = C(=O)—N($C_6H_4NO_2$—*p*)$_2$
Il, X = Br, R as in Ik
Im*, R = C(=O)—N($C_6H_4NH_2$-*p*)$_2$
Those symbols starred (*) have X = H



IIa*, R″ = *n*-C_5H_{11}
IIb*, R″ = *n*-C_4H_9



IIc*, NHR″ = $-N$⬡
IId*, R″ = NH_2
IIe, R = R″ = $CH_2C_6H_5$, R′ = H
IIf*, R″ = $CH_2C_6H_5$
Those symbols starred (*) have R = R′ = C_6H_5



IIIa, X = H
IIIb, X = NO_2

unaffected after one hour's refluxing in such bases as aniline, cyclohexylamine, morpholine, or phenylhydrazine. In piperidine as solvent, Ib gave a 30% yield of Ic while only a trace quantity of the expected piperidyl derivative (IIc) was isolated. While this lack of aminolytic reactivity of Ib may be due to its inability to receive base-catalysis, its stability could also be due to steric effects, the three bulky rings inhibiting the $B_{AC}2$ reaction of the central carbonyl group.[6]

Two anomalous reactions were encountered in the aminolyses of Ib. Thus, when refluxed in hydrazine, hydrate solution Ib did not yield the expected 4,4-diphenylsemicarbazide (IId) but gave instead a 95% yield of diphenylamine (IIIa), as well as 80% Ic. However, we found that under identical conditions IId itself is quantitatively hydrazinolyzed to diphenylamine. Secondly when refluxed in benzylamine Ib afforded 1,3-dibenzylurea (IIe) in 70% yield. However, under similar conditions, the anticipated product 1,1-diphenyl-3-benzylurea (IIf) also readily aminolyzes to IIe.[7] Hence both of these reactions are still not inconsistent with the operation of a preliminary $B_{AC}2$ reaction of Ib. Whether this involved the expulsion of pyrazolide ion with the production of a substituted urea, or the expulsion of diphenylamide ion to yield initially a 1-(*N*-substituted carbamyl)pyrazole such as Id, followed by its further aminolysis,[8,9] has not been established.

(4) After maintaining a solution of Ib in ethanol for 28 days at 75.0°C., its spectral characteristics were preserved within the following limits, λ_{max} 236 (±0.9) mμ, ϵ_{max} 16,830 (±340). The absorption spectrum of diphenylurethane is λ_{max} 238 mμ, ϵ_{max} 13,500. For further details of the kinetics of solvolysis (*sic*) of Ib and related substances, see F. L. Scott, *Chimia* (*Switz.*) **11**, 163 (1957) and F. L. Scott and R. Rubin, forthcoming paper in this series.

(5) This lability is most probably due to the anionic stability of pyrazolide ion. In related acyclic systems, this, or a comparable, labilizing moiety is absent and hence the necessity for base-catalysis therein. See D. G. Crosby and C. Niemann, *J. Am. Chem. Soc.*, **76**, 4458 (1954) for further discussions of such acyclic cases.

(6) See *e.g.*, F. H. Wetzel, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, **75**, 1150 (1953) and H. C. Brown, *J. Chem. Soc.*, 1248 (1956).

(7) This observation was made in a study of the aminolytic reactions of *N*,*N*-diphenylcarbamyl azide; see F. L. Scott and M. T. Scott, *J. Am. Chem. Soc.*, in press.

(8) We are indebted to a referee for a reminder of this fact.

(9) See F. L. Scott, D. G. O'Donovan, M. R. Kennedy, and J. Reilly, *J. Org. Chem.*, **22**, 820 (1957). The point under consideration is whether pyrazolide ion or another anion, *e.g.*, diphenylamide ion in the present instance, may compete for expulsion from the intermediary adduct of a $B_{AC}2$ process. A major determining factor ought to be the anionic stabilities of the competing moieties, which are of course reflected in the strengths of the corresponding conjugate acids. From available data in the literature the pK_a values for pyrazole and diphenylamine may be estimated as being 11–13 and 23, respectively. This would attribute to

We have commented elsewhere[9] on the general possibility of this latter reaction.

Some substitution reactions of Ib were also examined. Its reaction in chloroform with an excess of chlorine gave some of the corresponding 4-chloro-derivative (Ic) together with some resinous material whose structure was not further pursued. With bromine and iodine reaction was smoother and gave the corresponding monohalogenated derivatives in quantitative yields. The bromination product hydrazinolyzed, in an excess of hydrazine hydrate, to yield 4-bromo-3,5-dimethylpyrazole (If) and diphenylamine (IIIa) and was accordingly identified as 4-bromo-3,5-dimethyl-1-(*N*,*N*-diphenylcarbamyl)pyrazole (Ig). The iodination product was analogously regarded as Ih though its identification was rendered somewhat anomalous by the fact that its hydrazinolysis resulted in diphenylamine and largely 3,5-dimethylpyrazole,[10] only traces of 4-iodo-3,5-dimethylpyrazole (Ij) being detected. When Ib was nitrated under strongly acidic conditions, it afforded a dinitroderivative in 80% yield. This product hydrazinolyzed to Ic and 4,4′-dinitrodiphenylamine (IIIb) and was thereby itself recognized as 3,5-dimethyl-1-(*N*,*N*-4,′4″-dinitrodiphenylcarbamyl)pyrazole (Ik). When Ik was brominated and Ig was nitrated they were converted into a common product (Il), a result which further confirms the orientations offered. This difference in the behavior of Ib toward halogenation and nitration with exclusive heterocyclic reaction in the former process[11] and solely phenyl substitution in the latter[12] is attributable primarily to the deactivation by protonation of the substituted pyrazole nucleus under the strongly acidic nitration conditions. This deactivation is not realized to any appreciable extent under the mild acidities of the halogenation techniques adopted.

EXPERIMENTAL[13]

3,5-Dimethyl-1-(N,N-diphenylcarbamyl)pyrazole (Ib). To 2.0 g. of 4,4-diphenylsemicarbazide dissolved in 25 ml. of ethanol was added 0.8 ml. (1 molar equivalent) of freshly distilled acetylacetone. On allowing this solution to stand overnight at room temperature 1.65 g. of Ib separated. This after 2 recrystallizations from 95% ethanol melted at 134–135°.

Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.2; H, 5.8; N, 14.4. Found: C, 73.9; H, 5.7; N, 14.8.

A further quantity, 0.54 g. (total yield 85%), of Ib was obtained on work-up of the mother liquor. No change either in product or in yield was obtained when the reacting substances were refluxed together in ethanolic solution for 3 hours prior to the isolation of the product.

Aminolyses of Ib. (*1*) *In ethanolic or aqueous solution.* When Ib was refluxed with 1 molar equivalent of aniline, *n*-butylamine, *n*-hexylamine, hydrazine hydrate or phenylhydrazine for 30–60 min. in ethanolic solution, it was recovered in 90–100% yields. When it was refluxed for 2 hr. with an excess of 4*N* sodium acetate solution, or of 1*N* hydrochloric acid or of 2.5*N* sodium hydroxide solution it was quantitatively recovered.

(*2*) *In amines as solvents.* When Ib was dissolved in a 20-molar proportion of either aniline or phenylhydrazine, without additional solvent, the reaction liquor being maintained at 60° for 1 hr., Ib was recovered in 100 and 80% yields, respectively. With hydrazine hydrate as nucleophile under these conditions, 80% Ib was again recovered but also a 10% yield of 3,5-dimethylpyrazole (Ic) was obtained. The following example illustrates the final forcing technique adopted. To 2.0 g. of Ib was added 8 ml. of 85% aqueous hydrazine hydrate solution—this was a twenty-fold molar proportion of nucleophile—and the whole was then refluxed for 1 hr. This solution after being allowed to cool overnight on work-up yielded 1.10 g. (95% yield) of diphenylamine (IIIa), m.p. 54–55°, reported[14] m.p. 54°, whose mixture m.p. with an authentic sample was not depressed, and an 80% yield of 3,5-dimethylpyrazole (Ic), m.p. 105–106°, reported[15] m.p. 107°, similarly identified.[16] The expected main product in this reaction was not IIIa but 4,4-diphenylsemicarbazide (IId). The stability of the latter under the above conditions was then checked. It was hydrazinolyzed under the above treatment to IIIa in 98% yield. The other expected fragment, *i.e.*, carbohydrazide, was not isolated.

Under the above conditions, *n*-amylamine resulted in a 70% yield of Ic as well as an 85% yield of 1,1-diphenyl-3-*n*-amylurea (IIa), m.p. 70–71°, reported[17] m.p. 70–71°.

Anal. Calcd. for $C_{18}H_{22}N_2O$: C, 76.6; H, 7.8; N, 9.9. Found: C, 76.3; H, 7.5; N, 9.4.

When analogously treated, *n*-butylamine formed IIb and Ic in 75 and 60% yields, respectively. After recrystallization from aqueous ethanol, IIb melted at 93–94°.

Anal. Calcd. for $C_{17}H_{20}N_2O$: C, 76.1; H, 7.5; N, 10.4. Found: C, 75.6; H, 7.5; N, 9.9.

Finally, when Ib was similarly treated with benzylamine, except that a 90-min. reflux period was used, it resulted in a 75% yield of Ic and a 70% yield of 1,3-dibenzylurea (IIe), m.p. 164–166°, reported[18] m.p. 165–167°.

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 75.0; H, 6.7. Found: C, 75.0; H, 6.5.

Some related reactions. (a) When Ib was refluxed for 1-hr. periods without further solvent other than a 20-molar proportion of the following bases, aniline, cyclohexylamine, morpholine, phenylhydrazine, or piperidine it was recovered in 100, 100, 75, and 68% yields, respectively. Only with the last amine were some deacylation products detected, *viz.*, a

pyrazolide ion, an anionic stability greater by at least a factor of 10^{10} over diphenylamide ion and may help to explain the deacylation pattern of Ib.

(10) Compare L. F. Audrieth and B. A. Ogg, *The Chemistry of Hydrazine*, John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 134–9.

(11) Compare the halogenation of 1- and 3-phenylpyrazoles, A. Michaelis and G. Käding, *Ann.*, **373**, 202 (1900) and previous papers, and K. v. Auwers and B. Ottens, *Ber.*, 58, 2072 (1925).

(12) Compare K. v. Auwers and H. Mauss, *Ann.*, **452**, 182 (1927); E. Harrison, *J. Soc. Chem. Ind.*, **54**, 282T (1935); I. M. Kogan and D. F. Kutepov, *Zhur. Obshchei Khim.*, **21**, 1297 (1951).

(13) All melting points are uncorrected. All microanalyses are by Drs. Wieler and Strauss, Oxford, England.

(14) I. Heilbron and H. M. Bunbury, *Dictionary of Organic Compounds*, 4th ed., Eyre and Spottiswoode, London, 1953, p. 402.

(15) R. H. Wiley and P. E. Hexner, *Org. Syntheses*, **31**, 43 (1951).

(16) In all the aminolysis experiments wherein 3,5-dimethylpyrazole was obtained, it was identified both by mixture melting point with an authentic sample, and by mixture of its picrate with an authentic sample.

(17) Scott and Scott, *loc. cit.*

(18) P. P. Grad and R. J. Dunn, *Anal. Chem.*, **25**, 1211 (1953).

TABLE I

SUBSTITUTION PRODUCTS OF 3,5-DIMETHYL-1-(*N,N*-DIPHENYLCARBAMYL)PYRAZOLE

Reaction	Product	Molecular Formula	M.P., °C.	Yield, %	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Chlorination[a]	Ie[b,c]	$C_{19}H_{17}N_3Cl_4O$[d]	95–96	20	48.5	49.2	3.8	3.6	9.4	9.3[e]
Bromination[f]	Ig[g]	$C_{18}H_{16}N_3BrO$	147–148	98	58.4	58.3	4.3	4.3	11.4	11.4[h]
Iodination[i]	Ih[g]	$C_{18}H_{16}N_3IO$	167	98	51.8	51.7	3.8	3.6	10.1	10.1[j]
Nitration[k]	Ik[g,l]	$C_{18}H_{15}N_5O_5$	179–181	95	56.7	56.8	3.9	3.9	18.4	18.1
Reduction[m]	Im[n,l,o]	$C_{18}H_{20}N_5O_2$	247	20	63.9	64.3	5.9	5.4	20.7	20.1
Bromination[p]	II[g,q]	$C_{18}H_{14}N_5BrO_5$	186–188	85	47.0	47.2	3.0	2.8	15.2	15.1[r]

[a] Run in chloroform at room temperature, with an excess of gaseous chlorine. [b] Recrystallized from chloroform. [c] The main product was a colorless oil so far unidentified. [d] Contains 1 molecule of solvent of crystallization ($CHCl_3$). [e] Calcd.: Cl, 31.9; Found: Cl, 31.4. [f] Dropwise addition of an equimolar quantity of bromine to Ib dissolved in chloroform, with continuous stirring of the mixture. [g] Recrystallized from 95% ethanol. [h] Calcd.: Br, 21.6; Found: Br, 21.2. [i] By reaction of Ib in acetic acid with equimolar quantities of potassium iodide and potassium iodate, with 30 minutes reflux. Compare S. H. Tucker, *J. Chem. Soc.*, 546 (1926). After 13 hr. reflux of Ib with free iodine in aqueous ethanol, 82% was recovered, *ca.* 0.2% Ij was isolated and only 3% Ih. Reaction of Ib with iodine monochloride in glacial acetic acid was much more rapid, 70% Ih being isolated after 30 min. reflux, together with 30% Ib. [j] Calcd.: I, 30.5; Found: I, 30.4. [k] Effected by maintaining a solution of Ib in a mixture of concentrated nitric and sulfuric acids at 0° for 24 hr. and then pouring the liquor onto an excess of ice. When the nitration mixture was maintained at steam-bath temperatures for 4 hr. prior to quenching with ice, the yield of Ik fell to 80% and work-up of the filtrate revealed the formation of tars. No tars were detected in the experiment run at 0°C. [l] This was obtained as yellow microcrystals. [m] This involved reduction of Ik suspended in anhydrous ether by amalgamated aluminum foil over a period of 23 hr. at room temperature. Unchanged Ik was recovered in 60% yield. [n] Recrystallized from aqueous acetone. [o] Physical data are for the monohydrate. [p] This refers to bromination of Ik by the same technique as was used with Ib. The same product (II) is obtained (82% yield) by nitration of Ig. [q] Obtained as fine silken pale-green needles. [r] Calcd.: Br, 17.4; Found: Br, 17.4.

30% yield of Ic and a trace quantity (*ca.* 1%) of 1-(*N,N*-diphenylcarbamyl)piperidine (IIc), m.p. 110°, reported[19] m.p. 110°. (b) The following experiments were performed to emphasize the lack of reactivity of Ib. (1) A solution of 0.80 g. of 3,5-dimethyl-1-carbamylpyrazole[20] in 10.4 ml. of aniline was refluxed for 1 hr. It was then allowed to stand for 24 hr. and deposited a quantitative yield (1.06 g.) of 1,3-diphenylurea, m.p. 239°, reported[21] m.p. 238–239° which did not depress the melting point of an authentic sample. From the residual liquor a 70% yield of Ic was isolated. (2) After dissolving 0.80 g. of 3,5-dimethyl-1-(*N*-phenylcarbamyl)pyrazole[22] in 6.8 ml. of aniline, the solution was similarly treated as in (1) above and afforded identical results. (3) Analogously treated Ib was quantitatively recovered.

Substitution reactions of Ib. Because the techniques employed in the halogenation and nitration reactions of Ib are more or less standard, the synthetic procedures have been condensed in Table I. The following are some additional comments.

(a) When 1.0 g. of Ig was refluxed for 1 hr. in 3.0 ml. of 85% hydrazine hydrate solution, it afforded on cooling and subsequent work-up a mixture of 0.42 g. (91% yield) of diphenylamine, m.p. 54–55°, reported[14] m.p. 54°, mixture m.p. with an authentic sample 54–55°, and 0.40 g. (85% yield) of 4-bromo-3,5-dimethylpyrazole (If), m.p. 117–118°, reported[23] m.p. 118°, which also did not depress the m.p. of an authentic sample, on mixture m.p. determination.

(b) When Ih was analogously hydrazinolyzed, it resulted in a quantitative yield of diphenylamine, a 23% yield of Ic and only traces of Ij, identified by mixture m.p. with an authentic sample.[23] (c) When a sample of the dinitro product (Ik) was refluxed in 3.0 ml. of 85% aqueous hydrazine hydrate solution for 1 hour, the resulting brown reaction liquor, on work-up, gave a 65% yield of Ic and an 80% yield of 4,4′-dinitrodiphenylamine (IIIb), m.p 212–214°, reported[24] m.p. 214°, identified by mixture m.p. with an authentic sample.

Anal. Calcd. for $C_{12}H_9N_3O_4$: C, 55.6; H, 3.5; N, 16.2. Found: C, 55.3; H, 3.8; N, 16.2.

Thus the dinitration product of Ib was identified as 3,5-dimethyl-1-(*N,N*-4′4″-dinitrodiphenylcarbamyl)pyrazole (Ik).

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(19) T. W. Evans and W. M. Dehn, *J. Am. Chem. Soc.*, 52, 3646 (1930).

(20) Prepared as described by Scott, *et al.*, ref. 9.

(21) Reported by Crosby and Niemann, *loc. cit.*

(22) Synthesized by the method of R. A. Henry and W. Dehn, *J. Am. Chem. Soc.*, 71, 2297 (1949).

(23) Prepared by the method of G. T. Morgan and I. Ackermann, *J. Chem. Soc.*, 1308 (1923).

(24) H. Ryan and P. Ryan, *Proc. Roy. Irish. Acad.*, 34B, 212 (1919).

4,4′,6,6′-Tetramethyl,-2,2′-bipyridine

ROBERT H. LINNELL[1]

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Recent work[2] on the reaction of sodium with pyridine bases has shown that the 2-position is much more reactive than has heretofore been realized. It should therefore be possible to prepare the new compound 4,4′,6,6′-tetramethyl,-2,2′-bipyridine by

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(2) U. S. Patent 2,773,066, Dec. 4, 1956. To be published.

the reaction of sodium and 2,4-dimethyl pyridine. This new compound should be a Cu(I) specific[3] and would be of interest in studies on the effect of methyl group substitution on complex ions.[4]

EXPERIMENTAL

Two hundred forty ml. of freshly distilled 2,4-dimethyl pyridine was treated with 1.5 g. freshly cut slices of Na metal under reflux at 140°. Gas bubbles appeared at the surface of the Na and a brown color started at this surface and spread throughout the solution turning red-brown, blood red, and finally to a deep blue. After 4 hr. at 140° reaction was assumed complete and air was bubbled into the mixture until the color was a dirty brown, at which time oxidation was believed to be complete. Excess 2,4-dimethyl pyridine was then distilled at atmospheric pressure and the residue vacuum-distilled with the major fraction at 150°, 4–5 mm. pressure. The major fraction was recrystallized from 30–60° ligroin, decolorized with carbon in hot acetone, and finally recrystallized from hexane, yielding 5 g. white needles, m.p. 144–45°.

Anal.[5] Calcd. for $C_{14}H_{16}N_2$: C, 79.20; H, 7.60; N, 13.20. Found: C, 79.43; H, 7.78; N, 13.12.

A monopicrate was formed by adding picric acid in 95% EtOH to the tetramethyl bipyridine in the same solvent. The product was recrystallized from 95% EtOH yielding fine yellow needles with no sharp melting point (dec. starting at 200° and melting about 220°).

Anal.[5] Calcd. for $C_{20}H_{19}N_5O_7$: C, 54.40; H, 4.34; N, 15.96. Found: C, 53.70; H, 4.45; N, 16.27.

Infrared spectra (Nujol mull)[6] of 2,2′-bipyridine and of the assumed 4,4′,6,6′-tetramethyl,-2,2′-bipyridine of this work showed the presence of methyl groups in the latter.

The assumed tetramethyl bipyridine was oxidized with $KMnO_4$, the MnO_2 was removed, the *p*H adjusted with dilute HCl, and the white crystals were purified by recrystallization from H_2O. Repeated recrystallizations did not yield material with a sharp melting point but melting with decomposition near 230°. Trimesitic acid (2,4,6-pyridine-tricarboxylic acid) has a reported m.p. (dec.) of 227°.[7] Berberonic acid (2,4,5-pyridine tricarboxylic acid) has a m.p. of 235° and could arise if the 2,4-dimethyl pyridine had coupled in the 3-position. However coupling in the 3-position is excluded on the basis of complex ion formation.

The assumed 4,4′,6,6′-tetramethyl,-2,2′-bipyridine would not form a complex with Fe (II) ion, as was expected.[3] A complex with Cu(I) ion was formed, having λ_{max} 450 mμ and a molecular extinction coefficient of 6800.[8] This proves the presence of sterically hindered 2,2′-bipyridine linkage.

The tetramethyl bipyridine (0.0755 g.) was dissolved in 25 ml. of HOAc and titrated with 0.06496*N* $HClO_4$ in HOAc with a glass electrode-calomel electrode (MeOH modified) system.[9] Two breaks were found in the titration curve, at 5.64 and 11.25 ml. of titrant. Crystal violet did not give a good visual end point. The theor. mol. wt. of $C_{14}H_{16}N_2$ is 212.3. The titration yields 206.6 and 206.3. It is interesting to note that a similar titration with unsubstituted 2,2′-bipyridine yields only one break in the titration curve, corresponding to the monobasic compound and precipitation takes place. Steric factors probably prevent precipitation of the tetramethyl compound.

Acknowledgment. Thanks are due the Research Corp. for supporting this work. Thanks are also due to Dr. Antoine Zahlan and Mr. Alexander Kaczmarczyk for their help and interest.

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(3) J. Hoste, *Anal. Chim. Acta*, 4, 23 (1950).

(4) F. W. Cagle, Jr., and G. F. Smith, *J. Am. Chem. Soc.* 69, 1860 (1947).

(5) Analyses by Clark Microchemical Laboratory, Urbana, Ill.

(6) The author thanks Mr. John Whalen and the Reynolds Research Laboratory, Winston-Salem, N. C. for the infrared spectra.

(7) Beilstein XXII 185 (5).

(8) Thanks are due Dr. G. Frederick Smith of the University of Illinois for determining these values.

(9) The author thanks Mr. Robert H. Cundiff and the Reynolds Research Laboratory, Winston-Salem, N. C. for these titrations.

The Liebermann Reaction

T. A. TURNEY

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In a study of the reactions of nitrous acid with organic compounds we have recently investigated the Liebermann reaction for phenols. Since our conclusions include some observations not found in the literature we record these here.

The procedure used was that of Mann and Saunders[1] "To one minute crystal of sodium nitrite in a clean dry test tube add 0.5 g. of phenol and heat very gently for about 20 seconds; allow to cool and add twice the volume of concentrated sulphuric acid. On rotating the tube slowly in order to mix the contents, a deep green or blue coloration develops (sometimes only after a few minutes). Dilute cautiously with water; the solution turns red. Now add excess of sodium hydroxide solution, the green or blue color reappears."

This note gives some rationalization of the procedure as well as the inferences that can be drawn from the test.

The active reagent is the nitrosyl ion formed from sodium nitrite and concentrated sulfuric acid. In the preliminary heating the nitrite is covered by the phenol preventing its loss as nitrous fumes. With the more acidic phenols there is sometimes some reaction at this stage which does not affect the test. The heating is unnecessary for liquid phenols. The reaction is carried out under heterogeneous conditions to prevent the sulfonation of the phenol. The product is an indophenol formed by condensation of initially formed nitrosophenol and phenol. This condensation does not occur readily with less than 85% (w/w) sulfuric acid. A transient red color due to the intermediate is often observed before the formation of the blue or green color.

If a *phenol* gives a positive Liebermann reaction (*i.e.* blue or green in concentrated sulfuric acid, red in dilute sulfuric acid, blue or green in alkalies) then

(1) F. G. Mann and B. C. Saunders, *Practical Organic Chemistry* 2nd Edition, Longmans Green and Co., London, 1938, p. 218.

the position *para* to the —OH group is unoccupied. No exceptions are known to this rule.

Phenols containing activating groups stronger than alkyls, *e.g.*, —OH, —NH_2, —OCH_3 will *generally* not give the test even though the para position may be unoccupied.

An exception to this rule is *m*-methoxy phenol.

Phenols containing deactivating groups stronger than halogens, *e.g.*, —NO_2, —CHO, —COOH, —$COCH_3$ will *not* give the test even though the *para* position is unoccupied. An exception to this rule is orthomercurichloride phenol.

The above results are all explicable on the basis of the reactivity of the intermediate O=⟨⟩=N presumed formed in the formation of indophenol.

The nitrosyl ion is also produced in concentrated sulfuric acid by nitrosamines and esters of nitrous acid which therefore give a Liebermann reaction in the presence of phenol.

EXPERIMENTAL

The reaction as described was carried out on the following phenols. *Class A*. Phenols with the *para* position unoccupied which gave a *positive* reaction (*i.e.*, blue or green in concentrated sulfuric acid, red in dilute sulfuric acid, blue or green in alkali): phenol, *o*-cresol, *m*-cresol, *o*-chlorophenol, *o*-bromo phenol, carvacrol, thymol, *o*-hydroxy diphenyl, *m*-methoxy phenol, *o*-mercurichloride phenol, 2,5-xylenol.

Class B. Phenols with the *para* position unoccupied which did not give a *positive* reaction: 3,5-xylenol, saliginen, *o*-methoxy phenol, catechol, resorcinol, pyrogallol, phloroglucinol, *o*-amino phenol, *m*-amino phenol (activating groups), *o*-nitro phenol, *m*-nitro phenol, *o*-hydroxy benzaldehyde, *m*-hydroxy benzaldehyde, *o*-hydroxy benzoic acid, *m*-hydroxy benzoic acid, methyl salicylate, ethyl salicylate, phenyl salicylate, 2,4-dihydroxy benzoic acid, 2,3-cresotic acid, (deactivating groups).

Class C. Phenols with the para position occupied not giving a *positive* test: *p*-amino phenol, *p*-cresol, 2,4-dichlorophenol, *p*-methoxy phenol, *p*-hydroxy benzoic acid, *p*-chloro phenol, *p*-hydroxy phenol, *p*-cresol, 2,4,6-trichlorophenol, 2,4-dinitro phenol, pentachlorophenol, *p*-nitro phenol, *p*-chloro-*m*-cresol.

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2-Nitro-, 3-Nitro-, 2,4-Dinitro-, and 2,5-Dinitrothiophene[1]

A. H. BLATT, SHIRLEY BACH, AND LEONARD W. KRESCH

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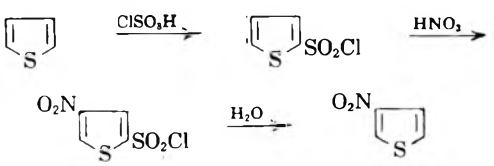
Some years ago we prepared sizeable quantities of 2-nitrothiophene and 2,4-dinitrothiophene and found that there was some confusion in the literature about the properties and/or behavior of these compounds and the related 3-nitrothiophene and 2,5-dinitrothiophene.[2] Since that time we have accumulated enough information about these compounds to clarify the situation for ourselves. Because the confusion in the literature does not appear to be generally recognized, we present in this note what we believe is an accurate description of the compounds in question.

The nitration of thiophene, best done by the nitric acid–acetic anhydride procedure described in Organic Syntheses,[3] leads to 2-nitrothiophene containing small amounts (up to a maximum of about 5%) of 3-nitrothiophene. The presence of 3-nitrothiophene in the mononitration product from thiophene was established by Steinkopf,[4] but there has been no description of a procedure for obtaining pure 2-nitrothiophene from the crude nitration product and for establishing the homogeneity of the 2-nitrothiophene thus obtained. We prepared pure 2-nitrothiophene from the crude mononitration product by crystallization to constant, sharp melting point from purified petroleum ether (b.p. 40–60°) and from ethanol–water. The melting point of this material in a Hershberg apparatus with calibrated thermometer is 43–44°; on a Fisher melting point block, the same material melts over less than a half degree. From the melting point ranges of mixtures of purified 2-nitrothiophene and purified 3-nitrothiophene (whose preparation and purification are described below) it may be concluded that 2-nitrothiophene which melts over less than half a degree range on the Fisher block is pure.

Melting ranges of mixtures of 2-nitrothiophene and 3-nitrothiophene:

% 2-Nitrothiophene	Melting range
95	39–45°
90	39.5–47
75	39–47
50	40–57
25	40–64
10	63–74
5	68–74

The only feasible preparation of 3-nitrothiophene is that described by Steinkopf and Höpner.[4a] We have modified and simplified the procedure, as described in the experimental section, so that 3-nitrothiophene can be prepared in about a 20% over-all



(together with some 5-nitroderivative)

(1) This note is based on undergraduate research done at Queens College by Mrs. Bach and Mr. Kresch.

(2) (a) "Thiophene and Its Derivatives," Howard D. Hartough, Interscience, New York, 1952, p. 221; (b) L. S. Levitt and Edgar Howard, Jr., *J. Am. Chem. Soc.*, **76**, 1951 (1954).

(3) V. S. Babasinian, *Org. Syntheses*, Coll. Vol. II, 466 (1943).

(4) (a) W. Steinkopf and T. Höpner, *Ann.*, 501, 174 (1933); (b) W. Steinkopf, *Ann.*, 545, 38 (1940).

yield from thiophene by the following three reactions.

Apparently 3-nitrothiophene has not hitherto been prepared in sufficient quantity to permit careful purification, for the melting points reported for the compound vary from 68° to 79°. 3-Nitrothiophene is higher melting and less soluble than the 2-nitro derivative and it can be purified easily by crystallization from ethanol. Material purified in this way to constant, sharp melting point melts at 75–76° in a Hershberg apparatus with calibrated thermometer; on the Fisher block the material melts over less than 0.5°-range and can be seen to sublime between the glass slides. From the melting point ranges given earlier for mixtures of 2-nitro- and 3-nitro-thiophene, the 3-nitro derivative can be considered pure when it melts over a half-degree range.

Two dinitrothiophenes have been prepared by nitration of the mononitrothiophenes; 3-nitrothiophene furnishes exclusively 2,4-dinitrothiophene, m.p. 49–50°, and 2-nitrothiophene furnishes predominantly the same product together with smaller amounts (~15%) of the isomeric *2,5-dinitrothiophene, m.p. 78–82°*. There is no satisfactory way of preparing 2,5-dinitrothiophene and only one sample of the material has been reported. That sample was obtained by heating the crude dinitration product from 2-nitrothiophene with nitric and sulfuric acids, which removes the 2,4-dinitrothiophene by oxidation and leaves the 2,5-dinitrothiophene unattacked.[4a] We have done no work with 2,5-dinitrothiophene, but we have prepared and purified 2,4-dinitrothiophene, m.p. 49.8–50.2° (corr.) and have confirmed the structure originally assigned to it by showing that it is identical with the product obtained from 2-iodo-3,5-dinitrothiophene when the iodine is replaced by hydrogen by means of dilute hydriodic acid.

The behavior of 2-nitrothiophene on nitration—formation principally of a 2,4-disubstituted derivative—is characteristic of those 2-monosubstituted thiophenes in which the substituent is strongly *meta* directing. As a consequence, direct substitution is not satisfactory for the preparation of 2,5-disubstituted thiophenes in which both substituents are *meta* directing, and for many such disubstituted thiophenes there is no good method of preparation. The orientation pattern just described was clearly stated by Steinkopf upon whose work it is principally based.[4a] Restatement is necessary because later workers have either overlooked or misread his work and have assigned the 2,5 structure to disubstitution products that are actually 2,4 derivatives.

The infrared spectra of 2-, 3-, and 2,4-dinitrothiophene have been determined by Dr. R. C. Gore of the Research Division of the American Cyanamid Co. and are included in the collection of the American Petroleum Institute. 2-Nitro, 3-nitro, and 2,4-dinitrothiophene give the characteristic colors with sodium iodide.[5] Neither 2- nor 3-nitrothiophene gives a positive isatin reaction.

EXPERIMENTAL

2-Nitrothiophene. Crude 2-nitrothiophene[3] was dissolved in petroleum ether (b.p. 40–60°, freshly distilled over potassium permanganate) by keeping the solvent and excess solute in a glass-stoppered flask in a water bath at 40°. The clear saturated solution was chilled overnight in a refrigerator. About 7 g. of 2-nitrothiophene dissolves in 100 ml. of the solvent and the recovery of crystallized product averages about 75%. Four crystallizations as just described followed by one crystallization from dilute ethanol (1.0 g. of solute, 10 ml. of ethanol, and 8 ml. of water) and a final crystallization from petroleum ether gave a product of m.p. 43–44° (corr.) in a Hershberg apparatus, and 43–43.4° (uncorr.) on a Fisher block. The melting point was not changed by the last three crystallizations.

3-Nitrothiophene. In a 400-ml. beaker, 100 g. of chlorosulfonic acid and 50 ml. of anhydrous chloroform were mixed and stirred mechanically while 25 ml. of thiophene was added during 4 min. The temperature of the reaction mixture was held at 0° by the direct addition of solid carbon dioxide. The reaction mixture was allowed to warm to room temperature and then chilled again with solid carbon dioxide while ice was added to decompose the excess chlorosulfonic acid. The layers were separated and the aqueous layer was extracted with 25 ml. of chloroform. The combined chloroform layers were washed with 50 ml. of water, dried over anhydrous sodium sulfate, and distilled. From six such runs there was obtained 119 g. (37%) of thiophene-2-sulfonyl chloride, b.p. 99–101°/6 mm., which solidified on cooling.

During 1 hr. 69.2 g. of thiophene-2-sulfonyl chloride was added dropwise to 281 ml. of fuming nitric acid (d. 1.59–1.60) that was stirred mechanically and held between 25 and 30° by a cold water bath. After the addition the reaction mixture was held at 40° for 1 hr., then was poured onto 1 kg. of ice and the organic material separated with the aid of 350 ml. of carbon tetrachloride. The carbon tetrachloride solution was washed with water, dried, and distilled. In this way from 119 g. of thiophene-2-sulfonyl chloride there was obtained 105 g. (76%) of 4-nitrothiophene-2-sulfonyl chloride boiling at 145–150°/4 mm. and less than 5 g. of 5-nitrophene-2-sulfonyl chloride boiling at 133–136°/4 mm.

The 105 g. of 4-nitrothiophene-2-sulfonyl chloride and 530 ml. of water were boiled under reflux for 4 hr. during which time all but traces of the acid chloride dissolved. The clear yellow solution was left overnight, then 655 g. of ice and 920 ml. of concentrated sulfuric acid were added and the resulting solution was divided in five portions and distilled with superheated steam. The solution was heated to 140° (thermometer in the liquid) before the superheated steam was introduced and was kept at this temperature during the distillation. Each portion of the reaction mixture required about 90 min. for the distillation and the entire distillate amounted to 1.2 l. The 3-nitrothiophene that precipitated in the distillate weighed 44 g. (74%).

The 3-nitrothiophene is readily purified by crystallization from ethanol. Using 3 ml. of solvent per gram of solute the recovery is between 75 and 80%. Two such crystallizations furnished pure material whose melting point (75–76° corr., in a Hershberg apparatus; 75–75.5°, uncorr., in a Fisher block) was not changed by a third crystallization from 60–90° ligroin.

Two comments on the preparation of 3-nitrothiophene are in order. The least satisfactory step is the reaction with chlorosulfonic acid. This step, which has the advantage of convenience, could probably be improved by the isolation

(5) A. H. Blatt and Norma Gross, *J. Org. Chem.*, 22, 1046 (1957).

of the sulfonic acid as the sodium salt and its conversion to the sulfonyl chloride,[6] but these operations require equipment not available in the ordinary laboratory. The nitration of the sulfonyl chloride according to the literature[4a] furnishes the 4-nitro and 5-nitro derivative in an 8:3 ratio. In our work the ratio of 4-nitro to 5-nitro was closer to 9:1.

2,4-Dinitrothiophene. Crude 2,4-dinitrothiophene obtained by the nitration of 2-nitrothiophene[4a] was purified by three crystallizations from ethanol and one from petroleum ether (b.p. 40–60°). Solutions were prepared and handled in the same way as with 2-nitrothiophene. About 2 g. of the dinitrothiophene will dissolve in 10 ml. of ethanol or 250 ml. of petroleum ether at 40°. The recovery from ethanol is about 15%, from petroleum ether about 60%. The pure dinitrothiophene melts at 49.8–50.2°, corr., in a Hershberg apparatus.

2,4-Dinitrothiophene from 2-Iodo-3,5-dinitrothiophene. A solution of 4.5 g. of sodium iodide in 15 ml. of acetone was added to 3.0 g. of 2-iodo-3,5-dinitrothiophene dissolved in 15 ml. of acetone and 5 ml. of glacial acetic acid. After two weeks the dark brown reaction mixture was poured into a solution of 5.0 g. of sodium bisulfite in 140 ml. of water and the dark oily precipitate was stirred until it became granular. The yellow-brown solid was dissolved in 25 ml. of hot ethanol and the solution, after it had been decolorized with Norit and filtered, was diluted with 40 ml. of water to yield 1.2 g. (66%) of 2,4-dinitrothiophene, m.p. 51–52°, whose identity was confirmed by a mixed melting point. In another experiment the solid was digested with ligroin; the extract on evaporation furnished 2,4-dinitrothiophene. The residue from the ligroin extraction when crystallized from ethanol gave unreacted 2-iodo-3,5-dinitrothiophene.

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(6) See reference 2a. p. 513.

An Improved Micro Synthesis of Thiamine-S^{35} [1]

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In connection with a study of the metabolism of thiamine which is in progress in this laboratory, it became necessary to prepare thiamine-S^{35} of a high specific activity. Williams and Ronzio[2] have synthesized labeled thiamine from thiourea-S^{35} and thiourea-2-C^{14}. We attempted to duplicate this synthesis, and obtained very low yields when less than 300 mg. of thiourea-S^{35} was used for the initial step of the synthesis. We therefore revised the steps of the synthesis and, starting with 50–100 mg. of carrier-free thiourea-S^{35}, have obtained high yields.

EXPERIMENTAL

2-Amino-5-methyl-4-(β-hydroxyethyl)thiazole-S^{35} hydrochloride. Thiourea-S^{35} (100 mg.)[3] was coupled with 330 mg. of γ-aceto-γ-chloropropanol (1:1.5 molar ratio, respectively) according to the method of Todd *et al.*[4] The substances were mixed in a 5-ml. beaker on the steam bath, and the mixture stirred continuously until the thiourea-S^{35} went into solution, and then 5 min. longer. The solution was removed from the steam bath, and stirred until the mass solidified. The solid mass was broken up, transferred to a centrifuge tube, extracted with anhydrous ether, and the ether was discarded. The residue was dissolved in the minimum amount of hot anhydrous ethanol (1–1.5 ml.). After the solution was cooled, absolute ether was added dropwise until crystallization began. A fivefold excess of ether was then added and the crystallization allowed to go to completion while standing for about 12 hr. in the refrigerator. The precipitate was filtered, rinsed with anhydrous ether, and dried in a vacuum desiccator to yield 220 mg. (86%) of 2-amino-5-methyl-4-(β-hydroxyethyl)thiazole-S^{35} hydrochloride, m.p. 148–150°.

It was found that when 75–100 mg. of thiourea were coupled with γ-aceto-γ-chloropropanol in a molar ratio of 1:1.5, respectively, an average yield of 82% of the 2-aminothiazole was obtained. When very small amounts (less than 75 mg.) of thiourea were used, increasing this ratio of reactants to 1:2 resulted in an average yield of 78%.

5-Methyl-4-(β-hydroxyethyl)thiazole-S^{35}. 2-Amino-5-methyl-4-(β-hydroxyethyl)thiazole-S^{35} hydrochloride (220 mg.) was dissolved in 5.8 ml. of concentrated hydrochloric acid, with cooling in a methanol–ice bath at −5°. Sodium nitrite (1.8 ml. of a 1*N* solution, precooled to 0°) was added dropwise. The mixture was allowed to stand for 30 min. at 0° to −5°. Then 5.8 ml. of water (also precooled to 0°) was slowly added in order to reduce the concentration of hydrochloric acid to 6*N*. During approximately 10 min., 2.6 ml. of cold 32% hypophosphorous acid was added, with the temperature maintained at −5°. The solution was stirred rapidly during all of the above additions. The reaction mixture was placed in the refrigerator at 0° to 2° for 12–15 hr., during which time nitrogen was evolved. The solution was cooled to −5° and neutralized by the addition of 30% sodium hydroxide. Excess base was then added to bring the *p*H to 11–12, and the solution was washed into a continuous extractor and extracted for 16 hr. with ether.[5] After removal from the extractor, the aqueous phase was extracted with several portions of ether in a separatory funnel. The combined ethereal extracts were dried over anhydrous magnesium sulfate, and the ether was removed by distillation from the steam bath. The yield of 5-methyl-4-(β-hydroxyethyl)thiazole-S^{35} was 70 mg. (50%). The reduced thiazole was obtained in yields ranging from 50–70% when 150–250 mg. of the 2-aminothiazole were used. The crude thiazole-S^{35} was identified by the conversion of a small amount to the picrate, which melted at 159–161° when precipitated from anhydrous ether.

Since the condensation of the crude thiazole with the pyrimidine moiety gave very low yields of thiamine, we found it necessary to purify the crude material by distillation under reduced pressure. The pure thiazole-S^{35} was obtained in recoveries of 85–90%, when 50–100 mg. of the crude material were distilled under reduced pressure (b.p. 126–128° at 2–3 mm. and 128–130° at 3–4 mm. pressure).

Thiamine-S^{35} bromide hydrobromide. The 5-methyl-4-(β-hydroxyethyl)thiazole-S^{35} (25 mg.) and 60 mg. of 2-methyl-4-amino-5-bromomethylpyrimidine hydrobromide (1:1 molar ratio) were dissolved in 2 ml. of anhydrous ethanol[6] in a 20-ml. pear-shaped flask fitted with a reflux condenser,

(1) This investigation was aided, in part, by Contract No. AT (30-1)-1056 between the U.S. Atomic Energy Commission and Fordham University.

(2) D. L. Williams and A. R. Ronzio, *J. Am. Chem. Soc.*, 74, 2409 (1952).

(3) Obtained from Abbott Laboratories, Division of Radio-Pharmaceuticals, North Chicago, Ill.

(4) A. R. Todd, F. Bergel, H. L. Fraenkel-Conrat, and A. Jacob, *J. Chem. Soc.*, 1601 (1936).

(5) The extraction period can be shortened from 40 hr. without any decrease in the yield of thiazole.[2]

(6) Williams and Ronzio[2] carried out the condensation in butanol at 125°. The side reaction (ether formation between the butanol and the β-hydroxyethyl group of the thiazole moiety) which occurs under those conditions was completely avoided when anhydrous ethanol was used as the solvent.

and the mixture was heated on the steam bath for 1 hr. After the reaction mixture was allowed to stand in the refrigerator overnight, the precipitated thiamine-S^{35} bromide hydrobromide was filtered. Additional material was obtained by dilution of the mother liquor with anhydrous ether. The crude reaction product melted at 239–240° with decomposition.[7] The crude thiamine-S^{35} was recrystallized by dissolving in 2 ml. of anhydrous methanol and diluting the solution with 20 ml. of anhydrous ether. The yield was 81 mg. (90%) of thiamine-S^{35} bromide hydrobromide with a m.p. 229–231° (with dec.).

It was found that condensation of 25–75 mg. of thiazole with an equimolar amount of pyrimidine gave thiamine yields from 74–93% of once-recrystallized material, the average yield being 87%. We observed that refluxing for more than 1 hr. did not improve the yield, and that the best yields were obtained when the condensation was allowed to take place in the minimum amount of ethanol necessary to dissolve the pyrimidine.

A sample of thiamine bromide hydrobromide prepared from nonradioactive thiourea according to the above procedure was analyzed.

Anal. Calcd. for $C_{12}H_{18}Br_2N_4OS$: N, 13.4; Br, 37.50. Found: N, 13.04; Br, 37.50.

When thiourea-S^{35} with a radioactivity content of 6 mc. per 100 mg. was used, the thiamine-S^{35} bromide hydrobromide obtained had a specific activity of about 1.4 mc. per 100 mg.

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(7) With respect to the melting points of thiamine preparations, see Williams and Ronzio.[2]

Synthetic Experiments in the Furocoumarin Series

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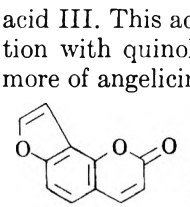
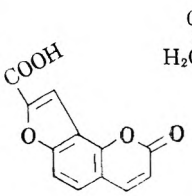
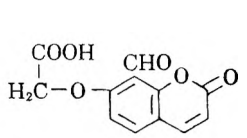
In the course of our investigations on the synthesis of some naturally occurring furocoumarins, we required angelicin (I) as the starting material. In our effort to prepare it according to Späth and Pailer,[1] we observed the melting point of 7-(8-formylcoumarinoxy)acetic acid (II) to be much higher (248–249°) than what they stated (178–181°). Moreover, this acid on heating with fused sodium acetate and acetic anhydride, gave a good yield of 2′-carboxyangelicin (III) along with angelicin (I). The authors do not appear to have isolated the acid III. This acid underwent smooth decarboxylation with quinoline and copper powder to furnish more of angelicin (I).



I



III

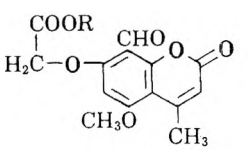


II

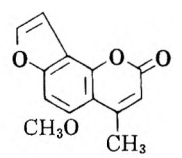
(1) E. Späth and M. Pailer, *Ber.*, **68B**, 941 (1935).

The Elbs persulfate oxidation of angelicin under the usual conditions[2] met with failure. Similarly a parallel oxidation of 3′,4-dimethyl-furo-7,8-(4′,5′)-coumarin prepared according to Limaye[3] also failed indicating the improbability of successfully effecting Elbs oxidation on coumarins with furan ring in the 7,8-position. An attempt to introduce a hydroxyl group in 6-position by Elbs oxidation of II was unsuccessful. A stable coumarinic acid derivative[4] was isolated, which regenerated the parent coumarin (II) on crystallization from acetic acid.

The interaction of 5-methoxy-7-hydroxy-4-methyl-8-formylcoumarin[5] with ethyl bromacetate gave poor yield of ethyl 7-(5-methoxy-4-methyl-8-formylcoumarinoxy)acetate (IV, R = C_2H_5) which furnished the corresponding acid (IV, R = H) on hydrolysis with 5% methanolic potassium hydroxide. On refluxing this acid with fused sodium acetate in acetic anhydride, 4-methylisobergaptene (V) was obtained in poor yield. Some other dark, alkali-soluble material was obtained, which failed to give a definite product. This indicates an alternative method of synthesis of isobergaptene.



IV



V

EXPERIMENTAL

All melting points are uncorrected.

Ethyl 7-(8-formylcoumarinoxy)acetate. A mixture of 7-hydroxy-8-formyl-coumarin[1] (2 g.), anhydrous potassium carbonate (6 g.) and ethyl bromoacetate (2.0 cc.) in dry acetone (100 c.c.), was gently refluxed on a water bath for 48 hr. The contents were filtered and the filtrate, on evaporation of acetone, yielded a white product along with the residual ethyl bromoacetate which was removed by closed steam distillation. The product crystallized from alcohol as shining flakes, m.p. 163°. Yield 1.6 g. Späth and Pailer[1] give m.p. 157° in a vacuum capillary.

7-(8-Formylcoumarinoxy)acetic acid (II). The preceding ester (1 g.) was kept at room temperature with sodium hydroxide (8 cc., 5%) for 3 hr. when the ester slowly went into solution. The product which separated on acidification, crystallized from acetic acid as thin white needles, m.p. 248–249° (decomp.) Yield 0.7 g. The hydrolysis could also be brought about by 80% sulfuric acid at room temperature or boiling with 5% alcoholic potassium hydroxide.

Since the previous authors[1] gave m.p. 178–181° (dec.) in a vacuum capillary, it was thought desirable to analyze the acid.

Anal. Calcd. for $C_{12}H_8O_6$: C, 58.1; H, 3.2. Found: C, 57.9; H, 3.3.

(2) S. Sethna and co-workers, *J. Ind. Chem. Soc.*, **27**, 369 (1950); **28**, 366 (1951); **30**, 610 (1953).

(3) D. B. Limaye, (a) *Ber.*, **65B**, 375 (1932); (b) with D. D. Gangal, *Rasāyanam*, **1**, 15 (1936); *Chem. Abstr.*, **31**, 2207 (1937).

(4) *Cf.* R. M. Naik and V. M. Thakor, *J. Org. Chem.*, **22**, 1626 (1957).

(5) R. M. Naik and V. M. Thakor, *J. Org. Chem.*, **22**, 1630 (1957).

Angelicin (I) *and 2'-carboxyangelicin* (III). The mixture of the above acid (II) (2 g.), freshly fused sodium acetate (5 g.) and distilled acetic anhydride (40 cc.) was refluxed in oil bath at 150–155° for 30 min. The reaction mixture was cooled and poured onto crushed ice whereupon the product separated. The contents were made alkaline with excess of sodium hydroxide, and then extracted with ether. Angelicin was isolated from the ether extract and crystallized from methanol as white needles, m.p. 138°. Yield 0.25 g. Späth and Pailer give m.p. 138–139.5°.

The alkaline layer was acidified and the product which separated was crystallized from acetic acid as thin white prisms m.p. > 315°. It melts sharply and leaves no residue. Yield 0.9 g.

Anal. Calcd. for $C_{12}H_6O_5$: C, 62.6; H, 2.6. Found: C, 62.5; H, 2.8.

Decarboxylation of 2'-carboxyangelicin (III) *to angelicin* (I). The acid (III) (0.2 g.), copper powder (50 mg.) and distilled quinoline (5 cc.) were heated in an oil bath at 225° for half an hour. Copious evolution of carbon dioxide was observed within 15 min. of heating. It was filtered and washed with acetone, and dilute hydrochloric acid was added to remove quinoline. The ether extract of the contents furnished angelicin (0.1 g.).

Attempted Elbs persulfate oxidation of angelicin (I). Potassium persulfate solution (2.7 g. in 60 cc. of water) was added dropwise to a cooled (0°) solution (obtained after warming) of angelicin (1.9 g.) in sodium hydroxide (20 cc.; 10%), and the reaction mixture was stirred. On working up the reaction mixture as usual,[2] blackish complex product was obtained which burned with conflagration and left behind some residue.

Ethyl 7-(5-methoxy-4-methyl-8-formylcoumarinoxy)acetate (IV, R = C_2H_5). The mixture of 5-methoxy-7-hydroxy-4-methyl-8-formylcoumarin (5 g.), anhydrous potassium carbonate (15 g.), ethyl bromacetate (5 cc.) and acetone (300 cc.) was refluxed on a steambath for 72 hr. The contents were then filtered while hot and a good quantity of the unreacted substance (about 2.5 g.) was recovered as insoluble potassium salt along with potassium carbonate. The filtrate, on evaporating acetone and working up as in the earlier experiment, furnished the ester which crystallized from acetic acid as thin wooly needles, m.p. 261°. Yield 1.2 g. It does not give any color with alcoholic ferric chloride.

Anal. Calcd. for $C_{16}H_{16}O_7$: C, 60.0; H, 5.0. Found: C, 59.9; H, 5.1.

7-(5-Methoxy-4-methyl-8-formylcoumarinoxy)acetic acid (IV, R = H). The preceding ester (IV, R = C_2H_5) (1 g.) was refluxed on a steambath for 30 min. with methanolic potassium hydroxide (20 cc., 5%) when the product went into solution. A greenish product was obtained on acidification. It was crystallized from excess of acetic acid, as amorphous needles, m.p. > 315°. Yield 0.5 g.

Anal. Calcd. for $C_{14}H_{12}O_7$: C, 57.5; H, 4.1. Found: C, 57.8; H, 4.2.

4-Methylisobergaptene (V). The mixture of the acid (IV, R = H) (1 g.) fused sodium acetate (2 g.) and acetic anhydride (15 cc.) was refluxed in oil bath at 150–155° for 2 hr. Most of the acetic anhydride was removed by distillation and then water and sodium hydroxide were added. The ether extract of this yielded 4-methylisobergaptene which crystallized from alcohol in thin needles, m.p. 288–289°. Yield 40 mg.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.8; H, 4.3. Found: C, 67.6; H, 4.3.

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Organic Sulfur Compounds. XXXIII. Action of Some Free Radicals of Long Life on Thiophenol and *p*-Nitrothiophenol

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Very little seems to be known about the reaction between free radicals of long life and mercaptans, while the action of mercaptans on free radicals of short life plays a great role in theoretical organic chemistry in connection with the addition of mercaptans to olefins under the influence of light.[1]

Experiments with triphenylmethyl and 9-phenylfluorenyl. Hexaphenylethane and 9,9'-diphenyl-9,9'-bifluorenyl (I) dissolved separately in benzene were allowed to react with thiophenol in a stream of CO_2. The action of triphenylmethyl on thiophenol led to the formation of triphenylmethane and triphenylphenylmercaptomethane, whereas the experiments with 9-phenylfluorenyl and thiophenol yielded 9-phenylfluorene and 9-phenyl-9-phenylmercaptofluorene. The formation of 9-phenylfluorene was also observed when I, dissolved in boiling benzene, was allowed to react with thioacetic acid.

It is possible that the reactions between triphenylmethyl and 9-phenylfluorenyl with thiophenol proceed according to A and B

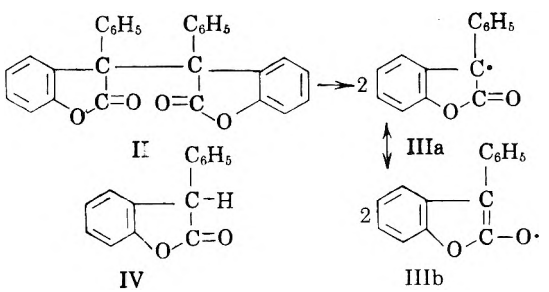
$$R_3C\cdot + R'SH \longrightarrow R_3CH + R'S\cdot \qquad (A)$$

$$R'S\cdot + R_3C\cdot \longrightarrow R_3CSR' \qquad (B)$$

or that hydrogen abstraction is essentially concerted with formation of a carbon to sulfur bond.

$$R_3C\cdot + C_6H_5SH + R_3C\cdot \longrightarrow R_3CH + C_6H_5SCR_3$$

Experiments with 2,2'-diketo-3,3'-diphenyl-3,3'-dicoumaranyl (II). II forms free radicals (IIIa ⟷ IIIb) in hot solutions. The dissociation[2] explains the fact that the cold solutions of II are colorless whereas the hot solutions are blue.



We have allowed II in hot chlorobenzene to react with thiophenol and *p*-nitrothiophenol. In both cases the sulfur compounds readily discharged the blue color of the solution. In the case of thiophenol

(1) W. A. Noyes, Jr., and W. Bockelheide in A. Weissberger *Technique of Organic Chemistry*, Interscience, Inc., New York, 1949, Vol. II, p. 138.

(2) A. Löwenbein and H. Simonis, *Ber.*, **57**, 2040 (1924).

we could only isolate *o*-hydroxydiphenylacetic acid lactone IV whereas in the case of *p*-nitrothiophenol this lactone and *p,p'*-dinitrodiphenyldisulfide were obtained.

EXPERIMENTAL

The benzene used was dried over sodium. The CO_2 stream was produced by the action of hydrochloric acid on marble and then dried with concd. H_2SO_4.

Action of thiophenol on hexaphenylethane. A solution of hexaphenylethane was prepared by refluxing for 45 min. a solution of 3 g. (0.0108 mole) of triphenylchloromethane in 20 ml. of benzene, after addition of 8 g. of copper bronze. After filtration an orange solution of hexaphenylethane (triphenylmethyl) was obtained. Its color was discharged very rapidly after the addition of 0.6 g. (0.0054 mole) thiophenol in 5 ml. of benzene. After refluxing for 3 hr., benzene was driven off under reduced pressure leaving residue A. All these manipulations were carried out in a stream of dry CO_2.

Residue A was extracted with 50 ml. of petroleum ether (60–80°) which yielded a residue after evaporation. The residue was fractionally crystallized from alcohol. The first fraction yielded 0.9 g. triphenylphenylmercaptomethane (0.0025 mole) and on concentration 0.5 g. (0.002 mole) of triphenylmethane. These two substances were identified by melting point and mixed melting point 104° and 92° respectively, with authentic samples. The phenylmercapto derivative[3] was also identified by its color reaction with concd. H_2SO_4; the substance dissolved in acetic acid gave no color reaction with sodium nitrite crystals which proved that no thiol group was present. The substance was also prepared from phenylmercury mercaptide and triphenylchloromethane.

Triphenylphenylmercaptomethane. To 0.25 g. (0.0006 mole) of bis(phenylmercapto)mercury[4] in 25 ml. hot benzene was added 0.75 g. of (0.0027 mole) triphenylchloromethane. After heating for 90 min. in a bath (60°) followed by refluxing for 1 hr., the benzene was removed by distillation and the residue was extracted with hot benzine (60–80°). After evaporation of the benzine the residue was twice crystallized from alcohol. Triphenylphenylmercaptomethane was obtained in colorless crystals m.p. 104°, no depression with an authentic sample.[3]

Anal. Calcd. for $C_{25}H_{20}S$: C, 85.2; H, 5.7; S, 9.1. Found: C, 85.4; H, 5.6; S, 8.8.

Action of 9,9'-diphenyl-9,9'-bifluorenyl (I) *on* (*a*) *Thiophenol.* Four-tenths of a gram (0.00083 mole) of I[5] and 0.2 g. (0.0018 mole) of thiophenol in 40 ml. of dry benzene were refluxed for three hours in a stream of carbon dioxide. The solvent was removed by distillation in a stream of carbon dioxide and the residue treated with 15 ml. of boiling alcohol (96%). The solution was quickly cooled in ice and then allowed to stand for 30 minutes at room temperature. The deposit (0.15 g. 0.00062 mole; m.p. 136–140°) yielded after crystallization from alcohol 9-phenylfluorene, melting point and mixed melting point with an authentic sample 148°. The crystals gave no color reaction with concd. sulfuric acid.

Anal. Calcd. for $C_{19}H_{14}$: C, 94.2; H, 5.8. Found: C, 94.0; H, 5.8.

The alcoholic filtrate was concentrated to 5 ml. whereupon crystals (0.1 g.; m.p. 110–114°) were obtained which after crystallization from benzine (60–80°) yielded 9-phenyl-9-phenylmercaptofluorene of m.p. 118°, no depression with a sample prepared according to the method described below.

(*b*) *Thioacetic acid.* Similarly from 0.6 g. (0.00125 mole) of I and 0.2 g. (0.0026 mole) of thioacetic acid in 50 ml. benzene after 3 hr. of refluxing, 0.25 g. of 9-phenylfluorene were obtained, identified (after crystallization from ethyl alcohol) by melting point and mixed melting point (142°).

9-Phenyl-9-phenylmercaptofluorene. The substance was obtained from 0.25 g. (0.00006 mole) of bis(phenylmercapto)-mercury and 0.7 g. (0.0025 mole) of 9-chloro-9-phenylfluorene in 25 ml. benzene as described in the case of phenylmercaptotriphenylmethane. Pale yellow crystals, m.p. 118°, were formed, which dissolved in concd. sulfuric acid with an orange color.

Anal. Calcd. for $C_{25}H_{18}S$: C, 85.7; H, 5.1; S, 9.1. Found: C, 85.3; H, 5.1; S, 8.6.

Action of 2,2'-diketo-3,3'-diphenyl-3,3'-dicoumarinyl (II) *on:* (*a*) *Thiophenol.* To 0.8 g. (0.0019 mole) of (II) in 20 ml. dry chlorobenzene was added 0.2 g. (0.0019 mole) of thiophenol. After refluxing for 30 min. in stream of carbon dioxide the blue color of the hot solution was almost completely discharged. The solvent was removed in a vacuum and the residue pressed on a porous plate. A solid was obtained which after recrystallization from petroleum ether (60–80°) yielded colorless crystals 0.15 g. (0.00071 mole) which proved to be the lactone of *o*-hydroxydiphenylacetic acid (IV); m.p. and mixed m.p. 110–112°.

(*b*) *p-Nitrothiophenol.* To 0.7 g. (0.0016 mole) of II in 20 ml. dry chlorobenzene was added 0.35 g. (0.0023 mole) of *p*-nitrothiophenol[6] and the mixture was heated as above for 60 min. The yellowish green solution was evaporated to dryness in a vacuum and the residue was extracted with 20 ml. of ether. The insoluble material (0.2 g.) (0.00066 mole) was crystallized from benzene and proved by melting point (181°) and mixed melting point to be *p,p*-dinitrophenyldisulfide. Evaporation of the ether yielded an oil from which 0.15 g. (0.00071 mole) of the lactone of *o*-hydroxydiphenylacetic acid was obtained; m.p. and mixed m.p. 110–112° after crystallization from petroleum ether (60–80°).

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(3) A. Schönberg *et al.*, *Ber.*, **66**, 240 (1933).
(4) H. Lecher, *Ber.*, **48**, 1429 (1915).
(5) W. Schlenk, *Ber.*, **43**, 1753 (1910).
(6) C. Willgerodt, *Ber.*, **18**, 331 (1885).

Photochemical Reactions in Sunlight. XX. Photoreaction between Benzaldehyde and Khellinquinone

ALEXANDER SCHÖNBERG AND MAHMOUD MOHAMED SIDKY

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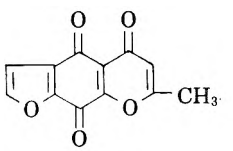
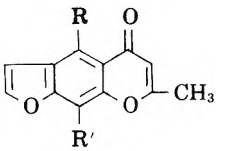
The photochemical addition of aldehydes to *p*-quinones leading to the formation of ketones is known in a number of cases[1]. Thus, *p*-benzoquinone and benzaldehyde give 1,4-dihydroxybenzophenone. A photoreaction leading to the formation of an ester seems, however, to have been observed only in the case of chloranil and benzaldehyde (ultraviolet light);[2] the monobenzoate of tetrachloroquinol being formed. We should like to report a second example of this type, namely, the reaction in sunlight between benzaldehyde and khellinquinone

(1) H. Klinger and W. Kolvenbach, *Ber.*, **31**, 1214, (1898); H. Klinger and W. Standke, *Ber.*, **24**, 1340, (1891).
(2) R. F. Moore and W. A. Waters, *J. Chem. Soc.*, 238 (1953).

(2-methylfuro-4′,5′-6,7-chromone-5,8-quinone) (I).[3] For the structure of the reaction product, which is phenolic in character (ferric chloride reaction), the choice lies between IIa and IIb. That formula IIa is correct could be seen from the fact that methylation with ethereal diazomethane (in the absence of methyl alcohol) could be effected with the formation of IIe. Chromones with hydroxyl groups in position 5 are very resistant toward ethereal diazomethane solutions,[4] this is believed to be due to chelation.[5] The photo-product is soluble in aqueous alkali, while the mono-hydroxy chromones with the hydroxyl group in position 5 are not.[4,6]



I



II

IIa, R = OCOPh, R′ = OH
b, R = OH, R′ = OCOPh
c, R = R′ = OH
d, R = OH, R′ = OCH_3
e, R = OCOPh, R′ = OCH_3

IIe could also be obtained by the treatment of 5-hydroxy-8-methoxy-2-methylfour-4′,5,′6,6-chromone (IId)[4] with benzoyl chloride in pyridine. A facile hydrolysis of IIa to IIc[7] using dilute hydrochloric acid was observed. The photoaddition of benzaldehyde to anthraquinone was tried without success.

EXPERIMENTAL

General remarks. The photoexperiments were carried out in Schlenk tubes[8] of Pyrex glass. The tubes were sealed while a stream of carbon dioxide was passing through. The benzene used was thiophene-free and dried over sodium. The ferric chloride tests were carried out by dissolving the substance in ethyl alcohol and adding ferric chloride in water.

Photochemical reaction between benzaldehyde and khellinquinone. Khellinquinone (I) (1.1 g., 1 mole) and freshly distilled benzaldehyde (1.5 g., 3 mole), in 30 ml. benzene, were exposed to sunlight for 60 days (Jan.–Feb.). At the end of the experiment, a yellow deposit (I is orange) was formed, filtered off, washed with benzene, and crystallized from ethyl alcohol. IIa forms almost colorless crystals m.p. 220° with decomposition, (yield, 0.7 g.). IIa is soluble in aqueous 10% sodium hydroxide, dissolves in concd. sulfuric acid with a yellow orange color, and gives a blue-green ferric chloride color reaction.

Anal. Calcd. for $C_{19}H_{12}O_6$: C, 67.8; H, 3.6. Found: C, 67.6; H, 3.5.

Action of diazomethane on IIa. To 1 g. of IIa was added an ethereal solution of diazomethane (from 6 g. of nitrosomethylurea). The reaction vessel was kept in the ice chest for 24 hr. The solid phase was filtered off and crystallized from ethyl alcohol as colorless crystals of IIe, m.p. 210°. Admixture with the product obtained as described below gave no depression, but on admixing with IIa, there was a depression in the m.p. to 190°. IIe is insoluble in 10% aqueous sodium hydroxide solution, soluble in concd. sulfuric acid with a yellow-orange color, and gives no color reaction with ferric chloride.

Anal. Calcd. for $C_{20}H_{14}O_6$: C, 68.6; H, 4.0. Found: C, 68.5; H, 3.9.

Benzoylation of IId. To 0.6 g. of IId in 10 ml. of pyridine (dried over potassium hydroxide and then distilled) was added about 1 g. of benzoyl chloride and the mixture was heated with shaking on a boiling water bath for 15 min. The mixture was left to cool and then acidified with 10% ice cold acetic acid. The deposit was filtered off, washed with water, and crystallized from ethyl alcohol as colorless crystals of IIe, m.p. 210°. It is insoluble in 10% aqueous sodium hydroxide and gives no color reaction with ferric chloride.

Anal. Calcd. for $C_{20}H_{14}O_6$: C, 68.6; H, 4.0. Found: C, 68.8; H, 4.1.

Hydrolysis of IIa. To 0.5 g. of IIa in 20 ml. of dioxane was added 15 ml. of hydrochloric acid (7.5 ml. of concd. hydrochloric acid of sp. gr. 1.18, mixed with 7.5 ml. water) and the solution was refluxed for 1 hr. The solution was allowed to cool and the product obtained was filtered off and crystallized from acetic acid as yellow crystals of IIc, m.p., 276°; admixture with an authentic sample[7] gave no depression.

Photochemical reaction between benzaldehyde and anthraquinone. A similar experiment was carried out as in the case of benzaldehyde and khellinquinone. Anthraquinone was recovered unchanged as proved by melting point, and mixed melting point.

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(3) A. Schönberg and N. Badran, *J. Am. Chem. Soc.*, **73**, 2960 (1951).
(4) A. Schönberg and G. Aziz, *J. Am. Chem. Soc.*, **75**, 3265 (1953).
(5) A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 746 (1946).
(6) H. Schmid, *Helv. Chim. Acta*, **32**, 814 (1949).
(7) A. Schönberg and A. Sina, *J. Am. Chem. Soc.*, **72**, 3396 (1950).
(8) W. Schlenk and A. Thal, *Ber.*, **46**, 2840 (1913).

Stereochemistry of the Tropane Alkaloids. XI.[1] Oxidation of Four Epimeric Ecgoninols by Silver Oxide

M. Halmos, Ö. Kovács, and G. Fodor

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A recent paper of this series[2] dealt with the preparation and configurations[3] of 2β-hydroxymethyltropan-3α-ol and 2α-hydroxymethyltropan-3α-ol,

(1) Part X, I. Vincze, J. Tóth, and G. Fodor, *J. Chem. Soc.*, in press.
(2) Ö. Kovács, I. Weisz, P. Zoller, and G. Fodor, *Helv. Chim. Acta*, **39**, 99 (1956).
(3) For stereochemical notations see Parts I and VI of this series: *J. Chem. Soc.*, 721 (1953) and 3504 (1955), respectively.

respectively. Oxidation of these together with the 2β,3β and 2α,3β-epimers described earlier[4,5] into the appropriate hydroxycarboxylic acids, *i.e.*, ecgonines, has been intended.[2] Up to that time (−) ecgonine and (+) ψ-ecgonine were known compounds but the third modification was known only as a racemate, while the fourth was unknown.

The synthesis of the hitherto unknown epimeric ecgonines has been attempted now. Hydrogenation of methyl tropinone-2-carboxylate leading to the third racemate[6] has been reinvestigated recently by Zeile and Schulz[7] as well as by Findlay.[8] Both German and American authors benzoylated the third racemate to a new (±) cocaine. Furthermore Findlay converted the third racemate into the fourth (±) ecgonine and (±) cocaine epimer ascribing simultaneously definite configurations to them. Synthesis of the optically active modifications by using optically active methyl tropinone-2-carboxylate as an intermediate has been outlined briefly.[8]

We now wish to record our experiments concerning oxidation of the four ecgoninols using a variety of reagents. Attempts at selective oxidations of a primary hydroxyl group leaving the unprotected secondary hydroxyl group intact are known to be unsuccessful even in the carbohydrate field.[9] Unfortunately, however, the reactants used for this purpose heretofore, as *e.g.* nitric acid, failed to give any definite product in reaction with 2β-hydroxymethyltropan-3β-ol. Use of silver oxide was rather promising, for this secured smooth conversion of vanillyl alcohol into vanillin.[9] Indeed ecgoninol hydrochloride gave on the steam bath with three moles of this reagent a mixture of the β-hydroxy acid together with some unchanged diol in 83% yield while the rest escaped identification.

A higher conversion has been achieved with ψ-ecgoninol, *i.e.* 2α-hydroxymethyltropan-3β-ol, which furnished 82% ψ-ecgonine. Unfortunately, however, neither the 2β,3α nor the 2α,3α epimer gave positive results when oxidized, 93% of the latter being recovered unchanged while the former underwent oxidation (a silver mirror being formed) but only unchanged diol was obtained in 43% yield. That the rest did not show any spot in paper chromatography after treatment with Dragendorff's reagent may indicate destruction of the basic moiety in the molecule. Though the four epimers behave in a markedly stereospecific manner towards silver oxide, our original aim could not be achieved.

EXPERIMENTAL

Oxidation of ecgoninol into ecgonine. 2β-Hydroxymethyltropan-3β-ol hydrochloride[5] (415 mg., 0.002 mole) was dissolved in 12.5 ml. of *N* NaOH, then freshly prepared silver oxide from 1.02 g. of silver nitrate (0.006) was added and the whole immersed in a steam bath for 1.5 hr. with intermittent stirring. Meanwhile a silver mirror appeared on the walls of the flask. Then the reaction mixture was allowed to cool, the precipitate removed by filtration, the filtrate adjusted to *p*H 2 with concentrated hydrochloric acid, then decolorized (charcoal) and filtered again. The solution was evaporated to dryness and the residue taken up in 20 ml. of anhydrous ethanol. After repeated filtration and evaporation the remaining material was recrystallized fractionally from ethanol (10 ml.) and ether. The first crop, after recrystallization from anhydrous ethanol–ether amounted to 172 mg. (42%) and showed a m.p. of 243–245° and $[\alpha]_D^{20}$ −55.8 (H_2O, c = 1.95).

Anal. Calcd. for $C_9H_{16}O_3NCl$: C, 48.76; H, 7.27; ionic Cl, 15.99. Found: C, 49.12; H, 7.18; ionic Cl, 15.64.

By virtue of these data the compound proved to be identical with ecgonine hydrochloride.[11,12,13]

The second crop, precipitated by further addition of ether showed a m.p. of 267–269° and $[\alpha]_D^{20}$ −37.0 (H_2O, c = 2.02). It has been identified as the hydrochloride of 2β-hydroxymethyl-3β-hydroxytropane, the starting material.[5]

Number	Compound	R_F Values
1.	2β-Hydroxymethyltropan-3β-ol	0.49
2.	2α-Hydroxymethyltropan-3β-ol	0.53
3.	2β-Hydroxymethyltropan-3α-ol	0.38
4.	2α-Hydroxymethyltropan-3α-ol	0.63
5.	2β-Carboxy-3β-hydroxy-tropane	0.07
6.	2α-Carboxy-3β-hydroxy-tropane	0.05
7.	Reaction mixture resulting from oxidation of 1	0.07 0.49
8.	Reaction mixture resulting from oxidation of 2	0.05
9.	Reaction mixture resulting from oxidation of 3	0.40
10.	Reaction mixture resulting from oxidation of 4	0.62

Pseudoecgonine hydrochloride from "pseudoecgoninol" (2α-hydroxymethyltropan-3β-ol). 2α-Hydroxymethyltropan-3β-ol[5] hydrochloride, 415 mg. (0.002 mole), underwent oxidation

(4) K. W. Rosenmund and F. Zymalhorsay, *Chem. Ber.*, **85**, 152 (1952).
(5) G. Fodor and Ö. Kovács, *J. Chem. Soc.*, 724 (1953); *cf.* Ö. Kovács, G. Fodor, and I. Weisz, *Helv. Chim. Acta*, **37**, 892 (1954).
(6) R. Willstätter, O. Wolfes, and O. Mäder, *Ann.*, **434**, 111 (1923).
(7) K. Zeile and W. Schulz, *Chem. Ber.*, **89**, 678 (1956).
(8) S. P. Findlay, *J. Org. Chem.*, **21**, 711 (1956).
(9) I. A. Pearl, *J. Am. Chem. Soc.*, **68**, 429 (1946).
(10) R. Lohmar and R. M. Goepp, Jr., in *Advances in Carbohydrate Chemistry*, Vol. IV, p. 226. Academic Press, N. Y. 1949; compare, however, with R. Bognár and L. Somogyi, *Szerves Kémiai Konferencia, Debrecen*, 1954, p. 179.
(11) C. Liebermann and F. Giesel, *Ber.*, **23**, 508 (1890).
(12) R. Willstätter and A. Bode, *Ann.*, **326**, 60 (1903).
(13) A. Einhorn, *Ber.*, **22**, 1495 (1889).
(14) J. Gadamer and T. Amenomiya, *Arch. Pharm.*, **242**, 9 (1904).

under the same conditions given above for the 2β-epimer to furnish, after recrystallization from dry ethanol-ether, a single crystalline product, 333 mg. (82%) of m.p. 234–236°, $[\alpha]_D^{20}$ +20.9 (H_2O, *c* 1.87) which proved identical in every respect with[11,14] pseudoecgonine hydrochloride.

Anal. Calcd. for $C_9H_{16}O_3NCl$: C, 48.76; H, 7.27; ionic Cl, 15.99. Found: C, 48.65; H, 6.99; ionic Cl, 15.71.

Attempts to oxidize 2β-hydroxymethyltropan-3α-ol. The hydrochloride of the 2β,3α-diol, 415 mg. (0.002 mole) of m.p. 258–260° and $[\alpha]_D^{20}$ −12.88° (H_2O, *c* 2.11), was treated with silver oxide exactly as given for the 2β,3β and 2β,3α epimers. A silver mirror separated while heating was in progress. The single crop of crystals amounted to 196 mg., which, after having been recrystallized from methanol and ether had a m.p. of 256–260°, $[\alpha]_D^{20}$ −12.4° (H_2O, *c* 1.98), properties identical with those of the starting diol.

The brownish residue has been subjected to paper and cellulose powder chromatography. Unfortunately, no spot could be detected when the paper was treated with Dragendorff's reagent. This may justify the conclusion that the products of oxidation of basic character initially formed were subsequently destroyed by silver oxide, while an amount of the starting material remained unaffected.

Attempt to oxidize 2α-hydroxymethyltropan-3α-ol. Under strictly identical conditions, this so-called fourth epimer withstood any attempt to be oxidized with wet silver oxide in the alkaline medium. From such a reaction mixture 380 mg. (93%) of the starting material, of m.p. 171–172°, and $[\alpha]_D^{20}$ 13.2 (H_2O) was recovered. No silver mirror formed during the reaction.

Separation of the four epimeric hydroxymethyltropan-3-ols by paper chromatography. Paper used: Whatman, No. 4. Solvent: 1-butanol: 0.043*N* ammonium hydroxide (1.5:1), descending. Temperature: 20°. Time: 8 hr. Developed by iodine vapors, and Dragendorff's reagent, respectively (5 min., 70°). Sample used: 30–40 γ.

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Derivatives of Sulfenic Acids. XXVIII. Ultraviolet Spectra of Diastereomers Obtained *via* Reactions of Sulfenyl Halides[1]

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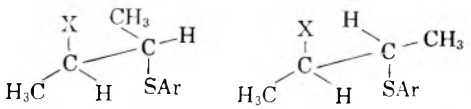
Received March 25, 1957

When 2,4-dinitrobenzenesulfenyl chloride or 2-nitro-4-carboxybenzenesulfenyl chloride add to the *cis* and *trans*-2-butenes, the diastereomeric racemates, I, I′ and II, II′ result; and acetolysis of these adducts yields the corresponding acetates, I-A, I′-A and II-A, II′-A (Ar-2, 4-dinitrophenyl or 2-nitro-4-carboxyphenyl).[3,4] Only one enantiomer of each racemate is shown.



I II

I, X = Cl; Ar = 2,4-dinitrophenyl
I-A, X = Acetate; Ar = 2,4-dinitrophenyl
I′, X = Cl; Ar = 2-nitro-4-carboxyphenyl
I′-A, X = Acetate; Ar = 2-nitro-4-carboxyphenyl
II, X = Cl; Ar = 2,4-dinitrophenyl
II-A, X = Acetate; Ar = 2,4-dinitrophenyl
II′, X = Cl; Ar = 2-nitro-4-carboxyphenyl
II′-A, X = Acetate; Ar = 2-nitro-4-carboxyphenyl

The availability of the above compounds suggested the present investigation, whose purpose was to determine if the ultraviolet absorption spectra of the diastereomeric racemates would reveal any differences; and whether or not these could be correlated with the configurations of the respective racemates.

While the ultraviolet spectra of diastereomers have been investigated in only a few instances, some interesting correlations have been revealed. Thus, Hawthorne and Cram[5] assigned stereochemical configurations to certain substituted dinitroanilines on the basis of the relative intensities at the wave length of their major absorption band and also noted small differences in the positions of the absorption maxima for pairs of diastereomeric racemates. Cromwell and co-workers[6] correlated the stereochemistry of certain ethyleneimine ketones with their ultraviolet spectra; and, in a system more closely related to the present one, Freed and Sancier[7] found that the absorption maxima for solutions of iodine in the respective 2-butenes differed (*cis* = 295 mμ; *trans* = 297 mμ) but did not rationalize this difference.

The ultraviolet spectra of the compounds investigated in the present study are summarized in Table I. As expected, the acetates and chlorides of each system have very closely related spectra, since the chromophoric system in each chloride is but little changed in the conversion to the acetate. There is, however, a marked regularity in the displacements of the absorptions to longer wave lengths in the isomers obtained from *trans*-2-butene. Thus, in the first maximum, the product I, I-A, I′ and I′-A (derived from *cis*-2-butene) clearly absorb at shorter wave lengths than do II, II-A, II′ and

(1) This study was supported, in part, by the Office of Ordnance Research, U. S. Army Contract DA-04-495-Ord. 306 and is abstracted from the Ph.D. dissertation of Anton J. Havlik, University of Southern California, 1954. For part XXVII, *cf. J. Chem. Ed.*, **33**, 585 (1956).

(2) Atomic Energy Commission Predoctoral Fellow, 1951–53.

(3) A. J. Havlik and N. Kharasch, *J. Am. Chem. Soc.*, **78**, 1207 (1956).

(4) N. Kharasch and A. J. Havlik, *J. Am. Chem. Soc.*, **75**, 3734 (1953).

(5) F. Hawthorne and D. J. Cram, *J. Am. Chem. Soc.*, **74**, 5859 (1952).

(6) N. H. Cromwell, N. G. Barker, R. A. Wanke, P. J. Vanderhorst, F. W. Olson, and J. H. Anglin, *J. Am. Chem. Soc.*, **73**, 1044 (1951).

(7) S. Freed and K. M. Sancier, *J. Am. Chem. Soc.*, **74**, 1273 (1952).

TABLE I

ULTRAVIOLET SPECTRA OF DIASTEREOMERIC RACEMATES OBTAINED VIA 2,4-DINITROBENZENESULFENYL CHLORIDE AND 2-NITRO-4-CARBOXYBENZENESULFENYL CHLORIDE AND THE *Cis* AND *Trans* 2-BUTENES

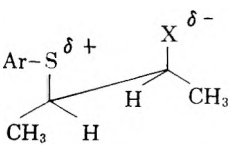
Compound[a]	$\lambda_{initial}$ ϵ	λ_{max} ϵ	λ_{min} ϵ	$\lambda'^{b,c}_{max}$ ϵ	λ'_{min} ϵ	λ''_{max} ϵ	λ''_{min} ϵ	λ_{final} ϵ
I	380	328	287	269.5	264			215
	3,400	11,250	3,740	5,730	5,570			11,050
II	380	331	287.5	270	264			215
	3,700	11,580	3,650	5,740	5,660			12,410
I-A	380	328	288	269	263			215
	3,615	10,720	3,530	5,420	5,220			11,000
II-A	380	331	289.5	270	264			215
	3,560	10,820	3,790	5,840	5,800			13,580
I′	380	359.5	318	287	273.5	261	237	215
	2,208	3,000	1,540	12,550	11,600	13,680	6,940	11,600
II′	380	360.5	319	289	274	263	237.5	215
	2,405	3,070	1,620	13,100	10,150	13,820	7,270	12,290
I′-A	380	360.5	317.5	286	274	262	235.5	215
	2,455	3,270	1,645	13,150	10,840	14,400	6,940	11,750
II′-A	380	361.5	320	289	274	263	241	215
	2,380	3,020	1,760	12,800	10,100	13,600	7,470	12,820

[a] The numbers correspond to those in the text. Compounds I, I-A, I′ and I′-A are the *threo* compounds, formed from the *cis*-2-butene. The methanol used for the spectral determinations was the pure reagent and was dried by refluxing with magnesium. The prime numbers refer to the compounds derived from 2-nitro-4-carboxybenzenesulfenyl chloride; those without prime marks are derived from 2,4-dinitrobenzenesulfenyl chloride. [b] This represents a shoulder in the absorption curves. [c] The two maxima, at about 270 mμ and 330 mμ, for the 2,4-dinitrophenyl function are characteristic and have been observed for numerous 2,4-dinitrophenylthio derivatives in this laboratory. Two of the absorbing systems involved can be considered to have been reported on by E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, 71, 84 (1949). Thus, *p*-nitrophenyl methyl sulfide absorbs at 338 mμ (log ϵ = 4.12) and another maximum at 215 mμ (log ϵ = 3.81); o-nitrophenyl methyl sulfide, 372 mμ (log ϵ = 3.55), 266 mμ (sh.), log ϵ = 3.21, and 244 mμ, log ϵ = 4.27. Also, application of the displacement value of L. Doub and J. M. Vandenbelt [*J. Am. Chem. Soc.*, 69, 2714 (1947)] to the maximum reported by Fehnel and Carmack for phenyl isopropyl sulfide (258 mμ; log ϵ = 3.75) suggests a value of about 285 mμ as the expected position of the maximum for the *p*-carboxyphenylthio chromophore. Since the maxima of the various chromophoric systems usually suffer a hypsochromic shift when these are involved in "cross conjugation," (cf. *e.g.*, G. E. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1947, p. 235; and H. Gilman, "Organic Chemistry," Vol. III, John Wiley and Sons, Inc., New York, N. Y., p. 167), it appears that certain of the maxima in Table I may represent the *p*-nitrophenylthio (328–331 mμ), *o*-nitrophenylthio-(359–60 mμ) and *p*-carboxyphenylthio- (287–289 mμ) chromophores.

II′-A (derived from *trans*-2-butene), and this pattern is continued at the other minima and maxima shown in Table I. This suggests that the chlorides and acetates are structurally related in a regular manner, which is also fully supported by the chemical evidence.[3,4]

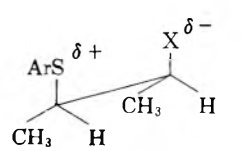
The energy differences between the absorption maxima as reported in Table I vary in value depending upon the wave length under observation. A series of calculations using the relation, $E = hc\bar{\nu}$, revealed that the differences were in the range of 200 to 1,000 cal./mole. These relatively small energy differences appear to be of the right order of magnitude for diastereomerically related alicyclic compounds.

The chromophoric systems in the derivatives of the 2-butenes under consideration are, essentially, the respective arylthio groups, and any differences in the spectra must be related to the effects of the remainders of the molecules on these absorbing systems. (*cf.* also footnote *c* of Table I). While the present data are insufficient to warrant a definite explanation of the observed differences in the spectra of the diastereomeric pairs of compounds, a suggested explanation—based on differences in degrees of stabilizations of conformations approaching III *vs.* those of IV has been put forward.[8]



III (and mirror image)

Conformation of racemate obtained by *trans* addition of ArSX to *cis*-2-butene, showing maximum interaction of ArS and X (X = Cl and $OCOCH_3$)



IV (and mirror image)

Corresponding conformation of racemate obtained by *trans* addition of ArSX to *trans*-2-butene.

Essentially, the suggestion is made that (a) the sulfur atom of ArS is slightly positive because of the electron-withdrawing effects of the particular Ar

(8) A. J. Havlik, Ph.D. dissertation, University of Southern California (1954).

groups (2,4-dinitrophenyl and 2-nitro-4-carboxyphenyl) attached to the sulfur atom; while X (Cl or $-OCOCH_3$) is slightly negative, as expected from the electronegativities of these substituent groups. (b) Some degree of stabilization is obtained by attraction between $ArS^{\delta+}$ and $^{\delta-}X$, in view of the partial charges on these groups and the fact (as inferred from models) that the groups can approach one another very closely. (c) Because of the overlapping of the methyl groups in IV (compare models), conformations approaching III will be more likely than those approaching IV. (d) Then, assuming there will be a difference between the energies necessary to raise III to its excited state (as compared for the same process for the less-stabilized IV), it is predicted that the racemate (III) obtained by *trans* addition of ArSX to *cis*-2-butene will require slightly greater energies to be raised to the excited state than will the racemate related to IV. Since the additions of sulfenyl halides to olefins are known to be *trans*,[3,4] and from the knowledge that the adducts as I,I′ and II, II′ undergo acetolysis in a stereospecific manner (involving participation by neighboring sulfur)[3], it follows that the adducts and acetates from *cis*-2-butene are the *threo* forms, related to III, which absorb at shorter wave lengths. Thus, the chemical evidence for the structures of the products agrees with the suggested rationalization of the spectral characteristics of the diastereomeric racemates.

EXPERIMENTAL

The preparations of the compounds of Table I have been previously reported.[3,4] The spectra were measured in absolute methanol solutions, on a Cary recording spectrophotometer.[9]

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Noncatalytic Fischer Indole Synthesis

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Although Wolff in 1912[1] mentioned that distillation of acetophenone phenylhydrazone gave a low yield of 2-phenylindole, it has not been generally realized that no catalyst is necessary in the Fischer indole synthesis. No reference is made to the noncatalytic reaction in the extensive reviews of indole chemistry by Elderfield[2] and Sumpter and Miller.[3] We have found that in general good yields of substituted indoles can be obtained by heating the corresponding phenylhydrazones in a solvent. In many

TABLE I

THERMAL CYCLIZATION OF PHENYLHYDRAZONES

Starting Material	Product	Solvent[a]	Time, Hr.	Yield, %	Method of Isolation and Purification
Methyl ethyl ketone phenylhydrazone	2,3-Dimethylindole	EG	3	70	[b]
Methyl ethyl ketone phenylhydrazone	2,3-Dimethylindole	EG[c]	4	68	[b]
Methyl ethyl ketone phenylhydrazone	2,3-Dimethylindole	TET	17	48	[d]
Acetone phenylhydrazone	2-Methylindole	DEG	3.5	36	[e]
n-Butyraldehyde phenylhydrazone	3-Ethylindole	EG	24	44	[e]
Propionaldehyde *p*-tolylhydrazone	3,5-Dimethylindole	EG	4	..	[b]
Propionaldehyde *N*-methylphenylhydrazone	1,3-Dimethylindole	EG	6	70	[f]
Methyl ethyl ketone *N*-methylphenylhydrazone	1,2,3-Trimethylindole	EG	8	65	[f]
Methyl ethyl ketone *o*-chlorophenylhydrazone	7-Chloro-2,3-dimethylindole[g]	DEG	2	55	[e]
Methyl ethyl ketone 2,5-dichlorophenylhydrazone	4,7-Dichloro-2,3-dimethylindole[h]	EG	6	66	[e]
Butyrophenone phenylhydrazone	3-Ethyl-2-phenylindole	EG	16	50	[b]
Acetophenone phenylhydrazone	2-Phenylindole	EG	48	54	[i]

[a] EG = ethylene glycol; DEG = diethylene glycol; TET = tetralin. [b] Precipitation with water followed by recrystallization from petroleum ether (Darco). [c] Contained 2% sodium hydroxide. [d] Precipitation with petroleum ether followed by recrystallization from petroleum ether (Darco). [e] Steam distillation followed by recrystallization from petroleum ether (Darco). [f] Reduced pressure distillation. [g] Previously unreported compound, m.p. 69–70.5°; nitrogen content: found 7.77%; required 7.80%. [h] Previously unreported compound, m.p. 90–91°; nitrogen content; found 6.66%; required 6.54%. [i] Precipitation with water followed by recrystallization from heptane (Darco).

(9) This is the same instrument, Model 11PMS, as used by Hawthorne and Cram.[5] The kind permission of the faculty of the University of California, Los Angeles, to use this facility, with the assistance of William Netusil, is gratefully acknowledged.

(1) Wolff, *Ann.*, 394, 107 (1912).
(2) Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, Inc. New York, 1952, Vol. 3, pp. 7–42.
(3) Sumpter and Miller, *The Chemistry of Heterocyclic Compounds*, Interscience Publishers, Inc. New York, 1954, Vol. 8, pp. 3–23.

cases the products are easier to work up because of the absence of an acid catalyst.

The method is widely applicable. 2-Phenylindole, 2,3-dimethylindole, 2-methyl-3-ethylindole, 3,5-dimethylindole, 1,3-dimethylindole, 1,2,3-trimethylindole, 7-chloro-2,3-dimethylindole, 4,7-dichloro-2,3-dimethylindole and 3-ethyl-2-phenylindole have all been made in fair to good yields. The optimum reaction conditions have not been determined for most of these compounds. With some, reaction is complete after two to three hours in boiling ethylene glycol; others require refluxing 24 hr. or more. In some cases the reaction rate is accelerated by the higher temperature obtained in refluxing diethylene glycol. The polarity of the solvent is not critical; tetralin works about as well as the glycols.

No theory has been formulated about the mechanism of the reaction. Robinson and Robinson's widely accepted mechanism[4,5] for the Fischer synthesis involving an acid-catalyzed benzidine type rearrangement does not appear to be adequate, since the cyclization takes place even in the presence of small amounts of alkali.

Reaction conditions and yields are given in Table I. All reactions were carried out by refluxing a solution of the phenylhydrazone in the specified solvent. Products were isolated by steam distillation, reduced pressure distillation, or precipitation, and purified by recrystallization or distillation.

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(4) Robinson and Robinson, *J. Chem. Soc.*, **113**, 639 (1918).

(5) Robinson and Robinson, *J. Chem. Soc.*, **125**, 827 (1924).

Preparation and Reactions of Some Aralkyl Cyanoacetic Esters

PETE D. GARDNER AND RICEARD L. BRANDON

Received April 8, 1957

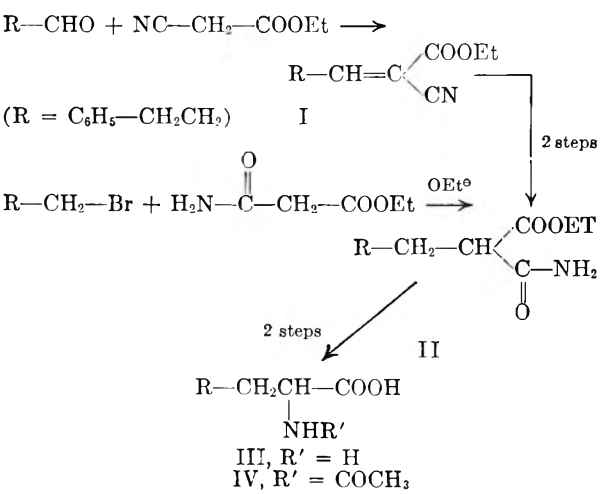
The occurrence in nature of cyclic structures possessing the acetamido function prompted an investigation of cyclization reactions of some aralkyl acids containing amine or acetamido functions.[1] The problem was twofold, that of synthesis of appropriate α-acetamido aralkyl acids and that of cyclizing such substances to the corresponding ketones without alteration of the substituent. Moreover, it was required that only these methods be considered which could be easily adapted to the use of variously substituted starting materials.

(1) One such cyclization using polyphosphoric acid has been reported. W. J. Horton and G. Thompson, *J. Am. Chem. Soc.*, 76, 1909 (1954).

α-Amino-δ-phenylvaleric acid (III) was prepared from hydrocinnamaldehyde by the sequence shown. Condensation of the aldehyde with ethyl cyanoacetate, by the general Knoevenagel[2] reaction using piperidine–acetic acid as a catalyst[3] gave I which was then converted by hydrogenation to ethyl α-cyano-δ-phenylvalerate. Hydrolysis of this cyano ester to α-carbethoxy-δ-phenylvaleramide (II) was effected by treatment with polyphosphoric acid.[4,5] The final conversion to the amine (III) was made by the Hofmann method.[6] Alternatively, II was prepared by the base-catalyzed condensation of 1-bromo-3-phenylpropane with ethyl malonamate.

Several attempts to cyclize the amino acid (III) or its acetyl derivative (IV) with polyphosphoric acid gave only recovered starting material. The carbethoxy amide (II) was equally resistant to cyclization by this reagent.

Another series of compounds of interest appeared to be obtainable by application of the above described sequence of reactions to *p*-hydroxybenzaldehyde. Thus, ethyl α-cyano-β-(*p*-hydroxyphenyl)-propionate (V, R = H) and the acetate (R = $COCH_3$) were prepared and the former converted to the amide (VI, R = H) *via* the imino ester hydrochloride. The use of polyphosphoric acid in this instance (R = H or $COCH_3$) was unsuccessful. Repeated attempts to prepare the corresponding amino acid from VI by the Hofmann method were unsuccessful. It has been reported that the corresponding methyl ether compound failed to undergo this reaction.[6] The failure of the Hofmann reaction as a general method appears to be a definite limitation in this approach to the α-amino acids.



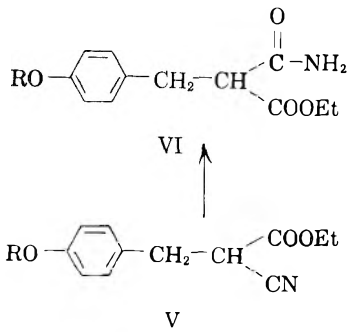
(2) J. Scheiber and F. Meisel, *Ber.*, **48**, 257 (1915).

(3) A. C. Cope, U. S. Patent 2,655,526; *Chem. Abstr.*, **48**, P11484 (1954).

(4) H. R. Snyder and C. T. Elston, *J. Am. Chem. Soc.*, **76**, 3039 (1954).

(5) C. R. Hauser and C. J. Eby, *J. Am. Chem. Soc.*, **79**, 725 (1957).

(6) See for example R. Gaudry, *Can. J. Research*, **23B**, 234 (1954).



EXPERIMENTAL

Ethyl hydrocinnamylidenecyanoacetate (I). A mixture of 33.5 g. (0.25 mole) of hydrocinnamaldehyde and 28.2 g. (0.25 mole) of ethyl cyanoacetate was dissolved in 75 ml. of dry dioxane and the solution cooled to 0°. Piperidine (0.85 g.) was added dropwise and the solution cooled occasionally to maintain the temperature at 0°. After standing at room temperature for 5 hr., the solution was diluted with ether and washed successively with dilute hydrochloric acid, dilute potassium carbonate solution, and water. The ether solution was dried over calcium chloride and solvent evaporated under reduced pressure. The residue was distilled to give 21.5 g. (35%) of I as a light yellow liquid; b.p. 172–174° (dec.) (3.0 mm.). In a run allowing 8 hr. for reaction, the yield was 53%.

Anal. Calcd. for $C_{14}H_{15}O_2N$: C, 73.35; H, 6.59; N, 6.12. Found: C, 73.46; H, 6.44; N, 6.30.

Ethyl α-cyano-δ-phenylvalerate. A solution of 15.0 g. (0.065 mole) of I in pure dioxane was reduced with hydrogen at one atmosphere pressure over 5% palladium-charcoal. The crude product, after isolation in the usual manner, was dissolved in ether and washed successively with dilute hydrochloric acid, dilute potassium carbonate solution, and water. The dried solution was freed of solvent and distilled to yield 11.1 g. (74%) of faintly yellow liquid; b.p. 139–141° (0.5 mm.).

Anal. Calcd. for $C_{14}H_{17}O_2N$: C, 72.74; H, 7.44; N, 6.06. Found: C, 72.74; H, 7.43; N, 6.15.

α-Carbethoxy-δ-phenylvaleramide (II). (*a*) *From ethyl α-cyano-δ-phenylvalerate.* A mixture of 10.0 g. (0.045 mole) of ethyl α-cyano-δ-phenylvalerate and 100 g. of polyphosphoric acid was heated for 45 min. at 75°. Addition of a mixture of ice and water to the complex resulted in the formation of a heavy white precipitate. After drying in vacuum and recrystallization from ethyl acetate–petroleum ether (60–68°) there was obtained 5.1 g. (47%) of II, m.p. 114°. When the heating time was extended to 2 hr. and the temperature maintained at 100°, the yield was 83%.

Anal. Calcd. for $C_{14}H_{19}O_3N$: C, 67.40; H, 7.70; N, 5.62. Found: C, 67.69; H, 7.72; N, 5.90.

(*b*) *By aralkylation of ethyl malonamate.* A solution of 6.6 g. (0.05 mole) of ethyl malonamate[7] in 10 ml. of absolute ethanol was added to 1.1 g. (0.05 atom) of sodium dissolved in 20 ml. of ethanol. A solution of 10.0 g. (0.05 mole) of 1-bromo-3-phenypropane in 10 ml. of ethanol was added in one portion and the mixture stirred for 1.5 hr. at room temperature. A solution of 3.0 g. (0.05 mole) of acetic acid in 150 ml. of ether was added and the ether solution washed with water. Evaporation of solvent and recrystallization of the residue from ethyl acetate–petroleum ether (60–68°) gave 2.4 g. (19%) of II having the same m.p. as that observed for the preparation described in (a).

α-(3-Phenylpropyl)malonamic acid was obtained in 48% yield by hydrolysis of the ester in methanolic potassium hydroxide during 2 hr. at room temperature. Recrystallization from ethyl acetate-cyclohexane gave the pure acid, m.p. 129–131° (dec.).

Anal. Calcd. for $C_{12}H_{15}O_3N$: C, 65.12; H, 6.83. Found: C, 65.51; H, 7.03.

α-Amino-δ-phenylvaleric acid (III). A solution comprised of 1.8 ml. of bromine and 10 g. of potassium hydroxide in 100 ml. of water was cooled to −10° in an ice-methanol mixture. To this was added, with stirring, 5.0 g. (0.022 mole) of α-(3-phenylpropyl)malonamic acid. The mixture was stirred until the acid had completely dissolved (50 min.) and the resulting yellow solution was heated nearly to the boiling point and maintained at that temperature for 10 min. The solution was cooled to 0° and neutralized with dilute hydrochloric acid. Precipitation of the amino acid occurred near *p*H 7. Collection of the precipitate, followed by recrystallization from water, gave 3.2 g. (73%); m.p. 208–212° (dec.) (lit.[8] 203–206°).

Anal. Calcd. for $C_{11}H_{15}O_2N$: C, 68.38; H, 7.83. Found: C, 68.62; H, 7.72.

Of the many Hofmann reactions attempted with substituted malonamic acids, this was the only one which gave isolable amino acid. It was largely due to these failures that the study was discontinued.

α-Acetamido-δ-phenylvaleric acid (IV). The acetylation of III was effected by treating 5.0 g. (0.030 mole) of the amino acid with 10 ml. of acetic anhydride and three drops of pyridine and heating the resulting solution on a steam bath for 15 min. Isolation in the usual manner by hydrolysis and ether extraction gave the product as a viscous liquid. Crystallization from ethyl acetate–cyclohexane gave 2.5 g. (42%) of colorless IV, m.p. 144–146°.

Anal. Calcd. for $C_{13}H_{17}ON$: C, 66.35; H, 6.96; N, 5.95. Found: C, 66.62; H, 7.07; N, 5.95.

Attempts to cyclize either III or IV by the use of polyphosphoric acid were unsuccessful.

Ethyl α-cyano-β-(p-hydroxyphenyl)propionate (V). A mixture of 24.0 g. (0.20 mole) of *p*-hydroxybenzaldehyde, 22.6 g. (0.20 mole) of ethyl cyanoacetate and 1.2 g. of acetic acid was dissolved in 80 ml. of purified dioxane. To this was added 0.84 g. of piperidine and the solution was shaken with 1 g. of 5% palladium-charcoal under one atmosphere of hydrogen. After the theoretical quantity of hydrogen had been absorbed, the mixture was processed as described above. Material obtained in a previous run proved to be thermally unstable. This preparation was, therefore, freed of solvent and unreacted ethyl cyanoacetate by heating briefly under reduced pressure and used without further purification (39 g.).

Ethyl α-(p-hydroxybenzyl)malonamate (VI). The 39 g. preparation of V described above was mixed with 9.0 g. of ethanol and placed in a system equipped for the addition of hydrogen chloride. The solution was stirred and hydrogen chloride bubbled through with occasional cooling to maintain the temperature between 40° and 45°. After 1.25 hr. the solution became too viscous to permit stirring and crystalline material began to separate. The mixture was allowed to stand for 0.5 hr. at room temperature and then heated over a low flame until a brisk evolution of gas occurred. After gas evolution had ceased, dry ether was added and the mixture stirred until crystallization occurred. Recrystallization from benzene afforded 15.0 g. (35%) of light yellow solid, m.p. 127–129°.

Anal. Calcd. for $C_{12}H_{15}O_4N$: C, 60.76; H, 6.37; N, 5.91. Found: C, 60.71; H, 6.33; N, 6.05.

No amino acid could be obtained from the reaction of this substance under Hofmann conditions.

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(7) A. Pinner, *Ber.*, 28, 479 (1895).

(8) J. von Braun and O. Kruber, *Ber.*, 45, 389 (1912).

Reaction of 4-Methyldioxolone-2 with Aqueous Ethylamine

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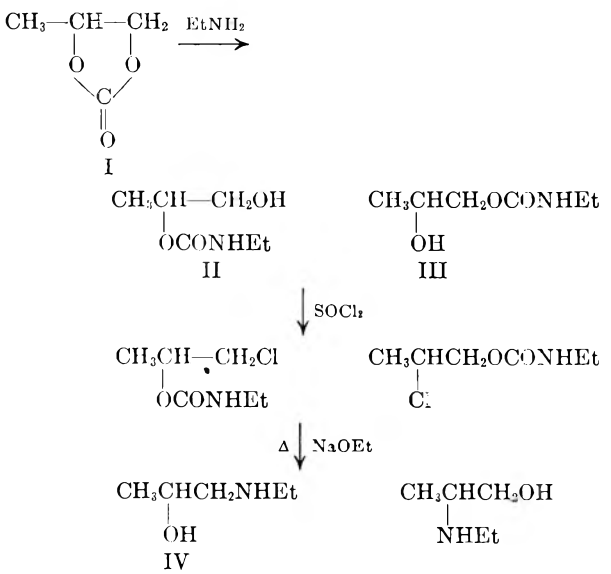
Received April 16, 1957

Najer *et al.*[1] have reported that 4-methyldioxolone-2 (I; the cyclic carbonate of propylene glycol) reacts with 33% ethylamine to give exclusively the *N*-ethyl carbamate of the secondary alcohol group (II) and none of its structural isomer (III). They based their conclusions on the fact that they isolated and identified 1-ethylamino-2-propanol (IV) upon degrading their carbamate according to the scheme shown in Chart I.

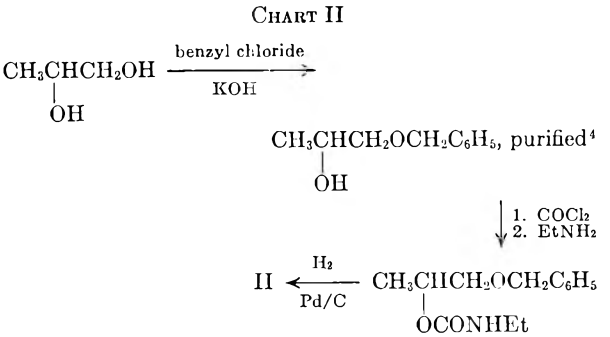
CHART I



Since we have shown in another case[2] that this type of structure proof is unreliable because a rearrangement occurs during the thionyl chloride reaction, and since our experience has been that dioxolones react with ammonia to give mixtures of carbamates[3] in which the primary carbamate predominates, we reinvestigated the French work.

Compound II was prepared by the sequence outlined in Chart II:

CHART II



The product was distilled through a four-inch Widmer-type column. It all boiled at 99–100°/0.5–0.6 mm. The n_D^{20} of several arbitrary cuts varied from 1.4512 to 1.4518. The phenylurethane melted at 83.8–85.0°.

Compound III was prepared by treating propylene glycol with a deficiency of phosgene[5] in benzene followed by reaction of the intermediate chlorocarbonate with ethylamine. The entire product, distilled through a small Widmer column, boiled at 99°/0.4 mm.; n_D^{20} 1.4548; m.p. of phenylurethane, 95.2–96.4°.

The material (V) prepared according to the procedure of Najer *et al.*[1] was distilled through a 55-cm. helix-packed column. After a small forerun, which was discarded, the product boiled at 92°/0.3 mm.; n_D^{20} 1.4510. The phenylurethane melted at 69–79° and could not be further purified by recrystallizations. This melting point spread suggested that V was a mixture of carbamates which had not been separated by the attempted fractional distillation. This conclusion was borne out by the infrared study of II, III, and V.

Whereas II and III have bands at 9.25 μ and 9.5 μ respectively, the relative extinction of III is the same at both wave lengths while II has a stronger absorption band at 9.5 μ than at 9.25 μ. III has a strong band at 9.75 μ which is shifted to 10.0 μ in the case of II and a band at 10.37 μ absent in II. Mixtures of II and III may be quantitatively analyzed by measuring the extinction in methylene chloride against methylene chloride in the blank cell at 9.25 μ and 9.5 μ. The French product V was analyzed in this way against II and III[6] as standards and was found to consist of approximately 30% of II and 70% of III. The similarity of this distribution of isomers to that obtained from the reaction of 4-(*o*-methoxyphenoxy)dioxolone-2 with alcoholic ammonia[2] is striking.

(1) H. Najer, P. Chabrier, and R. Giudicelli, *Bull. soc. chim. France*, 1142 (1954).

(2) M. M. Baizer, J. R. Clark, and J. Swidinsky, *J. Org. Chem.*, **22**, 1595 (1957).

(3) J. D. Malkemus, U.S. Pat. 2,627,524, February 3, 1953 states without presenting proof that the reaction of higher unsymmetrical analogs of ethylene carbonate with ammonia probably yields mixtures of structurally isomeric hydroxyalkyl carbamates.

(4) C. L. Butler, A. G. Renfrew, and M. Clapp, *J. Am. Chem. Soc.*, **60**, 1472 (1938).

(5) The assumption is made that reaction occurs preferentially at the primary alcohol group. *Cf.* Ref. (2) for a discussion of the confirmation of this assumption.

(6) It is possible that our sample of III contained a trace of II as an impurity, since the infrared spectrum of III shows a small shoulder at 10.00–10.05 μ in which region II has a strong absorption band.

Chlorination of either II or III or V yielded the identical chlorocarbamate, b.p. 69°/0.5 mm.; n_D^{20} 1.4530, for which we propose the structure VI on

$$\begin{array}{c} CH_3—CH—CH_2—Cl \\ \vdots \\ OCONHEt \end{array}$$

VI

the basis of analogy with previous findings.[2] This formulation is consistent with the results obtained by Najer *et al.*[1] on further degradation and again indicates that in the chlorination of an α-hydroxy-carbamate there is a rearrangement, where needed, to produce the 1-chloro-derivative.

EXPERIMENTAL[7]

1-Benzyloxy-2-(N-ethylcarbamoxy) propane. 1-Benzyloxy-2-propanol was prepared according to Butler *et al.* Purification of the crude by treatment with phthalic anhydride was included. The product boiled at 126–128°/11–12 mm.; n_D^{20} 1.5112. To a stirred solution at 3° of 54.5 g. (0.55 mole) of phosgene in 250 ml. of dry toluene was added in the course of 60 min. a solution of 83 g. (0.5 mole) of 1-benzyloxy-2-propanol and 72.5 g. (0.6 mole) of dimethylaniline in 200 ml. of dry toluene. The temperature was maintained at 0–5° by external cooling with ice-salt during another hour of stirring. The mixture was then washed with ice water, 40 ml. of 5% hydrochloric acid, and two 50-ml. portions of ice water. The washed chloroformate solution was stirred in an ice-salt bath and 184 g. (1.35 moles) of 33% ethylamine was added in 20 min. at an internal temperature below 15°. The mixture was stirred one more hour in the cold and one hour at room temperature, then washed with three 100-ml. portions of water. The toluene was stripped from the organic layer and the product distilled through a helix-packed column to yield 101.1 g. (85.5%) of 1-benzyloxy-2-(*N*-ethylcarbamoxy) propane, b.p. 144–147°/0.5–0.8 mm.; $n_D^{22.5}$ 1.5020.

Anal.[8] Calcd. for $C_{13}H_{19}NO_3$: C, 65.79; H, 8.07; N, 5.91. Found: C, 66.00; H, 8.30; N, 5.96.

2-(N-Ethylcarbamoxy)-1-propanol (II). 1-Benzyloxy-2-(N-ethylcarbamoxy)propane (23.7 g., 0.1 mole) in 200 ml. of 99% isopropyl alcohol was reduced with hydrogen at atmospheric pressure using 12 g. of 15% palladium-on-carbon previously saturated with hydrogen. The theoretical quantity of hydrogen was absorbed in 173 min. After filtration of the catalyst and stripping of the solvent, the product was fractionated through a short spiral-packed column. Four cuts, all boiling at 99–100°/0.5–0.6 mm. were taken: (1) 1.47 g., n_D^{20} 1.4490, (2) 3.13 g., n_D^{20} 1.4512, (3) 3.12 g. n_D^{20} 1.4516, (4) 4.76 g., n_D^{20} 1.4518. The total recovery was about 85%. Fraction 3 was analyzed.

Anal. Calcd. for $C_6H_{13}NO_3$: C, 48.98; H, 8.83; N, 9.52. Found: C, 48.18; H, 8.64; N, 9.85.

The *phenylurethane* was prepared by mixing equimolar amounts of the carbamate and phenyl isocyanate and allowing the mixture to stand for several days at room temperature. Trituration with cyclohexane caused crystallization. Recrystallization from diisopropyl ether yielded a product melting at 83.8–85°.

Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 59.20; H, 6.94; N, 9.97.

1-(N-Ethylcarbamoxy)-2-propanol (III). To a solution of 76 g. (1.0 mole) of propylene glycol in 250 ml. of dry benzene was added dropwise below 30° in the course of 30 min. a solution of 49.5 g. (0.5 mole) of phosgene in 250 ml. of benzene. Stirring was continued for another hour at about 30°. Then a solution of 61 g. (0.5 mole) of dimethylaniline in 200 ml. of dry benzene was added at an internal temperature of 25°. The mixture was stirred an additional 30 min., cooled to 5° and washed with 200 ml. of cold 20% sodium chloride, 5% hydrochloric acid in 100 ml. of saturated salt solution, and finally two 100-ml. portions of cold 20% salt solution. The benzene solution was then added with stirring in the course of 20 min. to 250 ml. of 33% ethylamine at 5–7°. Stirring was continued in the cold for 2 hr. and thereafter the mixture allowed to stand in the refrigerator for 64 hr. Fractionation through a 4-inch spiral packed column of the residue remaining after the removal of the benzene yielded 2.27 g. of product,[9] b.p. 99°/0.4 mm., n_D^{20} 1.4548.

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 48.98; H, 8.83; N, 9.52. Found: C, 49.62; H, 9.03; N, 10.09.

The *phenylurethane*, prepared as above, melted at 95.2–96.4°.

Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.92; H, 6.57; N, 10.51.

A mixture of the phenylurethane of III and the phenylurethane of II melted at 70–83°.

Product of Najer et al.[1] (V). The crude product prepared from 204 g. propylene glycol and 272 g. of 33% ethylamine according to the procedure of the French authors was fractionated through a 55-cm. column packed with glass helices. After a small forerun (24 g.) the entire remaining product boiled at 92°/0.3 mm.[10] Each of 15 arbitrary cuts had n_D^{20} 1.4510. The main fraction together with refractionated forerun and heel yielded a total of 270.4 g. (92%) of product.

Anal. Calcd. for $C_6H_{13}O_3N$: C, 48.98; H, 8.83; N, 9.52. Found: C, 49.54; H, 9.11; N, 10.10.

The crude *phenylurethane*, prepared as above, melted at 66–86°. Two recrystallizations raised the m.p. to 69–79°, unchanged by further recrystallizations.

Reaction of the carbamates II, III, V with thionyl chloride. The procedure used with V is typical. V (14.7 g., 0.1 mole) was well stirred while 23.8 g. (0.2 mole) of thionyl chloride was added slowly while cooling with a water bath. The mixture was then heated under reflux for 3 hr. The excess thionyl chloride was removed by distillation, the residue taken up in 100 ml. of benzene and the solution washed successively with water, four portions of 5% sodium bicarbonate, water, 25 ml. of 5% hydrochloric acid, and again water. After drying the solution over sodium sulfate, the benzene was stripped and the residue vacuum-fractionated: b.p. 68–69°/0.5 mm.[11]; n_D^{20} 1.4530; yield, 13.37 g. (80.5%).

Anal. Calcd. for $C_6H_{12}NO_2Cl$: C, 43.50; H, 7.24; N, 8.46. Found: C, 43.88; H, 7.20; N, 8.18.

The product from the reaction of II and thionyl chloride was obtained in 60% yield, n_D^{20} 1.4529; from III, n_D^{20} 1.4520.

All three chloro-carbamates gave identical infrared spectra.[12]

Quantitative analysis of V by infrared spectrophotometry. The extinctions of 5% solutions in spectroscopic dichloromethane of II, III, and V were measured at 9.25 μ and 9.5 μ against dichloromethane in the reference beam under the following conditions: resolution, 960; response, 2:2; gain, 4; speed, 2. Using I and III as standards, calculations from repeat measurements of V gave the following values for the composition of V: II, 36.4%, 34.3%; III, 63.6%, 65.7% respectively.

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(7) Melting points are corrected, boiling points are not.

(8) All analyses by Schwarzkopf Microanalytical Laboratory, Woodside, L. I., N. Y.

(9) The low yield is due to the high solubility of the intermediate chloroformate in water.

(10) Reported[1] b.p. 99–100°/0.06 mm.

(11) Reported[2] b.p. 80–81°/0.08 mm.

(12) The instrument used was a Perkin-Elmer Model 21.

Sodium Hypobromite Oxidation of Certain Cycloalkanones

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The hypohalite oxidation of methyl ketones to carboxylic acids is a well-recognized useful synthetic procedure.[1,2] More recently higher alkylaryl and alkylheterocyclic ketones have been converted to carboxylic acids in good yields by the use of alkaline hypohalite solutions.[3,4] The present work reports the hypohalite oxidation of cyclohexanone and cyclopentanone.

Cyclohexanone was smoothly converted to adipic acid by three equivalents of sodium hypobromite solution at room temperature. The attack of sodium hypobromite on cyclopentanone was considerably more vigorous however, and when the reaction was allowed to proceed at 30–35°, a very small amount of succinic acid was isolated. When conducted at 5–10° a fair yield of glutaric acid along with a smaller amount of succinic acid was isolated. With cyclopentanone the consumption of sodium hypobromite was more than the three moles required according to the stoichiometry as described by Levine and Stephens[4] as evidenced by the disappearance of oxidizing reagent during the course of addition of cyclopentanone.

EXPERIMENTAL

Oxidation of cyclohexanone. A sodium hypobromite solution was prepared according to the directions of Levine and Stephens[4] from 88.0 g. (2.2 moles) of sodium hydroxide and 28 ml. (0.55 mole) of bromine in 300 ml. of water. The solution was allowed to warm to 20° and was stirred rapidly while 14.7 g. (0.15 mole) of cyclohexanone was added over a 15-min. period with ice-bath cooling to maintain the temperature at 20–25°. After all the ketone had been added the solution was stirred 2 hr. longer at room temperature. The mixture was then acidified with concentrated hydrochloric acid, whereupon adipic acid precipitated. The slurry was cooled to 5° and filtered. The adipic acid was washed with ice water and dried at 75–80°. The yield of adipic acid, m.p. 150–152°, amounted to 17.3 g. (82%).

Oxidation of cyclopentanone. Cyclopentanone was added dropwise to a sodium hypobromite solution prepared from 88.0 g. of sodium hydroxide and 28 ml. of bromine in 300 ml. of water. In spite of ice-bath cooling, when the addition was started at 20°, the temperature rose to 30–35°. After 10.6 g. of cyclopentanone had been added during 15 min., the solution became colorless and gave a negative test with starch-potassium iodide test paper. The mixture was stirred 15 min. longer, acidified with hydrochloric acid, and evaporated to dryness in vacuum. The residue was extracted thoroughly with ether, and the ether solution was dried and evaporated. Trituration with ether-benzene induced crystallization, and after recrystallization from water there was obtained 2.5 g. of succinic acid, m.p. 186–188°. The mother liquor from trituration with ether-benzene was examined for glutaric acid but none could be isolated.

When the reaction mixture was maintained at 5–10° and the cyclopentanone (12.6 g.) added dropwise over a 0.5-hr. period, 1.7 g. of succinic acid and 8.8 g. of glutaric acid were obtained.

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(1) R. C. Fuson and B. A. Bull, *Chem. Revs.*, 15, 275 (1934).

(2) M. S. Newman and H. L. Holmes, *Org. Syntheses*, Coll. Vol. II, 428 (1943).

(3) M. W. Farrar and R. Levine, *J. Am. Chem. Soc.*, 71, 1496 (1949).

(4) R. Levine and J. A. Stephens, *J. Am. Chem. Soc.*, 72, 1642 (1950).

Inertness of Tetrachlorofulvenes in the Diels-Alder Reaction

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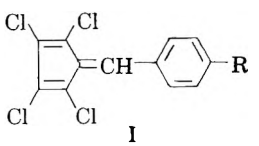
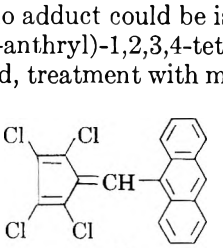
Recently the preparation of tetrachlorofulvenes was disclosed but no mention was made of their being tried in a diene synthesis.[1] It seemed to us that these compounds would be ideal in kinetic studies of the Diels-Alder reaction. Therefore, 1,2,3,4-tetrachloro-6-phenylfulvene (I, R = H) and four of its derivatives (I, R = NO_2, Cl, $N(CH_3)_2$, and OCH_3) were prepared.



I

The fulvenes in preliminary tests gave no evidence of reaction with maleic anhydride in benzene and finally were heated in molten maleic anhydride at 117° for a week. At the end of this time cooling gave colored crystals of the fulvenes in the maleic anhydride and no adduct could be isolated.

When 6-(9-anthryl)-1,2,3,4-tetrachlorofulvene (II) was prepared, treatment with maleic anhydride



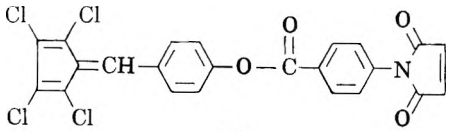
II

lead to only a mono adduct. The product still had the color typical of a fulvene and its spectrum indicated the maleic anhydride had reacted with the anthracene moiety.

The color of 1,2,3,4-tetrachloro-6-(2-furyl)fulvene pentadiene did not fade when heated at 100° with maleic anhydride for a week. In addition *p*-[6-(1,2,-

(1) E. T. McBee, R. K. Meyers, and C. F. Baranauckas, *J. Am. Chem. Soc.*, 77, 87 (1955).

3,4-tetrachloro fulvenyl)]phenyl *p*-maleimidobenzoate (III) was prepared.



III

This compound has a maleimido group which has been shown to be an active dieneophile. If the fulvene portion were a reactive diene, one would expect this compound to give a polymer via the Diels-Alder reaction, but the compound was found to be quite stable.

Compound III was dissolved in vinyl acetate and a trace of benzoyl peroxide was added. Heating gave a red polymer and no unchanged III could be isolated. The color of the polymer showed that the fulvene portion was not involved in any polymerization, but since the starting fulvene could not be recovered, copolymerization through the maleimido group with the vinyl acetate was indicated. This suggests variously colored *N*-substituted maleimides could be used to prepare colored plastics instead of mixing in dyes or pigments.

The inertness of the tetrachlorofulvenes in the Diels-Alder reaction is unexpected since 1,2,3,4-tetrachlorcyclopentadiene reacts with maleic anhydride[1] as does hexachlorocyclopentadiene.[2] Therefore, the negative inductive effect of the halogens does not seem by itself to preclude reaction of the fulvene. Steric hindrance of the aromatic group at the 6 position in these tetrachlorofulvenes is less than that in 6,6-diphenylfulvene which reacts with maleic anhydride.[3] Possibly the negative chlorine atoms and conjugation through the exo double bond have increased resonance stabilization enough to prevent the Diels-Alder reaction.

An attempt to hydrogenate the exo double bond in 1,2,3,4-tetrachloro-6-(*p*-anisyl)fulvene to give a more reactive diene resulted in the uptake of seven equivalents of hydrogen and the formation of hydrogen chloride. The product had an odor similar to anethole and was not investigated further.

EXPERIMENTAL

Tetrachlorofulvenes. Hexachlorocyclopentadiene was reduced to 1,2,3,4-tetrachlorocyclopentadiene according to previously published directions. This was condensed with furfural, anisaldehyde, benzaldehyde, *p*-chloro-, *p*-dimethylamino-, and *p*-hydroxybenzaldehyde to give known fulvenes.[1]

When a 2.45 g. sample of 1,2,3,4-tetrachlorocyclopentadiene was condensed with 1.81 g. of *p*-nitrobenzaldehyde, 1.73 g. of 6-(*p*-nitrophenyl)-1,2,3,4-tetrachlorofulvene was obtained. Recrystallization from absolute ethanol gave intensely red needles, with a blue opalescence, m.p. 196.5–197°.

Anal. Calcd. for $C_{12}H_5Cl_4NO_2$: C, 42.74, H, 1.50. Found: C, 42.62; H, 1.69.

From 2.33 g. of 9-anthraldehyde and 2.31 g. of 1,2,3,4-tetrachlorocyclopentadiene was obtained 2.42 g. of dark red crystals melting at 185–190°. Recrystallization from absolute ethanol gave red prisms of II, m.p. 193–195°.

Anal. Calcd. for $C_{20}H_{10}Cl_4$: C, 61.26: H, 2.57. Found: C, 61.07; H, 2.67.

p-Maleimidobenzoyl chloride. p-Maleimidobenzoic acid[4] (5 g.) when refluxed with thionyl chloride (16 ml.) for 4 hr. gave a quantitative yield (5.79 g.) of light yellow acid chloride. After purification by treatment with Darco in benzene, recrystallization from benzene and petroleum ether and sublimation *in vacuo* at 145–155° colorless crystals melting at 165.5–167° were obtained.

Anal. Calcd. for $C_{11}H_6ClNO_3$: C, 56.07; H, 2.57. Found: C, 56.11; H, 2.48.

Methyl p-maleimidobenzoate. Heating one gram of the acid chloride in methanol for 15 hr. gave 0.40 g. of ester, m.p. 129–133°. Recrystallization from methanol and decolorization with Darco gave white platelets, m. 133–135°.

Anal. Calcd. for $C_{12}H_9NO_4$: C, 62.34; H, 3.92. Found: C, 62.24; H, 3.92.

This ester was also prepared by treating the silver salt of the acid with methyl iodide.

p-[6-(1,2,3,4-Tetrachlorofulvenyl)]phenyl p-maleimidobenzoate. A solution of 1.06 g. of 6-(*p*-hydroxyphenyl)-1,2,3,4-tetrachlorofulvene and 1.10 g. of *p*-maleimidobenzoyl chloride in 15 ml. of benzene were heated under a reflux condenser for 15 hr. Cooling and diluting with petroleum ether (b.p. 60–70°) gave 1.01 g. of red solid, m.p. 245–249°. The analytical sample was obtained by recrystallization from benzene and melted at 249–250.5°.

Anal. Calcd. for $C_{23}H_{11}Cl_4NO_4$: C, 54.46; H, 2.18. Found: C, 54.56; H, 2.22.

Diels-Alder reactions. The molar extinction coefficient of 1,2,3,4-tetrachloro-6-(*p*-chlorophenyl)-fulvene in dry benzene was found to be 120 at 540 mμ by using solutions 3.28×10^{-3} to 8.21×10^{-3} molar. When a benzene solution 5.47×10^{-3} molar in fulvene and 4.51×10^{-2} molar in maleic anhydride was heated at 61°, no change in the optical density was found after 15 hr. Similarly when material in sealed tubes was heated at 117°, no change in the optical density was found after 5 days.

When 0.11 g. samples of the fulvenes were dissolved in 3.49 g. of maleic anhydride and heated at 117° for a week, the fulvene color did not change. Heating with water and filtering the residue gave only unchanged starting material in all cases.

A homogeneous solution of 0.56 g. of Compound II and 0.31 g. of maleic anhydride in 10 ml. of benzene was heated under a reflux condenser for one day. The orange solid which precipitated was collected by filtration, washed with benzene and dried, yield 0.35 g., m.p. 238–240.5°. One recrystallization from benzene gave light orange platelets, m.p. 239–241° (turning dark red).

Anal. Calcd. for $C_{24}H_{12}Cl_4O_3$: C, 58.78; H, 2.46. Found: C, 59.11; H, 2.50. Sap. Equiv. Calcd.: 245. Found, 242.

The ultraviolet spectrum of II and its maleic anhydride derivative indicated reaction had occurred with the anthracene ring rather than with the fulvene moiety.[5]

Copolymerization of vinyl acetate with p-[6-(1,2,3,4-tetrachlorofulvenyl)]phenyl p-maleimidobenzoate. A solution of 1.50 ml. of vinyl acetate, 0.0174 g. of *p*-6-(1,2,3,4-tetrachlorofulvenyl)phenyl *p*-maleimidobenzoate (3.431×10^{-5} mole), 3 granules of benzoyl peroxide and 6 ml. of acetone was sealed in a Pyrex test tube. The tube was heated at 87.9° for 98 hr. The tube was cooled and the red solution poured into water. The resulting red semi-solid was isolated from the aqueous solution by decantation. This material was completely soluble in both acetone and ethanol. When an ethanol solution was concentrated and chilled to −40°,

(2) E. A. Prill, *J. Am. Chem. Soc.*, **69**, 62 (1947).
(3) O. Diels, K. Alder, and P. Pries, *Ber.*, **62**, 2081 (1929).
(4) H. Barnstorff, Ph.D. Thesis, University of Colorado.
(5) P. Argabright, Ph.D. Thesis, University of Colorado.

no unreacted fulvene could be isolated. Other attempts to isolate the starting fulvene also were unsuccessful.

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Preparation of *o*-Phenylenebis(dichloroarsine) and *o*-Phenylenebis(dimethylarsine)

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Kalb[1] failed to convert *o*-benzenediarsonic acid by the action of concentrated hydrochloric acid and sulfur dioxide into *o*-phenylenebis(dichloroarsine), obtaining 1,3-dichloro-1,3-dihydrobenzofurarsan instead. This observation was also made by Hamilton and Ludeman.[2] Chatt and Mann[3] converted 1,3-dichloro-1,3-dihydrobenzofurarsan into *o*-phenylenebis(dichloroarsine) by the action of thionyl chloride. However, Goldsworthy and associates[4] converted *p*-benzenediarsonic acid into *p*-phenylenebis(dichloroarsine) in a single step by the action of alcoholic hydrogen chloride and sulfur dioxide. In our hands, by means of the modified procedures as detailed below, *o*-phenylenebis(dichloroarsine) has been prepared in 65% yield in a single step from *o*-benzenediarsonic acid, and *o*-phenylenebis(dimethylarsine) in 88% yield from the bis(dichloroarsine). The yields obtained are significantly higher by the simplified procedures than those previously reported.

EXPERIMENTAL

o-Benzenediarsonic acid. *o*-Benzenediarsonic acid was prepared by treating diazotized arsanilic acid with sodium arsenite solution according to the method of Kalb.[1] The yield of air-dried acid containing one molecule of water of crystallization (did not melt at 360°) was 56.2%.

o-Phenylenebis(dichloroarsine). A solution of 178.4 g. (0.5187 mole) of the above *o*-benzenediarsonic acid in 3000 ml. of concentrated hydrochloric acid (37.25%) containing 2.0 g. of potassium iodide was treated with a brisk stream of sulfur dioxide until precipitation ceased (35 min.). The orange-colored solid was removed by filtration and pressed as dry as possible on a sintered glass filter (435.8 g.). The moist, oily solid was treated with 400 ml. of carbon disulfide whereby some material dissolved, and two liquid layers were obtained. The aqueous layer was separated and discarded. Evaporation of the remaining carbon disulfide solution on a water bath and subsequent cooling yielded crystals. Recrystallization from carbon disulfide yielded colorless crystals of pure *o*-phenylenebis(dichloroarsine) (123.45 g. or 64.7%) melting at 96°.

Anal. Calcd. for $C_6H_4As_2Cl_4$: C, 19.59; H, 1.10; Cl, 38.57. Found: C, 19.44; H, 1.15; Cl, 38.61.

o-Phenylenebis(dimethylarsine). *o*-Phenylenebis(dimethylarsine) was prepared by a modification of the method of Chatt and Mann.[3] A Grignard solution was prepared in a 3-l. flask from 48.15 g. (1.98 atoms) of magnesium turnings, 281.05 g. (1.98 moles) of dry methyl iodide, and 500 ml. of sodium-dried ether. With rapid stirring and ice cooling in an argon atmosphere, a solution of 121.4 g. (0.330 mole) of *o*-phenylenebis(dichloroarsine) in 570 ml. of dry ether was added (1 hr.). After stirring at room temperature for another hour, a solution of 413.0 g. of ammonium chloride in 1150 ml. water was added with ice-cooling (40 min.). The organic layer was separated, then the inorganic layer was extracted with 300 ml. of ether and rejected. After drying the combined organic solutions with sodium sulfate under argon, the ether was removed by fractional distillation. The residual liquid was fractionated at reduced pressure, bleeding in argon, collecting the fraction boiling at 153–158° at 20 mm. The yield was 82.75 g. (87.6%) of pale yellow liquid, *o*-phenylenebis(dimethylarsine), having the following physical properties: f.p., −12° (sharp); and n_D^{25}, 1.6204. The substance is rapidly oxidized by air, and must be stored under argon.

Chatt and Mann[3] obtained a yield of 26%, and mentioned only the b.p. of the product (156° at 20 mm.).

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(1) L. Kalb, *Ann.*, **423**, 39 (1921).

(2) C. Hamilton and C. Ludeman, *J. Am. Chem. Soc.*, **52**, 3284 (1930).

(3) J. Chatt and F. Mann, *J. Chem. Soc.*, 610 (1939).

(4) L. Goldsworthy, W. Hook, J. John, S. Plant, J. Rushton, and L. Smith, *J. Chem. Soc.*, 2208 (1948).

Cyclization of an Unsaturated Benzyl Ether to a Hydrofuran

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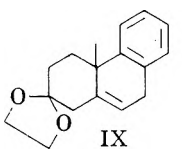
The work reported in this communication is the outgrowth of another problem and owes its genesis to the failure of the amino ketone I[1] to react with the methyl Grignard reagent. That this inertness probably is not due to steric factors was made evident by the normal reaction of II with this reagent. Some ketone was always recovered from the reaction mixture however. On refluxing with acetic anhydride–pyridine the tertiary alcohol from II lost the elements of water to give the dihydro compound III, the structural assignment being based on the following consideration: The ultraviolet absorption had too small an extinction coefficient for ring conjugated absorption, eliminating the possibility of a double bond shift. From the results of previous work on the relative stabilities of the *endo- vs.* the *exo*-double bond the *exo*-methylene structure can tenta-

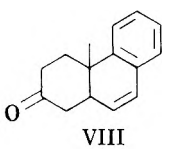
(1) E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 257 (1955).

tively be disregarded.[2] Skeletal rearrangement appears ruled out by the isolation of 1,2-dimethylnaphthalene in 20% yield after heating the compound at 275° for 1 hr. And the remaining possibility, involving migration of the side chain was eliminated by converting the compound into IV which had been synthesized by another route.[3] In the present instance compound IV was contaminated by the stereoisomer resulting from hydrogenation of the double bond. Identification was made by comparing the infrared diagrams of the two pure isomers with that of the mixture.

It was hoped that the double bond could be shifted into the 3,4-position. This transformation takes place readily and in high yield with 1,4-dihydronaphthalene,[4] but did not prove feasible in the present case. By the use of sodium amide in liquid ammonia it was possible to get an oil with an enhanced extinction coefficient at 264 mμ but the increment was not enough to indicate a method of synthetic value. Another example of the reluctance of this system to undergo isomerization was provided by Wenkert and Stevens who obtained VIII from IX in 15% yield after prolonged treat-



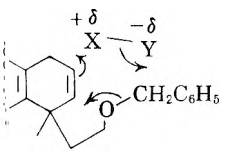
IX



VIII

ment with hot potassium hydroxide.[5] In both cases the double bond shift would shorten the distance between one of the *gem* groups and the group on the adjacent carbon, and it is possible that resistance to crowding accounts for the experimental results.

Bromine in carbon tetrachloride added rapidly to III giving benzyl bromide and a bromo compound showing strong absorption at 9.3 μ differing from the broader bands, 9.1–9.3 μ, of the benzyl ether and characteristic of a tetrahydrofuran structure.[6] By the action of base hydrogen bromide was eliminated and the product showed a maximum absorption in the ultraviolet at 263 mμ, ε = 6100, consistent with its formulation as VI. The unsaturated compound VI absorbed one molar equivalent of hydrogen to give a compound identical with that obtained by the action of hydrogen bromide in glacial acetic acid on the benzyl ether III. Both the reaction with bromine and with hydrogen bromide take place rapidly at room temperature, and indeed there is some evidence that the ring closure can be brought about by the action of hot acetic acid. This follows from the isolation of benzyl alcohol as one of the hydrolysis products from the action of base on the forerun obtained in the preparation of III. The remaining material showed infrared absorption with the sharp band characteristic of the tetrahydrofuran moiety. Hence it is unlikely that intermediate addition to the double bond or ether cleavage steps take place prior to the formation of the product. A concerted reaction such as is shown in figure



X

X rationalizes the above observations. Lack of carbonyl absorption in the lower boiling by-products indicates that acetic anhydride (X = CH_3CO, Y-CH_3COO) does not add to III in this manner, but the possibility of such an addition was not rigorously excluded. Models indicate that the benzene ring imposes a rigidity that makes existence of a *trans* ether ring impossible. If formation of the ring is by the more probable *trans* addition to the double bond[7] then substituents at 3α, 4, and 9*b* are *cis* to each other.

EXPERIMENTAL

1-(2-Benzyloxyethyl)-3,4-dihydro-2(1H)-naphthalenone. β-Tetralone (46.2 g.) was added within 5 min. to 27.2 g. (1.1 equiv.) of sodium amide in 100 ml. of dry benzene in an externally cooled three-neck flask equipped with stirrer, thermometer, and under a nitrogen atmosphere. Temperature was kept below 50°. Most of the solid dissolved. β-Chloroethyl benzyl ether, 54 g., (1 equiv.), in 50 ml. of benzene was added rapidly and the green solution was brought to reflux and maintained there for 18 hr. A solid enolate separated shortly after the beginning of the heating period. The dark solution was cooled and 150 ml. of 6*N* HCl was added with stirring. The benzene layer was separated, the solvent removed under reduced pressure, and the remaining oil distilled. The first fraction was collected up to 150° at 20 mm., and from this was recovered 16 g. of the sodium bisulfite adduct of β-tetralone. The second fraction distilled for the most part at 170–180° at 0.3 mm. and weighed 56.1 g. Yield, taking recovery into account, *ca.* 75% The sample for analysis distilled at 178–180° at 0.5 mm.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.38; H, 7.26.

1-(2-Benzyloxyethyl)-1-methyl-3,4-dihydro-2(1H)-naphthalenone (II). The above-described compound (56 g.) was added neat to 8.6 g. (1.1 equiv.) of sodium amide in 100 ml. of dry benzene in a three-neck flask equipped with stirrer and thermometer. A solid enolate separated. A solution of 31.2 g. (1.1 equiv.) methyl iodide in 20 ml. of dry benzene was then added and the temperature kept at 40° by occasional cooling. After 2 hr., water was added, the benzene layer separated, and the product recovered and distilled. In addition to forerun and residue, 51.1 g. (86%) of oil distilling *ca.* 160–170°/0.4 mm. was obtained. The analyzed sample distilled at 170–175° at 0.5 mm.

(2) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

(3) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957).

(4) W. Hückel and H. Bretschneider, *Ann.*, **540**, 157 (1939).

(5) E. Wenkert and T. E. Stevens, *J. Am. Chem. Soc.*, **78**, 2318 (1956).

(6) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 104.

(7) M. S. Newman, *Steric Effects in Organic Chemistry*, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 242.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.56; H, 7.47.

1-(2-Benzyloxyethyl)-2-hydroxy-1,2-dimethyl-1,2,3,4-tetrahydronaphthalene. To 190 ml. (1.2 equiv.) of 1.08*N* CH_3MgI in ether was added 50.2 g. of ketone II in an equal volume of dry ether. The ethereal solution refluxed and it became cloudy at the end of the addition. It was stirred for 20 min. and the adduct decomposed with dilute acetic acid. The ethereal solution was separated, the solvent removed, and the product distilled. Aside from a forerun, 50.5 g. distilling at 175–185° at 0.4 mm. was obtained. The analytical sample boiled at 183°/0.4 mm. The infrared diagram showed carbonyl absorption at 5.82μ in addition to hydroxyl absorption at 2.95μ.

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.41; H, 8.44.

1-(2-Benzyloxyethyl)-1,2-dimethyl-1,4-dihydronaphthalene (III). The tertiary alcohol in an equal volume of a 10–1 acetic anhydride–pyridine mixture was refluxed for 3–4 days. The solvent was removed under reduced pressure and the main portion of the product (70–80% of the weight of the starting material) distilled in the range 145–165° at *ca.* 0.3 mm. Infrared absorption at 5.76μ showed the presence of acetate. Hydrolysis by hot alcoholic sodium hydroxide caused disappearance of this band and revealed the carbonyl band at 5.83μ known to be present originally. From 25–35% of the material appeared to be the acetoxy compound. The substance was further purified by partial precipitation of the alcoholic and ketonic impurities from a petroleum ether solution by means of CH_3MgI. The analytical sample distilled at 146–149° at 0.4 mm. Infrared absorption still revealed a little carbonyl impurity.

Anal. Calcd. for $C_{21}H_{24}O$: C, 86.25; H, 8.27. Found: C, 86.02; H, 8.30.

Alkaline hydrolysis of the forerun material (strong acetate absorption at 5.77μ) yielded a fraction distilling at 105–110° at 21 mm. and which was identified as benzyl alcohol by means of its phenylisocyanate derivative. The remaining material, an oil distilling from 90–120° at 0.3 mm. showed strong absorption at 9.3μ characteristic of the tetrahydrofuran derivatives.

4-Bromo-1,2,3a,4,5,9b-hexahydro-3a,9b-dimethylnaphtho(2,1-b) furan (V). A carbon tetrachloride solution of 4.4 g. of the benzyl ether III in 5 ml. of carbon tetrachloride was chilled in ice and a solution of bromine (0.149 g./ml.) in carbon tetrachloride was added. Decolorization was immediate and *ca.* 14.8 ml. (92% of theory) was required to give an apparent end point. The solution was shaken with water and the organic layer removed. Distillation yielded a lachrymatory liquid at 50–90°/0.7 mm., wt. 1.5 g. Its infrared diagram was almost identical with that of an authentic sample of benzyl bromide. The second fraction distilled at *ca.* 130/0.3 mm., wt. 3.5 g. (84%). The infrared diagram showed strong absorption at 9.3μ.

Anal. Calcd. for $C_{14}H_{17}BrO$; C, 59.80; H, 6.09; Br, 28.42. Found: C, 61.29; H, 6.03; Br, 27.21.

1,2,3a,9b-Tetrahydro-3a,9b-dimethylnaphtho(2,1-b)furan (VI). An alcohol solution of 1.8 g. of the bromohydrofuran V with excess methyl amine in a sealed tube was heated on the steam bath for 1 hr. The solvent was distilled, ether added, solid amine salt filtered and the product distilled at 88–92°/0.8 mm., wt. 1.05 g., ultraviolet maximum in ethanol at 263 mμ (ϵ 6300), infrared ether band at 9.3μ.

Anal. Calcd. for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 81.66; H, 8.34.

1,2,3a,4,5,9b-Hexahydro-3a,9b-dimethylnaphtho(2,1-b)furan (VII). A. Hydrogenation of 1.8 g. of VI in alcohol solution with Adams' catalyst at room temperature was rapid and ceased after absorption of 1 mol. The product distilled at 85–88°/0.2 mm., wt. 1.5 g.

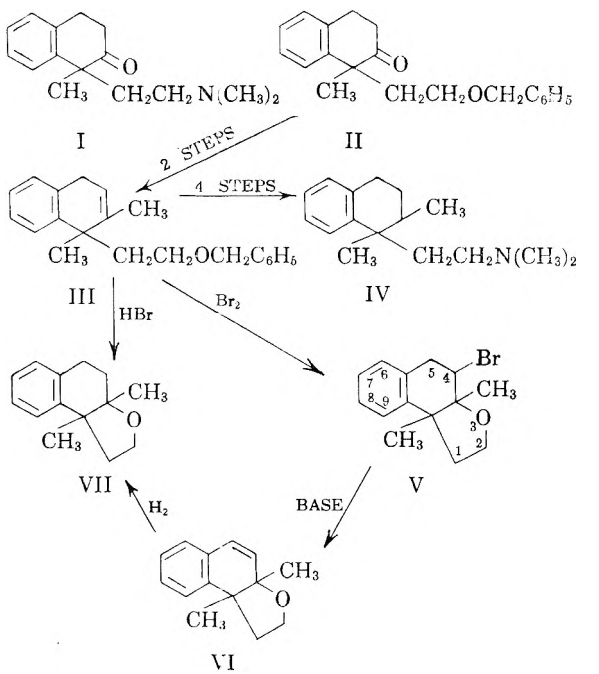
B. To 3.0 g., of the benzyl ether III (I.R. showed ketonic impurity) was added 6.0 ml. of HBr–HOAc (2.4*N* HBr). The temperature rose from 24–33°. After 15 min. the solvent was removed under reduced pressure and the first fraction collected from 90–100° at 18 mm. From the infrared diagram it appeared to be a mixture of benzyl bromide and benzyl acetate. The main fraction distilled at 90–97° at 0.5 mm., wt. 1.25 g. Its infrared diagram was identical with that of the compound described under A, showing ether absorption at 9.3μ and being negative in the hydroxyl region.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.90; H, 8.99.

1-(2-Hydroxyethyl)-1,2-dimethyl-1,2,3,4-tetrahydronaphthalene. Catalytic reduction of 7.3 g. of III followed by hydrolysis of the benzyl group by aqueous HBr–HOAc gave the alcohol contaminated by acetate. Hydrolysis with alcoholic sodium hydroxide gave the alcohol. It distilled at 113–116°/0.2 mm., wt. 3.1 g.

Anal. Calcd. for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.15; H, 9.81.

1-(2-Dimethylaminoethyl)-1,2-dimethyl-1,2,3,4-tetrahydronaphthalene. The above-described alcohol in 3.0 g., chloroform solution reacted with thionyl chloride to give *ca.* 50% yield of crude chloride. This material in benzene solution with excess dimethyl amine in a sealed tube was heated on the steam bath for 4 days. After distilling the solvent, the oil was triturated with dilute sodium hydroxide solution, then dissolved in ether. The solvent was distilled from this solution and the residue dissolved for the most part in a small excess of 2*N* HCl, the insoluble oil being removed with ether. The acid solution was concentrated to an oil under reduced



pressure whereupon it crystallized. Washed with ethyl acetate it weighed 0.18 g. Purified from ethyl acetate it melted at 198–199.5°. Its nonidentity with an isomer, m.p. 202–203.5°, prepared by another synthesis was established by a mixture melting point. Impure material, m.p. 166–173°, from the mother liquors of recrystallization gave an infrared diagram which was a composite of the diagrams of the two pure isomers.

Anal. Calcd. for $C_{16}H_{26}ClN$: C, 71.75; H, 9.78. Found: C, 71.71; H, 9.87.

Pyrolysis of 1-(2-benzyloxyethyl)-1,2-dimethyl-1,4-dihydronaphthalene (III) was achieved by heating 0.5 g. in a test tube at 275–287° for 1 hr. The oil was dissolved in an alcohol solution containing 0.2 g. of picric acid and a crystalline picrate was obtained. Purified from alcohol it weighed 0.14

g. (21%), m.p. 115–130°. Another crystallization gave a melting point of 128–131°, undepressed by admixture with authentic 1,2-dihydronaphthalene picrate.

Acknowledgments. Microanalyses are from the Institutes service analytical laboratory directed by Dr. William C. Alford, and infrared and ultraviolet spectra determinations are by Mr. William M. Jones and Mrs. Anne H. Wright, respectively.

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Organic Deuterium Compounds. I. 1,2-Dimethoxy-d_6-ethane-d_4 and 2-Methoxy-d_3-ethan-d_4-ol[1]

EUGENE R. BISSELL AND ROBERT E. SPENGER

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In connection with some nuclear magnetic resonance studies being conducted in this laboratory, a need arose for a material with the solvent properties of ethylene glycol dimethyl ether (1,2-dimethoxyethane) which would, however, show little or no nuclear magnetic resonance signal in the proton region. Since a completely deuterated ethylene glycol dimethyl ether would meet these requirements, we undertook its synthesis starting with deuterium oxide and a sample of ethylene-d_4 available to us.

Ethylene-d_4 was converted *via* its dibromide to ethylene-d_4 glycol diacetate which was then hydrolized to the free glycol.[2] The glycol thus obtained was converted *via* its monosodium derivative to a mixture of 1,2-dimethoxy-d_6-ethane-d_4, 2-methoxy-d_3-ethan-d_4-ol, and unchanged glycol by treatment with methyl-d_3 bromide. The 2-methoxy-d_3-glycol could be further methylated to the diether. The methyl-d_3 bromide was prepared from carbon suboxide[3,4] *via* malonic-d_2 acid-d_2 and acetic-d_3 acid-d.[5] The procedure of Nolin and Leitch[6] for the Hunsdiecker degradation was modified to eliminate the somewhat hazardous sealed tube operation.

Comparison of the nuclear magnetic resonance spectrum in the proton region of the 1,2-dimethoxy-d_6-ethane-d_4, obtained by this method, with that of normal material indicated that the isotopic purity of our deuterated material was at least 98.6 and probably better than 99 atom per cent deuterium. The isotopic purity of the deuterium oxide used was 99.6% and that of the ethylene-d_4 better than 99%.

EXPERIMENTAL[7]

Ethylene-d_4 glycol. Ethylene-d_4 was brominated in carbon tetrachloride solution at 0°. Distillation yielded 47.8 g. of dibromide b.p. 128–131°, n_D^{20} 1.53367 (Lit.[8] b.p. 129.5°, n_D^{20} 1.5360). The dibromide was converted in 78.5% yield to ethylene-d_4 glycol by the procedure of Bannard, Morse, and Leitch.[2] B.p. 113–115°/12 mm., n_D^{24} 1.42831 (Lit.[2] b.p. 86–87°/8 mm., n_D^{20} 1.4293).

Acetic-d_3 acid-d. Diacetyltartaric anhydride[3] was pyrolyzed according to the procedure of Hurd and Pilgrim[4] to afford an average yield of 42% of carbon suboxide, b.p. 7–8°. This was converted *via* malonic-d_2 acid-d_2 to acetic-d_3 acid-d in 89–97% yield by the method of Wilson.[5] d^{26} 1.137, $n_D^{25.2}$ 1.3675.

Methyl-d_3 bromide. Silver acetate-d_3, prepared from acetic-d_3 acid-d by the method of Nolin and Leitch,[6] was subjected to the Hunsdiecker degradation in an apparatus (Fig. 1)

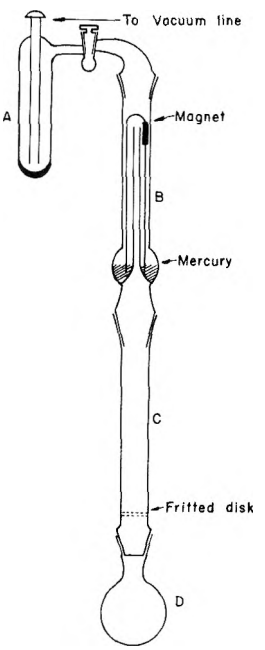

FIGURE 1

consisting of a trap (A) connected to a vacuum system, a mercury bubbler (B) containing about 0.5 inch of mercury, and a reaction tube (C) charged with 20–40 g. of silver acetate-d_3. Attached to the bottom of the reaction tube was a bromine reservoir (D) containing about 25 g. of 8-mesh Drierite and bromine in about 2% excess over that required to consume all of the silver acetate-d_3 in C.

After assembly of the apparatus with the center tube in the bubbler (B) raised with a magnet from the outside, the bromine reservoir was cooled to −78°, and the system was evacuated. The trap (A) was cooled in liquid nitrogen, and argon was admitted to the system to a pressure of 150 mm. The argon served to control the rate of flow of bromine vapor through the silver acetate-d_3 bed. The center tube in B was lowered and the bromine reservoir allowed to warm to room temperature. During the first hour or so of the reaction pe-

(1) This work was performed under the auspices of the U. S. Atomic Energy Commission, Contract No. W-7405-eng-48.

(2) R. A. Bannard, A. T. Morse, and L. C. Leitch, *Can. J. Chem.*, **31**, 351 (1953).

(3) A. Wohl and C. Oesterlin, *Ber.*, **34**, 1139 (1901).

(4) C. D. Hurd and F. D. Pilgrim, *J. Am. Chem. Soc.*, **55**, 757 (1933).

(5) C. L. Wilson, *J. Chem. Soc.*, **1**, 492 (1935).

(6) B. Nolin and L. C. Leitch, *Can. J. Chem.*, **31**, 153 (1953).

(7) Boiling points are uncorrected.

(8) L. C. Leitch and A. T. Morse, *Can. J. Chem.*, **30**, 924 (1952).

riod, the pressure rose to about 200 mm. The argon was carefully bled off to maintain the pressure at about 150 mm. A 0.25-mole run could be completed in 12–16 hr. When all of the silver salt had turned a bright yellow and bromine vapor was visible in the Pyrex wool plug and in the space above it, the system was evacuated very slowly (about 5 mm. per minute). When the pressure in the vacuum system had dropped to less than 100μ, the center tube in B was raised a bit at a time until clear of the mercury; the system was then evacuated to a hard vacuum ($< 1\ \mu$ pressure). If bromine was apparent in trap A, its contents were repeatedly passed through the mercury bubbler from trap A to reservoir D and back until all color had been removed. The center tube of B was raised to allow free passage on the A to D portion of the cycle and lowered on the D to A portion. The stopcock on the sidearm of trap A was closed and the contents of the trap distilled through two U-traps at −96° and at −130°, respectively. Any material passing through the −130° trap (mostly CO_2) was discarded. The methyl-d_3 bromide in the −130° trap was measured gasometrically and transferred to a storage bulb. The material in the −96° trap (presumably acetic-d_3 acid-d and acetyl-d_3 bromide) amounted to about 50 mg./g. of silver salt and had a density of 1.1 g./ml. and a vapor pressure of 20 mm. at 0°. It was not investigated further. The average yield of methyl-d_3 bromide was 78%. Its vapor pressure at −41° and at 0° was 81 mm. and 680 mm., respectively (Nolin and Leitch[6] give 681.5 mm. at 0°).

1,2-Dimethoxy-d_6-ethane-d_4 and 2-methoxy-d_3-ethan-d_4-ol. A reaction tube of about 200-ml. capacity, fitted with a breakseal and a neck constricted for sealing under vacuum, was loaded in a dry box with 2.30 g. (0.10 mole) of sodium. The reaction tube was then attached to a Dry Ice condenser having a side arm for the introduction of other reactants and protected from moisture with an ascarite filled drying tube. Approximately 50 ml. of sodium-dried liquid ammonia was distilled into the reaction tube from a flask attached by means of an adapter to the side arm of the condenser. The flask and adapter were then removed, and the side arm was capped with a rubber syringe stopper through which 6.61 g. (0.10 mole) of ethylene-d_4 glycol was slowly introduced by means of a hypodermic syringe and long needle. The reaction tube was maintained at −35° to −40° during the addition. When the addition of the glycol was complete the syringe was washed three times with 10-ml. portions of sodium-dried ether. If much unreacted sodium remained caked on the walls of the tube, the syringe was replaced by a stainless-steel wire and the solids chipped off the glass. The apparatus was then allowed to warm slowly to room temperature overnight to allow the ammonia and some of the ether to evaporate. The last traces of ammonia and ether and about 0.1 g. of unreacted glycol were removed by baking the reaction tube at 100° under hard vacuum ($< 1\ \mu$ pressure) for about 4 hr. Methyl-d_3 bromide (0.10 mole, measured gasometrically) was distilled into the tube which was then sealed off at the constriction. After 10 days at room temperature, the reaction tube was attached *via* its breakseal to a series of traps on a vacuum line, and the volatile components of its contents were distilled into the first trap. The last traces were removed from the reaction vessel by heating it at 100° for 4 hr. A small amount of noncondensible material was pumped off. Approximately 1–2 millimoles of volatile material was removed from the material in the trap by distilling it through a −96° trap. The liquid residues from two such experiments were combined and fractionated through a 15-in. heated Vigreux column to yield 0.93 g. of forerun, b.p. 78–81.5°, $d_{20.5}$ 0.978, $n_D^{25.2}$ 1.37644; 5.05 g. of 1,2-dimethoxy-d_6-ethane-d_4, b.p. 83–84°; 0.49 g. of an intermediate cut, b.p. 115–121°, $d_{20.5}$ 0.993, $n_D^{25.5}$ 1.38572; 4.38 g. of 2-methoxy-d_3-ethan-d_4-ol, b.p. 122–124°, $d_{20.5}$ 1.042, $n_D^{25.5}$ 1.39701 and 6.57 g. of residual ethylene-d_4 glycol. The 1,2-dimethoxy-d_6-ethane-d_4 was dried over freshly cut sodium and distilled on a vacuum line, $d_{22.3}$ 0.944, $n_D^{25.2}$ 1.37447. It had the following vapor pressures at the temperatures indicated: 67 mm. at 24.4°, 65 mm. at 23.9°, 64 mm. at 23.4°, 34 mm. at 12°, 18 mm. at 0°, 3 mm. at −23°, and about 1 mm. at −41°.

1,2-Dimethoxy-d_6-ethane-d_4 from 2-methoxy-d_3-ethan-d_4-ol. 2-Methoxy-d_3-ethan-d_4-ol (1.44 g., 0.017 mole) was treated with 0.40 g. (0.017 mole) of sodium and 17.4 millimoles of methyl-d_3 bromide using the procedure described above. There was obtained 0.9 millimole of material volatile at −96°. The material from the −96° trap was dried over sodium and distilled on the vacuum line to yield 1.46 g. (85%) of 1,2-dimethoxy-d_6-ethane-d_4.

Acknowledgments. The authors are indebted to Dr. Melvin P. Klein for the nuclear magnetic resonance measurements and to Drs. John W. Kury, Bert E. Holder, and Melvin P. Klein for suggestion of the problem.

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Preparation of α-Morpholinoacrylonitrile

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In connection with a study of vinyl monomers containing a basic substituent it became desirable to synthesize the title compound. The literature[1] reveals but one preparation of α-(substituted amino)-acrylonitriles; this procedure involves the use of liquid HCN and more than two moles of secondary amine.

$$ClCH_2CHO + HCN \longrightarrow ClCH_2CH(OH)CN \xrightarrow{2\ R_2NH} CH_2{=}C(NR_2)CN + R_2NH{\cdot}HCl \quad (I)$$

We have found that the previously unreported I, ($R_2 = C_4H_8O$), can be prepared in fair yields by an improved procedure which (*a*) avoids the use of liquid HCN, (*b*) substitutes caustic for an excess of the more expensive amine, and (c) permits the whole operation to be performed in one flask without the isolation of intermediates. Dimethyl chloroacetal is hydrolyzed with dilute mineral acid to the free aldehyde. To the resultant solution is added an aqueous solution of the amine hydrochoride and, after cooling, sodium cyanide to form the β-chloroaminonitrile. Dehydrochlorination, to give the title compound, is accomplished by addition of one equivalent of sodium hydroxide. The technique is applicable to other secondary amines.

The product was unstable and decomposed on standing at room temperature even in the dark.

EXPERIMENTAL[2]

To 63 g. (0.5 mole) of dimethyl chloroacetal (Carbide and Carbon Chemical Co.) was added 80 ml. of 0.75*N* hydro-

(1) O. Nicodemus, H. Lange, and H. Kranz, U.S. Patent 2,211,152 (to General Aniline and Film Corp.), August 13, 1941.

(2) Melting points are uncorrected.

chloric acid and the mixture warmed (80°) and stirred under reflux until a clear solution resulted (about 15 min.). A solution of morpholine hydrochloride (0.60 mole) in 160 ml. of water was then added and the flask contents cooled to below 10°. Then 30 g. of 95% sodium cyanide (0.60 mole) in 100 ml. of water was slowly introduced below the surface of the cooled, stirred solution. The flask was immersed in the cooling bath so that the liquid level was well below the surface of the bath. After 2 hr. in the cold, a solution of 24 g. (0.60 mole) of sodium hydroxide in 60 ml. of water was added. The mixture was stirred in the cold for an additional hour and then filtered. The white solid was collected, washed with cold water several times, and air dried. The yield of α-morpholinoacrylonitrile, m.p. 62.5–63.5° after recrystallization from 30–60° petroleum ether, was 40 g. (58%).

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 61.50; H, 7.15; N, 20.09.

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A New Method for the Preparation of Formamidine

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Received April 23, 1957

The formation of formamidine as an intermediate was first reported by Odo and Sugino by the electrolytic reduction of cyanamide in 8% $(NH_4)_2SO_4$ catholyte at a tin cathode.[1]

$$NH_2CN + 2H \longrightarrow NH_2{\cdot}CH{=}NH$$

Further study on the mechanism of this electrode reaction showed that the first step in the reduction of cyanamide to formamidine seems to be favored by carrying it out catalytically over palladium rather than electrochemically. The yield is almost quantitative. It was surprising to us that this simple method had not been previously reported.

EXPERIMENTAL[2]

Twenty grams of palladium-charcoal catalyst[3] (containing 1.4% Pd) in 200 cc. water was placed in a reduction bottle provided with two separatory funnels and with a stream of hydrogen flowing through it to exclude air. The bottle was first shaken to reduce the catalyst completely. To it, there was added 100 cc. of 12% H_2SO_4 (or 100 cc. of 9% HCl) from one funnel. Then, from the other funnel, an aqueous solution of 11 g. of freshly prepared cyanamide (purity 97% as silver cyanamide) in 100 cc. water was added portion-wise (1.5 cc. at intervals of 3 min.) for 3 hr. with shaking at room temperature, while the hydrogen continued to be taken up. The reduction was complete about 10 min. after the last portion had been added at which time 5.8 l. (0.25 mole, 100% of theoretical) of hydrogen had been absorbed.

After the reduction, the mixture was filtered and the filtrate was combined with catalyst washings. The resulting solution was adjusted to *p*H 4.8–5.0 by adding a small amount of Amberlite 1R4B and was evaporated to dryness below 60° under diminished pressure. The crystals of formamidine sulfate (or hydrochloride) separated. After recrystallization from methanol, 22.5 g. of pure formamidine sulfate (or 18.8 g. hydrochloride) was obtained, m.p. 156–158° (hydrochloride, 76–78°), yield 95% (hydrochloride, 92%).

Anal. of the sulfate. Calcd. for $CH_4N_2{\cdot}{}^1/_2H_2SO_4$: N, 30.11. Found: N, 29.82.

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Metalation of Aryl Fluorides in Tetrahydrofuran

HENRY GILMAN AND THEODORE S. SODDY

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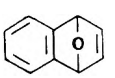
The metalation of fluorobenzene with phenyllithium at 0° in diethyl ether by Wittig and coworkers gave products which indicated that *o*-fluorophenyllithium was one of the intermediates.[1–3] Under the conditions that were employed, however, *o*-fluorophenyllithium was too reactive to be successfully detected by the formation of derivatives as such.

Later work demonstrated that the *o*-fluorophenyllithium gave rise to the more reactive "benzyne" intermediate which was indirectly responsible for products that were obtained such as triphenylene.[4–7]

More recent work in this laboratory has shown that *o*-fluorophenyllithium can be obtained in excellent yields from *o*-fluorobromobenzene and *n*-butyllithium at -60° by means of the halogen-metal interconversion reaction.[6] Evidence was also obtained for the formation of the "benzyne" intermediate by the isolation of 1,4-dihydronaphthalene-1,4-endoxide (I) when the *o*-fluorophenyllithium was permitted to warm to room temperature in the



I

(1) K. Odo, K. Sugino, *J. Electrochem. Soc.*, **104**, 160 (1957).

(2) All melting points are uncorrected.

(3) This catalyst consisted of activated charcoal with absorbed Pd, prepared according to the procedure of Wieland, *Ber.*, **45**, 484 (1912).

(1) G. Wittig, G. Pieper, and G. Fuhrmann, *Ber.*, **73** 1193 (1940).

(2) G. Wittig and W. Merkel, *Ber.*, **75**, 1491 (1942).

(3) G. Wittig, *Naturwiss.*, **30**, 696 (1942).

(4) G. Wittig and L. Pohmer, *Angew. Chem.*, **67**, 348 (1955).

(5) G. Wittig and L. Pohmer, *Chem. Ber.*, **89**, 1334 (1956).

(6) H. Gilman and R. D. Gorsich, *J. Am. Chem. Soc.*, **78**, 2217 (1956).

(7) H. Gilman and R. D. Gorsich, *J. Am. Chem. Soc.*, **79**, 2625 (1957).

TABLE I

PHYSICAL CONSTANTS AND RELATED DATA FOR ACIDS FROM ARYL FLUORIDES

Compound	Yield, %	M.P., °C.	Neutral Equivalent		Fluorine	
			Calcd.	Found	Calcd.	Found
o-Fluorobenzoic acid	60.0	123–124				
5-Methyl-2-fluorobenzoic acid	58.0	159–160	154	156, 159	12.33	12.45, 12.68
3-Methyl-2-fluorobenzoic acid	2.6	109–110	154	154, 155	12.33	12.10, 12.18
1-Fluoro-2-naphthoic acid	30.0	193–194	190	187, 187	9.99	9.97, 9.81

presence of furan.[7] The same adduct was isolated when *o*-fluorobromobenzene was shaken for 4 days at 25° with lithium amalgam in furan.[5]

When *n*-butyllithium which was prepared in tetrahydrofuran[8] was added to fluorobenzene at −40°, no reaction was noted, but on warming to −25° a very vigorous reaction occurred, and a small amount of triphenylene was isolated. In order to avoid this almost uncontrollable reaction, the temperature of the reaction mixture was maintained between −50 and −60° for 7 hr. On carbonation *o*-fluorobenzoic acid was obtained in a crude yield of 60%. By employing these conditions, the metalation of the following aryl fluorides was effected in the same manner (Table I).

EXPERIMENTAL[9]

The following reaction under method A for the metalation of fluorobenzene is described in detail, and this general procedure was employed for the metalation of the other aryl fluorides.

Fluorobenzene and n-butyllithium in tetrahydrofuran at −50°. Method A. Into a 3-necked, 500-ml., round-bottomed flask was introduced 9.6 g. (0.1 mole) of fluorobenzene in 100 ml. of tetrahydrofuran.[10] To this slowly stirred solution, which was cooled to −50° by means of a Dry Ice–acetone bath, was added over a period of 5 min. 0.1 mole of *n*-butyllithium in 55 ml. of tetrahydrofuran.[11] The reaction mixture was stirred at this temperature for 7 hr. and carbonated by pouring jet-wise onto a Dry Ice–ether slurry. The basic extract was acidified to yield 9 g. (60% of crude *o*-fluorobenzoic acid which melted between 110–116°. On crystallization from water, the m.p. was 123–124°. A mixed melting point with an authentic specimen was undepressed.

In two other preparations which were carried out as described above except that the times were 3 and 12 hours, respectively, the yields of crude *o*-fluorobenzoic acid were 36 and 33%. When *p*-fluorotoluene was treated in the same manner for a period of 3 or 12 hr., the yields of 5-methyl-2-fluorobenzoic acid were 20 and 33%, respectively.

Method B. To a stirred solution of 0.1 mole of *n*-butyllithium in 75 ml. of tetrahydrofuran, was added 9.6 g. (0.1 mole) of fluorobenzene. The temperature was kept at −40° for 35 min. and when no reaction was noted, the temperature was permitted to rise to −25°. At this point a vigorous reaction took place, and the temperature rose to 12°. The color of the reaction mixture was brown. The reaction mixture was carbonated and worked up in the preceding manner. No acid was obtained from the basic extract, but from the neutral layer 0.6 g. of triphenylene was isolated. The m.p. was 193–194° on crystallization from 1-propanol. A mixed m.p. with an authentic specimen was undepressed.

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(8) This solvent was employed because its base strength is greater than that of diethyl ether; H. C. Brown and R. M. Adams, *J. Am. Chem. Soc.*, 64, 2557 (1942).

(9) All melting points are uncorrected, and all reactions were carried out in a dry, oxygen-free atmosphere.

(10) The tetrahydrofuran was dried and purified by first shaking with sodium hydroxide pellets, refluxing over sodium metal for several hours, and finally distilling, immediately before use, from lithium aluminum hydride.

(11) H. Gilman and B. Gaj, *J. Org. Chem.*, 22, 447 (1957).

Reaction of Phenyl- and *p*-Tolyllithium with 1-Arylisoquinolines

HENRY GILMAN AND THEODORE SODDY

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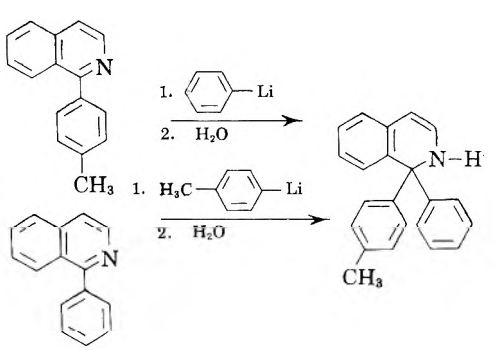
In the course of an investigation in this laboratory which involved the preparation of some 1-substituted isoquinolines, there arose the desirability of studying the addition of aryllithium reagents to 1-arylisoquinolines.

In an earlier investigation,[1] the addition of phenyl- and *p*-tolyllithium to 2-*p*-tolylquinoline and 2-phenylquinoline, respectively, was found to yield the identical compound, 2-phenyl-2-(*p*-tolyl)-1,2-dihydroquinoline which resulted from the attack at the azomethine linkage. At that time, also, there was an attempt made to prepare 1-phenyl-1-(*p*-tolyl)-1,2-dihydroisoquinoline by treating 1-*p*-tolyl- and 1-phenylisoquinoline with



(1) H. Gilman and G. C. Gainer, *J. Am. Chem. Soc.*, 69, 877 (1947).

phenyl- and *p*-tolyllithium, respectively,[2] but no product could be isolated. We have been able, however, to carry out this series of reactions and have obtained products which could be isolated and identified. The compounds were purified by fractional crystallization from absolute ethanol. The product from each of the reactions was found to be 1-phenyl-(1-*p*-tolyl)-1,2-dihydroisoquinoline. This fact was demonstrated by a mixture decomposition point and identical infrared spectra. Both of the spectra contained a 1,4 disubstituted phenyl band at 12.3 μ, a phenyl ring band at 6.15 μ, and a N–H band at 3.1 μ.

EXPERIMENTAL[3]

Reaction of p-Tolyllithium with 1-Phenylisoquinoline. Into a 500-ml., 3-necked, round-bottomed flask which was equipped with a mechanical stirrer, reflux condenser, and a dropping funnel, there was placed 16 g. (0.08 mole) of 1-phenylisoquinoline in 200 ml. of anhydrous ether. To this vigorously stirred solution, there was added dropwise a solution of *p*-tolyllithium (0.08 mole) in 90 ml. of anhydrous ether. After the addition of 2, 5, and 8 ml. of the *p*-tolyllithium solution, the reaction mixture became light red, light brown, and, finally, dark green in color. The dark green color was present throughout the remainder of the addition. On completion of the addition, the reaction mixture was refluxed for 45 min. at which time Color Test I[4] was negative. The reaction mixture was hydrolyzed with a saturated solution of ammonium chloride, and the ethereal extract was dried over anhydrous sodium sulfate. The ether was removed by distillation, and the residue was dissolved in absolute ethanol. This solution was treated with charcoal, filtered, and evaporated by means of dry air to give a compound which decomposed between 176–178°. The yield was 0.5 g. or 2.5%.

Anal. Calcd. for $C_{22}H_{18}N$: N, 4.69. Found: N, 4.68, 4.55.

Reaction of phenyllithium with 1-p-tolylisoquinoline. Into a 500-ml., 3-necked, round-bottomed flask, which was equipped as described above, there was placed 19 g. (0.09 mole) of 1-*p*-tolylisoquinoline in 200 ml. of anhydrous ether. To this solution there was added 0.09 mole of phenyllithium in 100 ml. of anhydrous ether. The color of the reaction mixture became dark green after the addition of the first 8 ml. of the phenyllithium solution, and the color was retained for the remainder of the addition. Color Test I[4] was negative within 15 min. after the addition was completed. The reaction mixture was worked up in the same manner as described above to give a product which decomposed between 176–178°. The yield was 0.5 g. or 2.5%.

Acknowledgment. The authors wish to express their appreciation to R. M. McCord, E. M. Layton, and Dr. V. A. Fassel of the Institute for Atomic Research, Iowa State College, for obtaining the infrared spectra of the compounds.

This work was supported by the United States Atomic Energy Commission under contract No. AT(11-1)-59, and the reactions were used in connection with organic liquid solution scintillators to be evaluated by Drs. W. H. Langham, F. N. Hayes, and D. G. Ott of the Los Alamos Laboratories.

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(2) G. C. Gainer, doctoral dissertation, Iowa State College, Ames, Iowa, 1946.

(3) All melting points are uncorrected.

(4) H. Gilman and J. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

Derivatives of *o*-Phenylenedioxyacetic Acid as Plant Growth-Regulators[1]

HOWARD A. HARTZFELD,[2] ROBERT G. JOHNSON,[3] AND HENRY GILMAN

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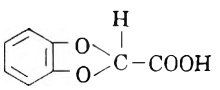
A reasonable extension of studies[4] on the plant growth-regulator activity of phenoxyacetic acid derivatives seemed to be the investigation of derivatives of *o*-phenylenedioxyacetic acid,[5] I.



I

Accordingly, we have prepared and are reporting here the synthesis of a number of derivatives of I. We are also reporting the plant growth-regulating activity of these compounds as measured by the leaf repression method.[6]

The acid (I) and its ethyl ester were reported initially by Christiansen and Dolliver.[7] Subsequently, Burger and coworkers[8] prepared the acid and a number of its derivatives for testing for antispasmodic activity. After the work reported here had been completed, a paper by Cavill and Ford[9] on the subject of *o*-phenylenedioxyacetic acid and its chloro derivatives appeared in the literature. These latter workers seem to be the only ones other

(1) Abstracted from a Dissertation submitted by H. A. H. to the Graduate School of Iowa State College in partial fulfillment of the requirements for the Ph.D. degree in chemistry, December 1953.

(2) Present address: Research Division, Phillips Petroleum Company, Bartlesville, Okla.

(3) Present address: Department of Chemistry, Xavier University, Cincinnati, Ohio.

(4) Studies carried out under contract with the Chemical Corps of the U.S. Army. Dr. R. L. Weintraub, Fort Detrick, Md., arranged for the biological testing.

(5) Cavill and Ford (ref. 9) name this compound, benzo-1:3-dioxolo-2-carboxylic acid and *Chemical Abstracts* refers to it as 1,3-benzodioxole-2-carboxylic acid.

(6) J. W. Brown and R. L. Weintraub, *Botan. Gaz.*, 111, 448 (1950).

(7) W. G. Christiansen and M. A. Dolliver, *J. Am. Chem. Soc.*, **66**, 312 (1944).

(8) A. Burger, D. G. Markees, W. R. Nes, and W. L. Yost, *J. Am. Chem. Soc.*, **71**, 3307 (1949).

(9) G. W. K. Cavill and D. L. Ford, *J. Chem. Soc.*, 1388 (1954).

than the writers to recognize the potential of derivatives of I as plant growth-regulators.[9a]

The method employed for the synthesis of the ethyl esters of I and its 4-chloro derivative was, in essence, that used earlier by other workers.[7] The ethyl ester of I was then converted to the corresponding amide, anilide, hydrazide, and *n*-butyl ester. The last three of these compounds and ethyl 4-chloro-*o*-phenylenedioxyacetate have not been reported previously.

The high order of chemical reactivity exhibited by ethyl *o*-phenylenedioxyacetate is worthy of note. The reaction of the ester with ammonia and with hydrazine occurred at room temperature and excellent yields of the products were obtained after short reaction times. It was observed also that a sample of this ethyl ester darkened considerably on storage for a period of several months.

An additional observation was that extraction with ether did not completely remove the ethyl ester of I from a 5% sodium hydroxide solution containing some ethanol; however, the extraction could be made from a 5% sodium bicarbonate solution. This suggests that the alpha-hydrogen in ethyl *o*-phenylenedioxyacetate exhibits a certain degree of acidic character.

EXPERIMENTAL[10]

Ethyl o-phenylenedioxyacetate. To a cold solution of sodium ethoxide prepared from 46.0 g. (2.0 g. atoms) of sodium and 1500 ml. of absolute ethanol was added 110 g. (1.0 mole) of catechol. Over a period of 20 min., 157 g. (1.0 mole) of ethyl dichloroacetate was added with stirring to the dark reaction mixture. The reaction mixture was stirred for 1 hr. at room temperature, then for 6 hr. at reflux temperature.

After the solvent had been removed at aspirator vacuum with the aid of a steam bath, the residue was stirred with a mixture of 600 ml. of ether and 300 ml. of 5% sodium bicarbonate solution. The layers were separated and the ether layer was extracted with an additional 300 ml. of 5% sodium bicarbonate solution, then washed with 100 ml. of water. A quantity of tar was separated with the aqueous phase. The ethereal solution of the ester was dried over anhydrous sodium sulfate. Following removal of the solvent, the residual ester was distilled under vacuum.

The crude yield of 68.1 g. of ester was collected over the range 81–89° (0.3 mm.). Since some catechol (mixture m.p.) had been carried over into the receiver during the distillation, the crude ester was washed with two 30 ml. portions of 5% sodium bicarbonate solution, then with 30 ml. of water.

After drying, 53.4 g. (28%) of ethyl *o*-phenylenedioxyacetate was collected at 79–81° (0.3 mm.), n_D^{24} 1.5127. Another sample distilled at 92–94° (0.7 mm.), n_D^{23} 1.5084.[11]

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19; mol. wt., 194. Found: C, 61.41, 61.38; H, 5.26, 5.36; mol. wt. (cryoscopic in benzene) 169, 175.

o-Phenylenedioxyacetic acid amide. A mixture of 3.9 g. (0.020 mole) of the ethyl ester of I and 20 ml. (0.30 mole) of concentrated ammonium hydroxide was shaken for 10 min. An exothermic reaction took place and a solid separated immediately. The solid material, 2.63 g. (80%), was removed by filtration. The m.p. of 110–112° for the crude material was not raised by recrystallization from water.[12] The amide was obtained as 2.12 g. of white flakes.

Anal. Calcd. for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.18, 58.18; H, 4.25, 4.32; N, 8.52, 8.53.

o-Phenylenedioxyacetic acid hydrazide. When 4.0 ml. (0.082 mole) of hydrazine hydrate (99–100%) was added to 3.9 g. (0.020 mole) of the ethyl ester of I, a white solid precipitated immediately. The mixture was heated on a steam bath for 10 min., 40 ml. of ethanol having been added to give a homogeneous solution at the reflux temperature. On cooling, there separated 2.15 g. (60%) of hydrazide, m.p. 182–185°. Recrystallization of the crude product from ethanol yielded 1.80 g. (50%) of white needles, m.p. 185–187°. There was no increase in the melting point after a second recrystallization from ethanol.

Anal. Calcd. for $C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.26, 53.37; H, 4.49, 4.51; N, 15.61, 15.63.

o-Phenylenedioxyacetic acid anilide. The anilide was prepared by a procedure analogous to that used by Hardy.[13]

A solution of ethylmagnesium bromide was prepared from 1.0 g. (0.041 g. atom) of magnesium and 5.0 g. (0.046 mole) of ethyl bromide in 30 ml. of anhydrous ether. To this cold solution of the Grignard reagent was added 4.0 g. (0.043 mole) of aniline. After evolution of gas (ethane) had ceased, 3.9 g. (0.020 mole) of the ethyl ester of I was added, and the mixture was warmed on a steam bath for 10 min. The reaction mixture was then cooled and acidified with 40 ml. of 1:2 hydrochloric acid. After removal of the ether by distillation, the residue was cooled and filtered. The yield of nearly white solid was 3.99 g. (83%), m.p. 118–128°. Recrystallization from ethanol-water gave 3.29 g. (69%) of white flakes, m.p. 135–137°. The melting point was not elevated by a second recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.71, 69.70; H, 4.64, 4.72; N, 5.89, 5.85.

n-Butyl o-phenylenedioxyacetate. A mixture of 15.5 g. (0.080 mole) of the ethyl ester of I, 46 ml. (0.50 mole) of 1-butanol, and 2 drops of concentrated hydrochloric acid was refluxed for 24 hr. Excess ethanol and butanol were removed by distillation on a steam bath at aspirator vacuum. The residue was distilled *in vacuo* to give 14.0 g. of colorless liquid, b.p. 84–102° (0.3 mm.). Since some catechol was evident in the distillate (mixture m.p.), the crude ester was washed with two 5-ml. portions of 5% sodium bicarbonate solution. The ester then was washed with 5 ml. of water, dried over calcium chloride, and distilled. Ten grams (56%) of colorless liquid was obtained, b.p. 100–102° (0.3 mm.), n_D^{29} 1.4907, d_4^{28} 1.1250.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35; MR_D, 56.76.[14] Found: C, 64.30, 64.39; H, 6.56, 6.52; MR_D, 57.19.

4-Chlorocatechol. This compound was prepared in 33%

(9a) A referee has called to the authors' attention a recent paper by Zimmerman *et al., Contrib. Boyce Thompson Inst.*, 18, 453 (1957). This paper which appeared at about the same time our Note was submitted for publication records the preparation of our structure I, a mono- and a dichloro-derivative of I, and the ethyl esters of these acids. The acids were tested on a wide variety of plants; it was concluded that the effects of these compounds were similar to those of 2,4-D except that higher concentrations of the former were required.

(10) All melting points and boiling points are uncorrected.

(11) For this compound, b.p. 115–117° (12.5 mm.) has been reported (ref. 7); however, the analysis of the earlier preparation is not entirely satisfactory.

(12) A melting point of 105–106° has been reported for this amide (ref. 8).

(13) D. V. N. Hardy, *J. Chem. Soc.*, 398 (1936).

(14) A. Weissberger, editor, *Physical Methods of Organic Chemistry*, 2nd. ed. rev., Interscience Publishers, Inc., New York, 1949, Part I, p. 1163.

yield by the method of Frejka, Sefranek, and Zika.[15] More satisfactory was the method of Wrede and Mühlroth[16] which afforded a 51% yield of the chlorophenol.

Ethyl 4-chloro-o-phenylenedioxyacetate. A solution of sodium ethoxide was prepared from 46.0 g. (2.0 g. atoms) of sodium and 1500 ml. of absolute ethanol. To this solution was added 145 g. (1.0 mole) of 4-chlorocatechol. Then 157 g. (1.0 mole) of ethyl dichloroacetate was added, under a nitrogen atmosphere, to the reaction mixture over a period of 20 min. The reaction mixture was stirred at room temperature for 1 hr., then refluxed for an additional 6 hr. The solvent was removed on a steam bath at aspirator vacuum and the residue was stirred with a mixture of 800 ml. of ether and 400 ml. of 5% sodium bicarbonate solution. The ether layer was separated and extracted with an additional 400 ml. of 5% sodium bicarbonate solution followed by two 200-ml. portions of water. The ethereal extract then was dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residue was distilled through a Vigreux column at reduced pressure. The yellow-colored ester (81.4 g., 36%) was collected at 108–109° (0.4–0.5 mm.), n_D^{29} 1.5331, d_4^{28} 1.325.

Anal. Calcd. for $C_{10}H_9ClO_4$: Cl, 15.51; MR_D, 52.39.[14] Found: Cl, 15.14, 15.14; MR_D, 53.56.

Plant growth-regulator activity. The MOLARA[6] values for those compounds tested are: ethyl *o*-phenylenedioxyacetate, 57; *o*-phenylenedioxyacetic acid amide, 634; *o*-phenylenedioxyacetic acid anilide, 185; *o*-phenylenedioxyacetic acid hydrazide, 147; and ethyl 4-chloro-*o*-phenylenedioxyacetate, 215.

Though these compounds did exhibit activity as measured by the leaf repression method of assay, the activity values were of a very low order of magnitude; *cf.* 2,4-D which has a MOLARA of 21,900.[17]

As might have been expected, the chlorine-containing ester was found to be almost four times as active as the corresponding unchlorinated compound (I). Further studies on chlorinated *o*-phenylenedioxyacetic acids and derivatives thereof are currently in progress.

The relatively high activity of *o*-phenylenedioxyacetic acid amide was unexpected but might be attributed, at least in part, to the appreciable solubility of the amide in water (and hence in plant fluids).

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(15) J. Frejka, B. Sefranek, and J. Zika, *Collection Czechoslov. Chem. Commun.*, 9, 238 (1937); *Chem. Abstr.*, 31, 7046 (1937).

(16) F. Wrede and O. Mühlroth, *Ber.*, 63, 1931 (1930).

(17) R. L. Weintraub, J. W. Brown, and J. A. Throne, *J. Agr. Food Chem.*, 2, 996 (1954).

Polymorphic Forms of 2-Methylthio-4-amino-5-hydroxymethylpyrimidine. I

TAKUO OKUDA AND CHARLES C. PRICE[1]

Received April 29, 1957

Samples of I[2] recrystallized by different procedures were found to give quite different infrared patterns when measured in the crystal state in potassium bromide disks (Fig. 1). The existence of three crystal forms has been confirmed by the entirely different x-ray powder diagram for the three phases (Table I). That these forms are the same compound is confirmed by the fact that they give the same infrared and ultraviolet spectra in solution and that, after heating above the melting point, the potassium bromide disks show the same infrared absorption.

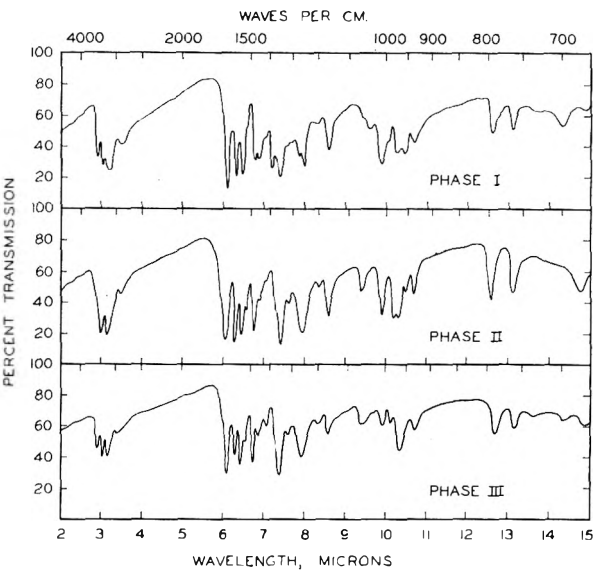

FIG. 1. INFRARED ABSORPTION SPECTRA IN POTASSIUM BROMIDE. Disks of different polymorphic phases of 2-methylthio-4-amino-5-hydroxymethylpyrimidine.

TABLE I

X-RAY PATTERNS FOR THREE PHASES OF 2-METHYLTHIO-4-AMINO-5-HYDROXYMETHYLPYRIMIDINE[a]

Phase I		Phase II		Phase III	
d, Å.	Relative intensities	d, Å.	Relative intensities	d, Å.	Relative intensities
12.20	80	7.94	33	8.26	>100
7.16	45	5.98	39	5.19	16
6.49	38	5.60	11	4.34	22
6.07	>100	4.93	19	4.30	80
5.30	8	3.82	95	4.10	11
4.42	25	3.49	8	3.86	17
4.36	94	3.42	100	3.71	5
4.25	13	3.22	72	3.49	64
4.10	37	3.00	8	2.98	6
4.03	>100	2.67	8	2.79	48
3.82	13	1.81	22	2.71	8
3.74	11	1.80	17	2.39	7
3.33	40			2.37	6
3.22	23			2.11	9
3.18	8			2.03	6
3.04	20			1.96	5
3.01	39			1.92	6
2.66	29			1.82	7
2.55	7				
2.49	8				
2.39	7				
2.17	16				
1.99	6				
1.97	7				
1.95	6				

[a] We are indebted to R. E. Hughes and N. Kornblau for these data, obtained with Ni-filtered CuK_α radiation at 85 kv. and 20 ma. with a Norelco diffractometer.

[1] Supported by a grant from the National Cancer Institute (CY-2714).

(2) T. L. V. Ulbricht and C. C. Price, *J. Org. Chem.*, 21, 567 (1956).

Interconversion of crystal forms. (*a*) *From phase II to phase I.* To a hot saturated benzene solution of phase II was added a small crystal of phase I. On slow cooling to room temperature, fine colorless needles separated, m.p. 124–126°.

(*b*) *From phase III to phase I.* To a hot saturated benzene solution of phase III was added a small crystal of phase I and the solution was cooled down slowly to room temperature. Colorless fine needles were formed, m.p. 124–126°.

(*c*) *From phase I to phase II.* The above crystals of phase I were dissolved in boiling benzene to make a saturated solution and a few small crystals of phase II were added, and then solvent was partially distilled off. Slightly yellowish plates of phase II were obtained, m.p. 126.5–128°.

(*d*) *From phase II to phase III.* This conversion was accomplished by dissolving phase I or II in hot chloroform, then allowing the solution to cool slowly. Large prisms of phase III separated, m.p. 127–129°.

Ultraviolet spectra of samples of phase I, II, and III in ethanol were identical, with λ_{max} 227, 251, and 286 mμ and log ε 4.28, 4.15, and 3.96, respectively.

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4-Halogenated Derivatives of 1-Dehydrocortisone Acetate

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The increased antiinflammatory activity of 1-dehydrocortisone as compared to cortisone[1] has made the introduction of double bonds in a steroid adjacent to a 3-keto group a problem of some importance. Chemically, this has been accomplished by only three different general methods: (*a*) dibromination of a 3-keto saturated allo or normal steroid, followed by dehydrobromination with collidine;[2] (*b*) reaction of lead tetraacetate with a 3-keto-Δ^4-steroid;[3] (*c*) reaction of a 3-keto-Δ^4-steroid or 3-keto saturated allo or normal steroid with selenium dioxide.[4] We had observed independently the formation of 1-dehydrocortisone acetate from cortisone acetate, 17α,21-dihydroxypregnane-3,11,20-trione 21-acetate or 17α,21-dihydroxyallopregnane-3,11,20-trione 21-acetate using selenium dioxide, but since our results do not differ significantly from those of other investigators,[4b-d] we shall not describe them. We should like to report, however, on the extension of this reaction to the preparation of 4-halogenated derivatives of 1-dehydrocortisone acetate.

When 4-bromo-17α,21-dihydroxypregnane-3,11,-20-trione 21-acetate (I) was refluxed for 4 hr. with selenium dioxide in xylene, a new compound was obtained with m.p. 235° (dec.), $[\alpha]_D$ +213.7° (dioxane), λ_{max}^{MeOH} 243 mμ (ε 9,700). This compound still contained one atom of bromine, which could not be removed by vigorous treatment with zinc. Based on these properties, and its non-identity with 4-bromocortisone acetate,[5] the structure of 4-bromo-1-dehydrocortisone acetate (III) is assigned.

In a similar fashion, 4-chloro-17α,21-dihydroxypregnane-3,11,20-trione 21-acetate (II) with selenium dioxide in chlorobenzene gave 4-chloro-1-dehydrocortisone acetate (IV), m.p. 254° (dec.), λ_{max}^{MeOH} 242 mμ (ε 10,600). This compound was not identical with 4-chlorocortisone acetate[5] and could not be dehalogenated with zinc. As further evidence for its structure, treatment with hydrogen and palladium in methanol gave only starting material.

Clinical evaluation of IV indicates that the metabolic effects in man are considerably diminished by the substitution of a chlorine atom for a hydrogen atom at C-4.

EXPERIMENTAL[6]

4-Bromo-1-dehydrocortisone acetate (III). A mixture of 40 g. of 4-bromo-17α,21-dihydroxypregnane-3,11,20-trione 21-acetate, 40 g. of selenium dioxide, and 2.0 l. of xylene was refluxed for 4 hr. The mixture was cooled to room temperature and filtered, and the filtrate concentrated to a residue under reduced pressure. This was taken up in 2 l. of methylene chloride and washed with dilute sodium hydroxide and dilute hydrochloric acid, then with water to neutrality, dried, and concentrated to a residue of 30.3 g. This was mixed with 100 ml. of ether and filtered to yield a residue of 12.43 g. (31%), m.p. 216° (dec.). Recrystallization from methanol-Darco yielded 11.0 g. (28%), m.p. 235° (dec.), $[\alpha]_D$ +213.7° (dioxane), λ_{max}^{MeOH} 243 mμ (ε 9,700).

(1) H. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. Perlman, and M. Pechet, *Science*, 121, 176 (1955).

(2) *Cf.* H. Herzog, C. Payne, M. Jevnik, D. Gould, E. Shapiro, E. Oliveto, and E. B. Hershberg, *J. Am. Chem. Soc.*, 77, 4781 (1955).

(3) R. Clarke, K. Dobriner, A. Moorad:an, and C. Martini, *J. Am. Chem. Soc.*, 77, 661 (1955); S. Burstein and R. Dorfman, *J. Am. Chem. Soc.*, 77, 4668 (1955).

(4) (a) H. Ringold, G. Rosenkranz, and F. Sondheimer, *J. Org. Chem.*, 21, 239 (1956). (b) C. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, 39, 734 (1956). (c) K. Florey and A. Restivo, p. 45, Abstracts of Papers, Delaware Valley Regional Meeting, Feb. 16, 1956, Philadelphia, Pa. (d) S. Szpilfogel, T. Posthumus, M. De Winter, and D. Van Dorp, *Rec. trav. chim.*, 75, 475 (1956).

(5) E. Oliveto, C. Gerold, and E. B. Hershberg, *J. Am. Chem. Soc.*, 79, 3596 (1957).

(6) All melting points are corrected. All rotations were taken in a 1-dm. tube at a concentration of *ca.* 1% at 25°. Analyses and optical data were obtained by the Microanalytical and Physical Chemistry Departments of these laboratories.

Anal. Calcd. for $C_{23}H_{27}O_6Br$: C, 57.62; H, 5.68; Br, 16.67. C, 57.31; H, 5.54; Br, 16.26.

Its 3-semicarbazone, prepared by refluxing III with semicarbazide acetate in aqueous methanol had m.p. ca. 250° (dec.), λ_{max}^{EtOH} 275 mμ (ε 21,000).

Anal. Calcd. for $C_{24}H_{31}N_3O_6Br$: N, 7.8; Found: N, 7.4.

4-Chloro-1-dehydrocortisone acetate (IV). A mixture of 8.0 g. of 4-chloro-17α,21-dihydroxypregnane-3,11,20-trione 21-acetate, 8.0 g. of selenium dioxide, and 400 ml. of chlorobenzene was refluxed for 4 hr. After cooling to room temperature and filtering, 10g. of sodium acetate and 100 ml. of water were added, and the solution steam-distilled. The aqueous residue was made slightly acid with dilute hydrochloric acid, extracted with methylene chloride, and the organic layer washed with dilute sodium hydroxide solution and water, dried, and evaporated to give 1.89 g. (24%), m.p. 248° (dec.), λ_{max}^{MeOH} 241 mμ (ε 10,500). To remove residual selenium, this material was dissolved in 500 ml. of methanol and treated with hydrogen and 190 mg. 5% Pd-on-charcoal for 1 hr. After filtration and concentration, the residue was recrystallized from methanol to yield 1.06 g., m.p. 254° (dec.), $[\alpha]_D$ +215.1° (diox.), λ_{max}^{MeOH} 242 mμ (ε 10,600).

Anal. Calcd. for $C_{23}H_{27}O_6Cl$: Cl, 8.16. Found: Cl, 8.09.

Neither III nor IV, on refluxing with zinc in 80% EtOH-20% HOAc for 3 hr., gave halogen-free products.

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Thiazolidine Chemistry. IV. Alkylation of 2-Phenyl-3-*n*-alkyl-4-thiazolidinones[1,2]

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It was of interest to study the alkylation of some 2-phenyl-3-*n*-alkyl-4-thiazolidinones prepared in this laboratory. Erlenmeyer and Oberlin had reported[5] that the two hydrogens on the 5-position of the thiazolidine ring of 2-phenyl-3-*p*-ethoxyphenyl-4-thiazolidinone had been replaced by two allyl groups. When this alkylation procedure was applied to 2-phenyl-3-*n*-butyl-4-thiazolidinone, the starting material was recovered unchanged. Alkylation with another agent was then attempted. The 2-phenyl-3-*n*-octadecyl-4-thiazolidinone was refluxed for 8 hr. with an equimolar quantity of methyl sulfate. The reaction mixture yielded a white waxy material with a faint pungent odor. A mixture melting point as well as ultraviolet and infrared absorption spectra indicated the product to be entirely different from the starting material. The waxy nature of the product suggested that the *n*-octadecyl group had remained intact. Analytical results and an examination of the spectra suggested that the cleavage compound was *N*-(*n*-octadecyl)methylmercaptoacetamide, $H_3CSCH_2CONH(CH_2)_{17}CH_3$. This was proved by unequivocal synthesis, by condensing *n*-octadecyl amine with the chloride of *S*-methylmercaptoacetic acid, and the identity of the two compounds demonstrated in a conclusive way.

The reproducibility of the cleavage with methyl sulfate was shown by repeated experiments not only on the 2-phenyl-3-*n*-octadecyl-4-thiazolidinone compound, but also on the *n*-butyl and *n*-tetradecyl homologs. The structure of these cleavage products was demonstrated by unequivocal synthesis of the postulated compounds. A literature search failed to show any reactions of a similar nature, although the rupture of the thiazolidine ring under various conditions has been reported.[6,7]

EXPERIMENTAL[8]

N-(n-Tetradecyl)methylmercaptoacetamide. In a 100-ml. round-bottom flask were placed 10.4 g. (0.0277 mole) of 2-phenyl-3-*n*-tetradecyl-4-thiazolidinone, 3.5 g. (0.0278 mole) of methyl sulfate, and 8 ml. of benzene. The mixture was refluxed gently for 7 hr., during which the contents of the flask became red. After cooling, the contents were concentrated *in vacuo*. To the red viscous mass remaining, 50 ml. of methanol and 10 g. of finely divided barium carbonate were slowly added. After the carbon dioxide was evolved the mixture was gently warmed on the steam bath and filtered. The residue was warmed with a fresh 25-ml. portion of methanol and filtered. The combined filtrates were evaporated to dryness and the residue taken up in a minimum amount of hot acetone. Upon cooling and filtering, 4.5 g. of a tan waxy powder were obtained. This was recrystallized twice more from acetone, yielding 2.4 g. (29%) of white waxy crystals with a mild pungent odor; m.p. 64–65°.

Anal.[9] Calcd. for $C_{17}H_{35}NOS$: C, 67.71; H, 11.70; S, 10.63. Found: C, 67.79; H, 11.65; S, 10.93.

N-(n-Octadecyl)methylmercaptoacetamide. This compound was similarly prepared from 0.03 mole of 2-phenyl-3-*n*-octadecyl-4-thiazolidinone and 0.03 mole of methyl sulfate in 10 ml. of benzene. Upon refluxing for 8 hr., there was subsequently obtained 4.1 g. (36%) of white waxy material with a weak pungent odor; m.p. 75.9–76.9°. After purification by vacuum sublimation it still retained a weak pungent odor.

Anal. Calcd. for $C_{21}H_{43}NOS$: C, 70.53; H, 12.12; S, 8.97. Found: C, 70.83; H, 11.91; S, 8.89.

N-(n-Butyl)methylmercaptoacetamide. This compound was similarly prepared from 0.06 mole of 2-phenyl-3-*n*-butyl-4-thiazolidinone and 0.06 mole of methyl sulfate in 10 ml. of benzene. Upon refluxing for 2 hr., there was eventually obtained, after vacuum distillation, 2.5 g. (26%) of a pale red oil, n_D^{25} 1.50289, with a strong pungent odor.

S-Methylmercaptoacetic acid. The alkylation of mercapto acids described (Method B) by Mooradian *et al.*[10] was followed. From mercaptoacetic acid and methyl sulfate there

(1) Part III, I. R. Schmolka and P. E. Spoerri, *J. Am. Chem. Soc.*, **79**, 4716 (1957).

(2) Abstracted from the Ph.D. Thesis of Irving R. Schmolka, Polytechnic Institute of Brooklyn, June 1955. Presented before the sixth Meeting in Miniature of the Metropolitan Long Island Subsection of the New York Section, AMERICAN CHEMICAL SOCIETY, Feb. 25, 1955.

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(5) H. Erlenmeyer and V. Oberlin, *Helv. Chim. Acta*, **30**, 1329 (1947).

(6) W. M. McLamore, W. D. Celmer, V. V. Bogert, F. C. Pennington, B. A. Sobin, and I. A. Solomons, *J. Am. Chem. Soc.*, **75**, 105 (1953).

(7) H. T. Clarke, J. R. Johnson, and R. Robinson, *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949, pp. 921–937.

(8) Melting points are corrected, boiling points are not.

(9) Analyses by Drs. Weiler and Strauss, Oxford, England, and the Analytical Division of the Colgate Palmolive Co. Research Department.

was obtained 50.3 g. (47.4%) of water-white liquid of an unpleasant odor; b.p. 69° at 0.8 mm.[11]

S-Methylmercaptoacetic acid chloride. The preparation of alkyl mercapto acid chlorides (Method D) reported by Mooradian *et al.*[10] was followed. From freshly distilled *S*-methylmercaptoacetic acid and freshly distilled and purified thionyl chloride[12] a pale red oil was obtained. A double distillation *in vacuo* gave 56.1 g. (95.5%) of a pale yellow oil; b.p. 49–50° at 14 mm.[10]

N-(n-Tetradecyl)methylmercaptoacetamide In a flask were placed 7.0 g. (0.033 mole) of freshly vacuum distilled *n*-tetradecyl amine, 11 ml. (0.137 mole) of pyridine, and 600 ml. of anhydrous ether. The flask was placed in an ice bath and mixed until the contents had cooled to 5°. Slowly, and with good agitation, 4.1 g. (0.033 mole) of freshly distilled *S*-methylmercaptoacetic acid chloride were added dropwise over a period of 15 min. A white precipitate formed immediately and the solution turned yellow. Agitation continued for 5 hr., while the contents of the flask slowly warmed up to room temperature. The mixture was extracted several times with a 5% hydrochloric acid solution until the washings were acid. The ether solution was washed with water until neutral, and the ether evaporated. The dry waxy residue was taken up in hot 95% ethanol. After cooling down in an ice bath a white waxy material was filtered off. It was recrystallized from acetone and 5.9 g. (60%) of white waxy material with a faint pungent odor were obtained. A mixture melting point of this material with that previously prepared gave no depression. Infrared absorption curves showed the products obtained from both methods to be identical.

N-(n-Octadecyl)methylmercaptoacetamide. In a similar fashion this compound was prepared in 70% yield. A mixture melting point and infrared absorption curves showed the product obtained from both methods to be identical.

N-(n-Butyl)methylmercaptoacetamide. This compound was similarly prepared. The product obtained was a yellow oil, of unpleasant odor; b.p. 123–124° at 7 mm., n_D^{25} 1.49400, d_4^{25} 1.020, M_D 46.03 (calcd. 45.89). An examination of the infrared absorption curves shows both products exhibit a band for the thioether group at 737 cm.$^{-1}$, and bands for a monosubstituted amide at 1545, 1660, and 3280 cm.$^{-1}$

Anal. Calcd. for $C_7H_{15}NSO$: C, 52.13; H, 9.38. Found: C, 51.90; H, 9.21.

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(10) A. Mooradian, C. J. Cavallito, A. J. Bergman, E. J. Lawson, and C. M. Suter, *J. Am. Chem. Soc.*, **71**, 3372 (1949).

(11) E. Larsson, *Ber.*, **63**, 1347 (1930).

(12) L. F. Fieser, *Experiments in Organic Chemistry*, D. C. Heath and Co., Boston, Mass., 2nd ed., 1941, p. 381.

Some 2,2-Diethyl-3-oxoglutarimides

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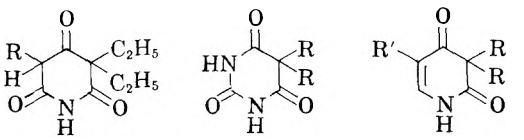
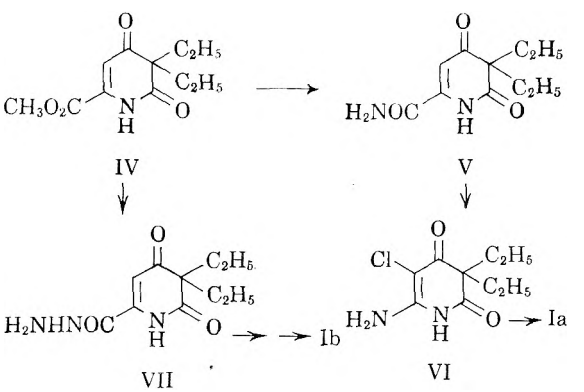
This paper is concerned with the preparation of several compounds of the type represented by structure I. These substances were of interest for testing as possible hypnotic agents because of their close structural resemblance to the well known barbituric acids (II). In the past a number of diketopyridines (III) have been synthesized[1] and reported to possess hypnotic properties.[1,2] The compounds III differ from the barbiturates structurally in that a CO—NH portion of the ring system is replaced by CH=CR. Since the compounds III appear to possess a rather low order of hypnotic activity, we believed it desirable to prepare and test the related compounds, I, which differ from the barbiturate structure only in the replacement of a NH of the ring by CHR. Indeed Ib has been described, previously,[3] but its pharmacological activity has not been well documented.



I II III

a, R = Cl; b, R = H

The sequence of reactions for the synthesis of I and related types started from the known pyridinedionecarboxylic ester (IV).[4] The reaction of the amide (V) with hypochlorite gave the chloro compound (VI), which was hydrolyzed to 2-chloro-4,4-diethyl-3-oxoglutarimide (Ia) by boiling with concentrated hydrochloric acid. To avoid the introduction of halogen, IV was converted through the hydrazide (VII) to the azide, and this, after decomposition and hydrolysis of the resulting product with hydrochloric acid, gave Ib.[3] These compounds were remarkably stable toward long heating with concentrated acid.



IV V VII VI

(1) O. Schinder, H. Frick, and A. H. Lutz, *Experientia*, **10**, 135 (1954).

(2) A. Krautwald, G. Kuschinsky, and H. Riedel, *Arch. exptl. Pathol. Pharmakol.*, **193**, 219 (1939); [*Chem. Abstr.*, **34**, 3367 (1940)]. T. Kopanyi, R. P. Herwick, C. R. Linegar, and R. H. K. Foster, *Arch. intern. pharmacodynamie*, **64**, 123 (1940); [*Chem. Abstr.*, **34**, 5937 (1940)].

(3) H. Erlenmeyer and H. Meyenburg, *Helv. Chim. Acta.*, **20**, 1388 (1937). H. Röhnert, *Ber.* **90**, 118 (1957).

(4) German Pat. **668489**, Dec. 5, 1938; [*Chem. Abstr.*, **33**, 2150 (1939)].

Compounds Ia, Ib, V, VI, and VII as well as the ester IV were tested in rats for both hypnotic and anticonvulsant activities. All were inactive except the amide (V), which had both hypnotic and anticonvulsant properties but the activity was too low to have any practical value.

EXPERIMENTAL

Diethyl 2,2-diethyl-3,5-dioxohexanedicarboxylate-1,6.[4] This was prepared on a one-mole scale by condensation of ethyl oxalate with ethyl α,α-diethylacetoacetate[5] using sodium sand in toluene at 50°. The product was a liquid; b.p. 180–182° (14 mm.), 172° (11 mm.); n_D^{25} 1.4675; yield 71%.

Anal. Calcd. for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 58.61; H, 7.86.

Diethyl 2,2-diethyl-3-oxo-5-aminohexene-4-dicarboxylate-1,6.[4] This compound was obtained by treating the above ester with excess 15% alcoholic ammonia, followed by heating the resulting salt at 60° for 1.5 hr. to effect dehydration. The liquid product was distilled; b.p. 180–185° (14 mm.), 177° (10 mm.); n_D^{25} 1.4775; yield 59%.

Anal. Calcd. for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.13. Found: C, 58.90; H, 8.01.

Methyl 2,4-dioxo-3,3-diethyl-1,2,3,4-tetrahydrohydropyridine-6-carboxylate (IV).[4] This was obtained in very poor yield by heating diethyl 2,2-diethyl-3-keto-5-aminohexene-4-dicarboxylate-1,6 with one equivalent of sodium methoxide in methanol. It was obtained as a yellow crystalline solid, m.p. 79–80°, after recrystallization from water.

Anal. Calcd. for $C_{11}H_{15}NO_4$: N, 6.22. Found: N, 6.33.

3,3-Diethyl-2,4-dioxo-1,2,3,4-tetrahydropyridyl-6-carboxamide (V). A small quantity, *ca.* 5 g., of the methyl ester was added to 50 ml. of liquid ammonia. The ester dissolved immediately, forming a clear yellow solution. The ammonia was allowed to evaporate. The viscous residue was dissolved in 50 ml. of warm ether and 10 ml. of chloroform was added. The crystalline precipitate was collected by filtration and dried on a porous plate; m.p. 118–120°. A sample on recrystallization from water melted at 119–119.5°.

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 56.95; H, 6.62; N, 13.19.

2-Amino-3-chloro-5,5-diethyl-4,6-dioxo-1,4,5,6-tetrahydropyridine (VI). A solution of sodium hypochlorite was prepared by adding 3.1 g. of chlorine to a mixture of 14 g. of sodium hydroxide in 14 ml. of water containing 25 g. of crushed ice. To this was added 45 g. of ice, followed by 8.4 g. (0.04 mole) of the amide. The amide dissolved immediately and the mixture was allowed to warm to room temperature. The solution was heated on the steam bath for 30 min., cooled, and the *p*H adjusted to 7.1 by addition of concentrated hydrochloric acid. The yellow solid which was formed was collected by filtration, washed with cold water, and air dried. This material weighed 3.8 g. (52%); m.p. 286–290° dec. A sample was recrystallized twice from ethanol; m.p. 290° dec.

Anal. Calcd. for $C_9H_{13}ClN_2O_2$: C, 49.89; H, 6.05; N, 12.93; Cl, 16.32. Found: C, 50.16; H, 6.02; N, 12.69; Cl, 16.59.

2-Chloro-4,4-diethyl-3-oxoglutarimide (Ia). A mixture of 10.8 g. (0.05 mole) of the amino compound in 50 ml. of concentrated hydrochloric acid was heated under reflux for 24 hr. The hot solution was filtered to remove a small amount of insoluble material, and the filtrate on chilling and scratching precipitated a tan, granular solid. This was collected by filtration, washed with cold water, and dried. There was obtained 10.3 g. (95%) of solid; m.p. 184–186°. A small sample, on sublimation at 225°/1 mm., gave a white crystalline solid; m.p. 188°.

Anal. Calcd. for $C_9H_{12}ClNO_3$: C, 49.66; H, 5.51; N, 6.43. Found: C, 49.60; H, 5.60; N, 6.61.

3,3-Diethyl-2,4-dioxo-1,2,3,4-tetrahydropyridyl-6-carboxylic acid hydrazide (VII). To a solution of 56.3 g. (0.25 mole) of the methyl ester in 200 ml. of ethanol was added 13.7 g. (0.275 mole) of hydrazine hydrate. The clear solution was heated under reflux for 1 hr. and the ethanol then removed *in vacuo*. The residue was recrystallized from hot water to give 29.5 g. (52.5%) of a yellow solid; m.p. 159–162°. A sample was recrystallized twice from ethanol; m.p. 162–163°.

Anal. Calcd. for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.66. Found: C, 53.59; H, 6.91; N, 18.74.

2,2-Diethyl-3-oxoglutarimide (Ib). The hydrazide, 11.3 g. (0.05 mole), was dissolved in 75 ml. of cold water containing 8 ml. of 6N hydrochloric acid. To this was added 100 ml. of ethyl ether and the mixture was stirred vigorously. A solution of 3.8 g. of sodium nitrite in 10 ml. of water was added while keeping the temperature below 10° by adding ice directly to the reaction mixture. The mixture was stirred for 10 min., then the ether layer was separated. The aqueous layer was extracted once with more ether. The combined ether solutions were washed with dilute aqueous sodium bicarbonate, water, then dried over anhydrous calcium chloride. The ether was decanted into a flask containing 100 ml. of ethanol. The ether was distilled off slowly on the steam bath and the remaining ethanol solution warmed for 1 hr. to complete decomposition of the azide. The ethanol was removed *in vacuo* to give a yellow, glassy residue. A mixture of 20 ml. of concentrated hydrochloric acid and 10 ml. of glacial acetic acid was added and the mixture was heated at reflux for 1 hr., and then heated on the steam bath overnight. The solvents were removed *in vacuo* and the residue treated with 100 ml. of warm water. A water-insoluble solid was separated; 1.9 g.; m.p. 225–227°. The aqueous filtrate was evaporated to give a second solid; 3.6 g.; m.p. 135–145° with gas evolution. A sample of this material on redissolving in water gave a precipitate with silver nitrate, indicating the presence of ionic chlorine. This water-soluble material was added to 50 ml. of 1:1 hydrochloric acid and water and the mixture refluxed for 6 hr. The solvents were removed *in vacuo* to give a semi-crystalline residue. This was dissolved in a small volume of dilute aqueous sodium hydroxide, filtered, and the filtrate acidified with concentrated hydrochloric acid. Chilling and scratching produced a white, granular precipitate. This was removed by filtration and dried; m.p. 224–226°. A mixture melting point with the water insoluble hydrolysis product from above showed no depression. The combined solids were dissolved in aqueous sodium hydroxide, filtered, and the filtrate acidified. The white solid was collected by filtration, washed with cold water, and dried; m.p. 225–226°. A sample on recrystallization from ethanol showed no increase in melting point.

Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15. Found: C, 59.17; H, 7.35.

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(5) F. J. Marshall and W. N. Cannon, *J. Org. Chem.*, **21**, 245 (1956).

Pyrolysis of 5,5-Bis(chloromethyl)-1,3,2-dioxathiane 2-Oxide

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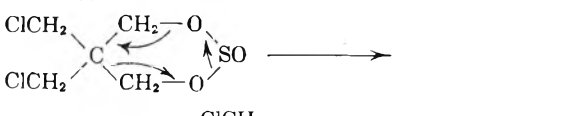
The pyrolysis of cyclic sulfites of 1,2-glycols has been studied by Denivelle[1] and by Price and

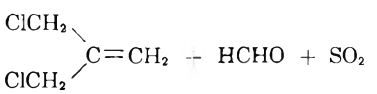
(1) L. Denivelle, *Compt. rend.*, **208**, 1024 (1939).

Berti.[2] The latter authors found that the sulfites decomposed smoothly at 240–300° and gave aldehydes or ketones in good yield. The rearrangements were explained on the basis of the stereochemistry of the cyclic sulfites. Apparently no one has studied the pyrolysis of cyclic sulfites of 1,3-diols.

In connection with another problem we were interested in the products of pyrolysis of 5,5-bis(chloromethyl)-1,3,2-dioxathiane 2-oxide (I), the cyclic sulfite of 2,2-bis(chloromethyl)-1,3-propanediol. At 500° this compound decomposed smoothly to give formaldehyde, sulfur dioxide, and a 91% yield of 3-chloro-2-chloromethyl-1-propene (II). Since the cyclic sulfite is readily prepared from pentaerythritol and thionyl chloride,[3] this probably constitutes a more convenient synthesis of this disubstituted isobutylene than those previously reported in the literature.[4,5] Although the reaction may be pictured as taking place by a series of steps analogous to those postulated by Price and Berti, it is most readily explained as involving a concerted shift of electrons.



I



II

EXPERIMENTAL

The apparatus consisted of a distilling flask surmounted by a dropping funnel and connected to a 2.5-cm. i.d. Vycor tube packed with 35 cm. of quartz chips. The outlet of the tube was connected to two traps, the first cooled with ice and the second with Dry Ice. The apparatus was flushed with nitrogen, evacuated to 15 mm., and the packed portion of the tube heated to 500°. Then 20 g. of the cyclic sulfite[3] was flash-distilled into the tube over a period of 2 hr. Distillation of the material in the ice-cooled receiver yielded 4.2 g. (91% based on reacted sulfite) of 3-chloro-2-chloromethyl-1-propene, b.p. 138°, m.p. −11°, n_D^{20} 1.4756 (lit. b.p. 138°, m.p. −15 to −13°, n_D^{20} 1.4754),[4] and 9.8 g. of undecomposed cyclic sulfite, b.p. 81° at 0.15 mm. An additional 2.1 g. of sulfite was recovered from the tube, a total of 59%. The Dry Ice trap contained 1.8 g. (76%) of sulfur dioxide, and 1.0 g. (90%) of paraformaldehyde, identified as its 2,4-dinitrophenylhydrazone, m.p. 165–166° (lit. m.p. 166°).[6] The effect of reaction variables on yield and conversion was not investigated.

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(2) C. C. Price and G. Berti, *J. Am. Chem. Soc.*, **76**, 1211 (1954).

(3) H. Pietsch, U. S. Patent 2,708,198 (1955); H. Pietsch and H. Nagel, U. S. Patent 2,708,200 (1955).

(4) A. Mooradian and J. B. Cloke, *J. Am. Chem. Soc.*, **67**, 942 (1945).

(5) J. T. Gragson, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Am. Chem. Soc.*, **75**, 3344 (1953).

(6) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, 2nd Ed., John Wiley and Sons, Inc., New York, 1940, p. 143.

Novel Separation of 2- and 4-Benzoylpyridine

JOHN I. STEVENS,[1] GENE SUMRELL, AND GEORGE E. HAM

Received May 6, 1957

2-Benzoylpyridine and 4-benzoylpyridine have become increasingly useful in recent years as intermediates in the preparation of fine chemicals and pharmaceuticals. They are usually prepared by oxidation of the corresponding benzyl compounds. The latter are generally obtained by the reaction of benzyl chloride with pyridine in the presence of a suitable catalyst.[2] The monobenzylpyridines formed are easily separated from higher benzylated products by simple distillation, but separation of the mixture of 2- and 4-benzylpyridine is more difficult because of the closeness of their boiling points. The fact that their boiling points are so high renders it even more difficult to carry out an efficient fractionation on a large scale. Other means of separation reported in the literature also have their limitations for large scale work.[3]

The observation that 2-benzoylpyridine is markedly less basic than its 4-isomer was made by Crook and McElvain.[3a] However, no attempt to separate the two by a method utilizing their difference in basicity appears to have been made. We are reporting a successful separation of 2- and 4-benzoylpyridine by partition between dilute hydrochloric acid and benzene, with the less basic 2-isomer remaining in the benzene phase while the 4-isomer is extracted into the aqueous phase as the hydrochloride.

EXPERIMENTAL[4]

Benzylpyridines. A mixture of 10 moles of benzyl chloride, 5 moles of pyridine, and 50 g. of anhydrous cupric chloride[5] was heated in a 5-l. flask (fitted with a mechanical stirrer, dropping funnel, and condenser, with a thermometer suspended down the latter) until the temperature rose to 90°. At this point the reaction became exothermic and the

(1) Present address: Fairfield Division, Food Machinery and Chemical Corporation, Baltimore, Md.

(2) See K. E. Crook, *J. Am. Chem. Soc.*, **70**, 416 (1948) and references cited therein.

(3) (a) K. E. Crook and S. M. McElvain, *J. Am. Chem. Soc.*, **52**, 4006 (1930) resorted to fractional distillation followed by recrystallization of the picrate to obtain pure 2-benzylpyridine for oxidation to 2-benzoylpyridine. They obtained pure 4-benzoylpyridine by recrystallization of the picrate after oxidation of impure 4-benzylpyridine. (b) Separation of 2- and 4-benzoylpyridine in small amounts has been reported by passage of a benzene solution through an alumina column, see K. Tsuda, Y. Sato, and S. Saeki, *Pharm. Bull. (Japan)*, 1, 307 (1953); *Chem. Abstr.*, 49, 10946 (1955). See also (c) F. B. LaForge, *J. Am. Chem. Soc.*, **50**, 2484 (1928); and (d) P. C. Teague, *J. Am. Chem. Soc.*, **69**, 714 (1947).

(4) Melting points and boiling points are uncorrected.

(5) Prepared by heating 63.5 g. of the dihydrate for several hours at 90–100°.

temperature rapidly rose to 170° with mild refluxing.[6] An additional 5 moles of pyridine was then added at such a rate as to maintain reflux, followed by heating the stirred mixture under reflux for 15 hr. It was then allowed to cool to about 100°, diluted with water, and worked up essentially by the method described by Crook,[2] except that benzene alone was used for the extraction instead of a benzene-ligroin mixture. Distillation through a 30-cm. Vigreux column yielded 762 g. (45%) of a mixture of 2- and 4-benzylpyridine at 150–160°/25 mm.

Oxidation. A solution of 348 g. of potassium permanganate in 1740 ml. of water was prepared at about 60°. To this was added with stirring 500 ml. of benzene containing 254 g. (1.5 moles) of the mixture of monobenzylpyridines obtained above. The mixture slowly rose to boiling and refluxed mildly for 3 hr. without external heating. Then the temperature dropped and the mixture was heated under reflux for 15 hr. Heating was discontinued and a solution of 30 ml. of conc. sulfuric acid in 60 ml. of water was added dropwise. Stirring was continued for 1 hr. Then the dense, finely divided manganese dioxide formed in the reaction was allowed to settle and the two phase benzene-water mixture was decanted, or siphoned off and separated. The water layer (mildly basic at this point) was discarded and the benzene layer saved for extraction as described below.

Separation of 2- and 4-benzoylpyridine.[7] A solution of 1600 ml. of 0.75*N* hydrochloric acid was prepared. The benzene solution obtained above was extracted with two 100-ml. portions of this acid solution and these acid extracts were discarded.[8] The benzene solution was then extracted four times with 350-ml. portions of acid and followed at the end with a 100-ml. water wash. The benzene layer was dried briefly over sodium sulfate and the benzene distilled leaving a residue of about 100 g. of 2-benzoylpyridine. Though somewhat discolored, this material was essentially pure, giving a picrate of m.p. 127–129°. Fractionation gave a quantitative recovery at 177–179°/15 mm., n_D^{23} 1.6070 (lit.[3d] b.p. 315–319°/750 mm.; picrate, m.p. 128–129°).

The four acid extracts and the water wash were combined and extracted three times with 150-ml. portions of benzene.[9] The aqueous phase was then heated on the steam bath to remove dissolved benzene, then cooled and rendered basic with sodium hydroxide while stirring. The crude 4-benzoylpyridine which crystallized amounted to 95 g. and had m.p. 60–65°. Recrystallization from a mixture of isopropyl alcohol and water yielded 70 g. (two crops) of material of m.p. 71–73° (lit.[3d] m.p. 72°).

Acknowledgment. The authors are pleased to acknowledge the assistance rendered in this work by C. F. Hartman and J. W. Parsons.

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(6) When the theoretical amount of pyridine was present during this exothermic phase, the reaction usually became uncontrollable. The reaction was carried out on a scale several times that described here without difficulty when only half of the theoretical amount of pyridine was added initially, and the remainder after the temperature reached its peak.

(7) The authors have not investigated the use of countercurrent extraction for this separation. This modification would obviously simplify the process and make the separation more quantitative.

(8) These acid extracts contain about 25 g. of a mixture of unreacted monobenzylpyridines and 4-benzoylpyridine. This material can be recovered by the addition of sodium hydroxide and used on a later oxidation.

(9) These benzene extracts were found to contain a total of about 30 g. of material consisting mostly of 2-benzoylpyridine, but contaminated with some of the 4-isomer.

Separation and Identification of Aliphatic Mercaptans by Chromatography of the 2,4-Dinitrophenylsulfides

JOHN F. CARSON AND FRANCIS F. WONG

Received June 10, 1957

This communication reports the separation of 2,4-dinitrophenylsulfides of some of the aliphatic mercaptans by adsorption chromatography on silicic acid containing fluorescent zinc sulfide. Although sensitive methods for the isolation and identification of mercaptans as the heavy metal mercaptides or as the dinitrophenylsulfides are well known, resolution of mixtures of the derivatives has not been reported except where fractional crystallization was employed.[1]

For chromatography, the general procedure of Sease[2] was employed except that celite was omitted. A commercial grade of silicic acid[3] was used without pretreatment and was mixed with one percent of its weight of fluorescent zinc sulfide.[4] The dinitrophenylsulfides were applied to the silicic acid–zinc sulfide columns in benzene solution and the adsorbed bands resolved by development with solutions of hexane containing acetone, ethyl acetate, or diethyl ether in ratios of 25–50:1. Illumination of the column in the dark with a mercury ultraviolet lamp revealed individual bands of dinitrophenylsulfides as grey to purple shadows on a yellow fluorescing background. Although the derivatives themselves are yellow to orange, detection of the zones in daylight is usually difficult and observation of the quenching of fluorescence is necessary for sharp definition. The rates of movement of alkyl dinitrophenylsulfides were found to increase in the order: $CH_3 < C_2H_5 < CH_2{=}CH{-}CH_2 < nC_3H_7 < nC_4H_9 < nC_5H_{11} < tC_4H_9 < nC_6H_{13}$. Mixtures of any of these derivatives could be resolved into separate distinct bands which could be isolated as pure compounds. However, mixtures of isomeric alkyl-2,4- dinitrophenylsulfides, with the exception of the *t*-butyl derivative, could not be resolved into separate distinct bands. For example, mixtures of isopropyl and *n*-propyl derivatives or of isobutyl- and *n*-butyl dinitrophenylsulfides moved as broad diffuse zones without splitting into separate bands. The rates of movement of the bands generally in-

(1) C. Mannich and Ph. Fresenius [*Arch. der Pharm.*, 274, 461–72 (1936)] separated a mixture of *sec*-butyl- and propenyl 2,4-dinitrophenylsulfides by fractional crystallization.

(2) J. W. Sease, *J. Am. Chem. Soc.*, 69, 2242 (1947); 70, 3630 (1948).

(3) Mallinckrodt 100 mesh, Analytical Reagent. Mention of commercial products does not imply endorsement by the Department of Agriculture or recommendation over other products.

(4) No. 62 fluorescent zinc sulfide, Patterson Screen Division, E. I. du Pont de Nemours and Co., Inc., Towanda, Pa.

creased with developing solvent in the order: ether < ethyl acetate < acetone as expected, and hexane-ether solutions generally gave better separations as was observed by Sease.[2]

In the attempt to separate isomeric mercaptan derivatives, chromatography of the 2,4-dinitrophenyl alkylsulfones on silicic acid–zinc sulfide was attempted. The derivatives were more strongly adsorbed than the corresponding sulfides and moved as sharp bands when developed with hexane–acetone (25:1), but quenching of fluorescence was weaker. These derivatives possessed no apparent advantage over the sulfides and again mixtures of the isomeric derivatives could not be resolved into separate bands.

Chromatography of dinitrophenyl sulfides when combined with lithium aluminum hydride reduction[5] of disulfides has been found particularly useful for characterization of small quantities of unsymmetrical aliphatic disulfides. The 2,4-dinitrophenylsulfides can be prepared directly from the reduction mixture after destruction of excess lithium aluminum hydride. In some cases, a purer derivative may be obtained in this manner from the disulfide than from the mercaptan as we have observed with the derivative of allyl mercaptan. On the other hand, reduction with metals and acids is difficult with small quantities if isolation is necessary and is not applicable to allylic disulfides. Reductions with sodium in ether[1] or with sodium or sodium-potassium alloy in xylene[6] are time-consuming and, in our hands, have not been satisfactory for small quantities of diallyl disulfide.

Lithium aluminum hydride reduction, formation of dinitrophenylsulfides, and chromatographic separation of the derivatives has been applied to a 100-μl. sample of synthetic allyl propyl disulfide and to a 60-μl sample of methyl *n* propyl disulfide isolated by gas-liquid partition chromatography of volatile material from onions. In each case, the crystalline 2,4-dinitrophenylsulfides were obtained as pure compounds after chromatography.

EXPERIMENTAL

Materials. The saturated aliphatic mercaptans were of Eastman "White Label" Grade except for *iso*propyl- and *t*-butyl mercaptans which were Eastman Technical Grade. Before use, the purity of the mercaptans was usually established by gas-liquid chromatography on columns packed with a polyethylene glycol as the liquid phase. Allyl mercaptan was prepared by alkaline hydrolysis of allyl isothiourea hydrobromide and freshly prepared material was used in preparing the dinitrophenylsulfide. 2,4-dinitrophenylsulfides were prepared according to the procedure of Bost.[7] It was also found that these derivatives could be prepared conveniently from lead mercaptides by refluxing a suspension of lead mercaptide in ethanol containing an excess of 2,4-dinitrochlorobenzene or 2,4-dinitrofluorobenzene.

Preparation of chromatographic columns. Silicic acid[3] was mixed with 1% of its weight of fluorescent zinc sulfide[4] and the mixture shaken and tumbled for 5–10 min. The chromatograph tubes were packed with dry adsorbent with suction and the columns prewashed with one bed volume of anhydrous ether followed by two or three volumes of hexane. The dinitrophenylsulfides in benzene solution were added to the top of a column with a pipet and the column was again washed with two or three bed volumes of hexane before applying the developing solvents. For the separation of mixtures containing 1–5 mg. of derivative, a 11 × 200 mm. Pyrex glass tube was used, and for mixtures of dinitrophenylsulfides prepared from the reduction products of 50–100 mg. of disulfides a column 46 × 300 mm. was used.

Reduction of methyl-n-propyl disulfide and formation of 2,4-dinitrophenylsulfides. Sixty μl. of methyl *n*-propyl disulfide, previously identified by infrared spectra, was dissolved in 10 ml. of dry ether and placed in a 50-ml. round-bottom flask equipped with reflux condenser and a drying tube. Approximately 0.3 g. of lithium aluminum hydride (the quantity of reagent is not critical provided an excess is used) was added in small quantities over a 15-min. period. The mixture was refluxed gently for 2 hr. on a steam bath and then cooled in a Dry Ice bath. Excess lithium aluminum hydride was destroyed by the addition of 1 ml. of ethyl acetate followed a few minutes later by 1 ml. of water in 5 ml. of ethanol. After standing for 30 min. at room temperature, the mixture was poured into 50 ml. of ethanol containing 190 mg. of 2,4-dinitrochlorobenzene. The light amber suspension was warmed on the steam bath for 10–15 min., filtered from hydroxides and salts, and the gelatinous precipitate washed with 20 ml. of warm ethanol. The combined filtrates containing the dinitrophenylsulfides were concentrated *in vacuo* to a dry yellow solid which was extracted with 100 ml. of benzene. The benzene extract was washed with normal sodium hydroxide (to remove any dinitrophenol which interferes in chromatography), dried with calcium chloride, and concentrated *in vacuo* to 25 ml.

Chromatography of dinitrophenylsulfides. The benzene solution of dinitrophenylsulfides was poured on a column of silicic acid–zinc sulfide (1%), 46 × 200 mm., which had been prewashed with 120 ml. of ether and 400 ml. of hexane to give a yellow band, 0.5 cm. in thickness at the top. Washing with 400 ml. of hexane followed by development with 1750 ml. of hexane–ethyl acetate (25:1) resolved the band into an upper band (1 cm. wide) which had moved 3.5 cm. and a lower band (2.5 cm. wide) which had moved 13–14 cm. The slow-moving band was carved out of the column and extracted with acetone. Evaporation of the acetone and recrystallization of the yellow solid residue from 7 ml. of ethanol yielded 62 mg. of methyldinitrophenylsulfide as canary yellow micaceous plates identified by melting point, 120°, and mixed melting point. The faster moving band was eluted from the column with acetone. Removal of solvent yielded semi-crystalline material which was crystallized from 5 ml. of ethanol to yield 82.5 mg. of *n*-propyl dinitrophenylsulfide as stubby amber prisms, m.p. 84–85°.

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(5) R. C. Arnold, A. P. Lien, and R. M. Alm, *J. Am. Chem. Soc.*, 72, 731 (1950).

(6) R. E. Stutz and R. L. Shriner, *J. Am. Chem. Soc.*, 55, 1242 (1933).

(7) R. W. Bost, J. O. Turner, and R. D. Norton, *J. Am. Chem. Soc.*, 54, 1985 (1932).

Reactions of Carbohydrates with Nitrogenous Substances. V. The Supposed Influence of Water on the Preparation of *N*-*p*-Tolyl-D-Glucosylamine[1,2]

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Two isomers (A and B) of *N*-phenyl-D-ribosylamine and of *N*-*p*-tolyl-D-glucosylamine have been obtained.[3,4] For the ribose derivatives, the reaction temperature during preparation was considered originally to be the factor determining the particular isomer obtained.[3] Later Ellis and Honeyman[4] provided evidence that for a number of glycosylamines the presence or absence of water was the factor determining the isomer that was formed. For *N*-*p*-tolyl-D-glucosylamine, Isomer A($[\alpha]_D^{18}$ + 209 → −45°, methanol) was reported to be the isomer formed under anhydrous conditions. Isomer B ($[\alpha]_D$ −100 (variable) → −45°, methanol) was obtained in the presence of water.

In our laboratory, *N*-*p*-tolyl-D-glucosylamine is usually prepared by refluxing D-glucose with a 33% molar excess of *p*-toluidine in ordinary commercial absolute methyl alcohol (Baker's reagent grade). The reaction mixture is then concentrated under reduced pressure and successive crops are collected. Water should be present, since it is formed in the reaction. In our earlier work, the usual form of *N*-*p*-tolyl-D-glucosylamine that was obtained was levorotatory (Isomer B[4,5]), in conformity with the results of Ellis and Honeyman. In more recent work, we have obtained the dextrorotatory Isomer A,[4,5] as the first crop from repeated preparations, even when water was deliberately added to the reaction system. Successive crops from the same preparation appeared to be mixtures of both isomers, since the initial specific rotation in methanol varied from −206° to −89°, and all crops mutarotated to a constant value of approximately −45°.

We infer from these results that, as might be expected, the particular crystalline isomer or mixture of isomers which is obtained in this laboratory depends upon the composition of the reaction mixture at and during the time of crystallization, upon the possibility of the establishment of equilibrium between the isomers, and upon the presence in the laboratory of seed crystals of the two forms. Water does not seem to be the determining factor, but might have some effect in accelerating the interconversion of the isomers. The sensitivity of these reactions to acid catalysts[6] suggests that accidental traces of acids may also produce variable rates of re-establishment of equilibria during crystallization.

EXPERIMENTAL

Anhydrous methanol was prepared by treating methyl alcohol absolute, Baker reagent, with magnesium turnings.[7]

The specific rotations of *N*-*p*-tolyl-D-glucosylamine were determined using a 2 dm. tube. Anhydrous methanol was used as the solvent. The readings were made at 20°, but on occasion in order to increase the rate of mutarotation, the anhydrous solutions of *N*-*p*-tolyl-D-glucosylamine were kept at 37° to 38° between readings.

Anhydrous D-glucose (Cerelose, Corn Products) was used, and the *p*-toluidine (Eastman, White Label) was recrystallized before use.

All melting points were accompanied by decomposition (browning) and were determined on a Fisher-Johns block and are uncorrected.

The following are different preparations of *N*-*p*-tolyl-D-glucosylamine. All crops were dried to constant weight *in vacuo* over calcium chloride and sodium hydroxide.

Preparation A: Anhydrous D-glucose (15 g., 0.083 mole) and *p*-toluidine (12 g., 0.11 mole) were refluxed 150 min. in 175 ml. methanol. The light tan clear solution was concentrated under reduced pressure at room temperature to a thin sirup (27 ml.), to which 10 ml. ethanol was added, and worked in. The sirup was allowed to stand overnight. The first crop of crystals was collected and washed twice with ethanol to yield 7.4 g. (33%). A second crop (3rd day) (4.7 g., 21%) and a third crop (8th day) (3.8 g., 17%) were also collected from the mother liquor and washed and dried as above. No further crops were collected due to extensive browning of the mother liquor. The physical constants were: Crop 1, m.p. 133–134° (dec.), $[\alpha]_D^{20}$ + 206.4° (5 min.) → −44.9° (constant) (*c* 1.0); Crop 2, m.p. 127–131° (dec.) $[\alpha]_D^{20}$ + 59.3° (7 min.) → −43.7° (constant) (*c* 1.1); Crop 3, m.p. 126–130° (dec.), $[\alpha]_D^{20}$ −28.7° (6 min.) → −43.5° (constant) (*c* 1.4).

Preparation B: Anhydrous D-glucose (18 g., 0.10 mole) and *p*-toluidine (14 g., 0.13 mole) were refluxed 165 min. in a solvent composed of 150 ml. anhydrous methanol and 2.0 ml. water (0.11 mole). The reaction mixture was concentrated under reduced pressure at room temperature to 35 ml. Two crops were collected: the first (3.6 g., 13%) after the sirup stood overnight, and the second (12.2 g., 45%) on the third day. The physical constants were: Crop 1, m.p. 134–135° (dec.), $[\alpha]_D^{20}$ + 200° (6 min.) → −43.8° (constant) (*c* 0.34); Crop 2, m.p. 127–130° (dec.), $[\alpha]_D^{20}$ +31.6° (5 min.) → −44.2° (constant) (*c* 0.50).

Preparation C: This was made identically to preparation B but in another laboratory after careful washing of the equipment. The first crop (11.1 g., 41%) was collected after 36 hr. and the second crop (6.0 g., 22%), 4 days later. Physical constants follow: Crop 1, m.p. 119–122° (dec.), $[\alpha]_D^{20}$ −84.2° (6 min.) → −43.6° (constant) (c 1.1); Crop 2, m.p. 117–119° (dec.) $[\alpha]_D^{20}$ −89.4° (4 min.) → −44.2° (constant) (*c* 1.1).

(1) This work was supported by a grant from the National Science Foundation.

(2) Previous paper, this series: L. Rosen, J. W. Woods, and W. Pigman, *Chem. Ber.*, 90, 1038 (1957).

(3) L. Berger and J. Lee, *J. Org. Chem.*, 11, 75 (1946).

(4) G. P. Ellis and J. Honeyman, *J. Chem. Soc.*, 1490 (1952). They report the stereoisomer which is obtained under anhydrous conditions as Isomer A, the other isomer being Isomer B.

(5) G. P. Ellis and J. Honeyman, *Advances in Carbohydrate Chem.*, **10**, 95 (1955). In this review article the isomeric forms, A and B, of *N*-*p*-tolyl-D-glucosylamine are designated as *N*-*p*-tolyl-α- and *N*-*p*-tolyl-β-D-glucosylamine respectively (see p. 147).

(6) H. S. Isbell and H. L. Frush, *J. Research Natl. Bur. Standards*, **46**, 132 (1951).

(7) L. F. Fieser, *Experiments in Organic Chemistry*, 2nd Edition, p. 360, D. C. Heath and Company, New York, N. Y., 1941.

Preparation D: Anhydrous D-glucose (30 g., 0.17 mole), and *p*-toluidine (24 g., 0.22 mole) were refluxed 180 min. in 200 ml. methanol. After 2 days at room temperature, the brownish solution was concentrated under reduced pressure between 35–50° to a thick sirup, approximately 25 ml. Crystallization occurred at once and after 2 days at room temperature, a crop was collected, washed, and dried in the usual manner. The crop (28 g., 62%) had the following physical constants: m.p. 126–128° (dec.), $[\alpha]_D^{20}$ + 14.0° (6 min.) → −44.7° (constant) (*c* 0.35).

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Reactions of *N*-Bromoamides and *N*-Bromoimides with Styrene[1]

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Received May 13, 1957

N-Bromoacetamide has been reported[2,3] to react rapidly with styrene to give the dibromide. *N*-Bromosuccinimide, however, gave little or no reaction with styrene.[3] In all reactions including decomposition *N*-bromosuccinimide was found qualitatively to be less reactive than *N*-bromoacetamide. This type of result has been related to the tendency of *N*-bromosuccinimide to brominate the allyl position so successfully.[3] For this reason a number of *N*-bromoamides and *N*-bromoimides have been tested as to their reactivity with styrene. The results are summarized in Table I.

The *N*-bromoimides were the least reactive in general while the simple *N*-bromoamides were the most reactive. Along with 1-bromo-5,5-dimethylhydantoin the *N,N'*-dibromodiamides were of intermediate reactivity except for *N,N'*-dibromomalonamide which was very unreactive. *N*-Bromoglutarimide appeared to be consumed by a slow reaction, but only a small yield of the dibromide was obtained after an extended reaction period.

Of the *N*-bromo compounds which were relatively unreactive to styrene 1-bromo-5,5-dimethylhydantoin[4] and 1,3-dibromo-5,5-dimethylhydantoin[5] have been reported as successful brominating agents for allyl and benzyl positions. *N*-Bromophthalimide was reported[6] as brominating the allyl position but giving dibromide and a 1:1 adduct as by-products. *N*-bromoglutarimide was found in the present investigation to react with cyclohexene to give 3-bromocyclohexene in 66% yield in contrast to its reported[6] unreactivity.

The reaction of styrene with *N,N*-dibromobenzenesulfonamide evidently gave rise to a 1:1 adduct analogous to that reported[7] for *N,N*-dibromo-*p*-toluenesulfonamide. The products isolated, however, were *N*-benzenesulfonylstyreneimide, when the reaction mixture was treated with base, and *N*-(2-bromo-1-phenylethyl)-*N*-(1-bromo-2-phenyl-ethyl) benzenesulfonamide when excess styrene was present. The structures of these compounds were assigned on the basis of analogous derivatives described[7] for *N,N*-dibromo-*p*-toluenesulfonamide.

EXPERIMENTAL

N-Bromo compounds. Samples of the *N*-bromo compounds used were kindly supplied by Dr. Thomas D. Waugh,

TABLE I

REACTIONS OF *N*-BROMO COMPOUNDS WITH STYRENE IN BOILING CHLOROFORM

N-Bromo Compound		Reaction Time, hrs.	% Yield		
Name	Mole		Amide or imide	*N*-Bromo compd.	Dibromide[a]
N-Bromophenylacetamide	0.025	0.5	91	0	53
N-Bromo-*o*-toluamide	0.01	1.0	59	0	23
N-Bromobenzamide	0.025	1.25	50	0	52
N,N'-Dibromosuccinamide	0.018	4.5	86	0	30
N,N'-Dibromoterephthalamide	0.018	10	0	67	31
N,N'-Dibromooxamide	0.025	24	0	42	32
1-Bromo-5,5-dimethylhydantoin	0.04	34	53	0	30
N,N'-Dibromomalonamide	0.025	25	0	97	0
N-Bromophthalimide	0.025	24	0	92	0
N-Bromoglutarimide	0.025	60	29	0	6
1,3-Dibromobarbituric acid	0.01	24	0	95	0
1,3-Dibromo-5,5-dimethylhydantoin	0.025	24	0	97	0

[a] Yield of dibromide based on the amount of *N*-bromo compound consumed during the reaction.

(1) Taken from part of the Ph.D. dissertation of William J. Probst.

(2) R. E. Buckles, *J. Am. Chem. Soc.*, **71**, 1157 (1949).

(3) R. E. Buckles, R. C. Johnson, and W. J. Probst, *J. Org. Chem.*, **22**, 55 (1957).

(4) O. O. Orazi and J. Meseri, *Anales asoc. quim. argentina*, **37**, 192, 263 (1949).

(5) O. O. Orazi and J. Meseri, *Anales asoc. quim. argentina*, **38**, 5 (1950).

(6) K. Ziegler, A. Späth, E. Schaaf, W. Schumann and E. Winkelmann, *Ann.*, **551**, 80 (1942).

(7) M. S. Kharasch and H. M. Priestley, *J. Am. Chem. Soc.*, **61**, 3425 (1939).

Arapahoe Chemicals, Inc., Boulder, Colo. Some of the *N*-bromoglutarimide was prepared as described below.

Glutarimide. A solution of 70 g. (0.53 mole) of glutaric acid in 150 ml. of concentrated aqueous ammonia was heated under a steam-heated reflux condenser for 7 hr. as the temperature of the mixture rose from 90–180°. The temperature was held at 170–180° until the evolution of ammonia ceased (about 1.5 hr.). The reaction mixture solidified on cooling. Crystallization from acetone yielded two crops totalling 37.4 g. (63%) of glutarimide, m.p. 145–146° which was somewhat lower than 151–152° reported.[8,9]

N-Bromoglutarimide. The general method[10] involving bromination of the silver salt of the imide in trifluoroacetic acid was used. To a mixture of 32.0 g. (0.14 mole) of silver oxide in 200 ml. of trifluoroacetic acid was added 32.1 g. (0.28 mole) of glutarimide. After an hour of stirring 45.6 g. (0.29 mole) of bromine was added over a 3-hr. period. The silver bromide was removed by filtration, and the solution was concentrated at reduced pressure. Absolute ether (150 ml.) precipitated 45 g. (84%) of *N*-bromoglutarimide, m.p. 135–140°.

Reactions of N-bromo compounds with styrene. The reactions were carried out on each *N*-bromo compound with half the equivalent amount of styrene (stabilized with *p-tert*-butylcatechol) based on available bromine in the *N*-bromo compound. In each case the solvent was 50 ml. of alcohol-free chloroform. Each mixture was heated under reflux until a negative test with acidified potassium iodide solution was obtained or until at least 10 hr. had elapsed. At the end of the reaction time the solution was filtered hot to remove any insoluble products, then cooled in an ice-salt bath and filtered again if further precipitate was produced. After filtration the chloroform was removed under reduced pressure and the resulting residue recrystallized from 95% ethyl alcohol in order to obtain any styrene dibromide formed during the reaction. The results are summarized in Table I.

Reaction of N-bromoglutarimide with cyclohexene. A mixture of 9.7 g. (0.118 mole) of cyclohexene, 5.0 g. (0.026 mole) of *N*-bromoglutarimide, and 50 ml. of carbon tetrachloride was heated under reflux for 2.5 hr. under an ultraviolet lamp. The reaction mixture was cooled and filtered to give 2.72 g. (92%) of glutarimide. Distillation of the filtrate yielded 2.75 g. (66%) of 3-bromocyclohexene, b.p. 76–78° (3 mm.); d_4^{25} 1.365; n_D^{25} 1.5285.

Reaction of N,N-dibromobenzenesulfonamide with styrene. A mixture of 1.3 g. (0.0125 mole) of styrene and 4.0 g. (0.0127 mole) of *N,N*-dibromobenzenesulfonamide in 60 ml. of chloroform was boiled under reflux for 20 min. The solution was washed twice with 10% sodium hydroxide and was then dried over calcium sulfate. Evaporation of the chloroform yielded a residue which was crystallized from 95% ethyl alcohol to give 1.54 g. (48%) of *N*-benzenesulfonylstyreneimine, m.p. 75–76°.

Anal. Calcd. for $C_{14}H_{13}NO_2S$: C, 64.8; H, 5.05; N, 5.40. Found: C, 64.1; H, 4.96; N, 5.35.

In a similar experiment twice as much styrene was used; the reaction mixture was heated under reflux for 25 hr.; and no sodium hydroxide solution was used. The product was crystallized from alcohol to give 6.0 g. (90%) of *N*-(2-bromo-1-phenylethyl)-*N*-(1-bromo-2-phenylethyl)benzenesulfonamide, m.p. 136–137°.

Anal. Calcd. for $C_{22}H_{21}NO_2Br_2S$: C, 50.5; H, 4.05; N, 2.68. Found: C, 50.8; H, 4.12; N, 2.86.

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(8) S. S. G. Sircar, *J. Chem. Soc.*, 600 (1927).
(9) O. Bernheimer, *Gazz. chim. ital.*, 12, 281 (1882).
(10) A. L. Henne and W. F. Zimmer, *J. Am. Chem. Soc.*, **73**, 1103 (1951).

Regeneration of Alkaloids from Their Picrates with an Anion-Exchange Resin[1]

JAMES M. BOBBITT

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The characterization of organic nitrogen bases as salts of the polynitro phenols, picric acid (2,4,6-trinitrophenol) and styphnic acid (2,4,6-trinitroresorcinol) is almost a universal practice and has been the subject of much work.[2] These salts are easily prepared and are generally well defined, nonhygroscopic, crystalline compounds amenable to analysis. The picrates can often be purified by recrystallization and then decomposed with aqueous inorganic bases to yield the pure, free amines. The decomposition of picrates by aqueous base is complicated by the low solubility of sodium, potassium, and ammonium picrates in water.[3,4] This complication can be alleviated with lithium hydroxide[3] or ethanolamine[4,5] producing the more soluble lithium and ethanolamine picrates. Difficulty has also been encountered in the decomposition, by base, of the picrates of organic nitrogen compounds which are base-labile,[6] easily oxidized,[6] or contain phenol groups conferring solubility in aqueous base.[7] The use of lamb's wool[6] (giving good yields, 80–97%, of the base-hydrochlorides) or hot aqueous potassium chloride[7] (poor yields) has partially overcome these obstacles.

The decomposition of *inorganic* salts of alkaloids and similar compounds on anion-exchange resins and subsequent titration of alkaloid in the eluate has been developed as an analytical tool, and has been critically reviewed.[8] Tropone and 6-hydroxytropinone have been obtained from their picrates with the weakly basic resin Amberlite IR-45 and strongly basic Dowex 2, respectively.[9]

This paper suggests the use of the bicarbonate salt of the strongly basic resin, Amberlite IRA-400 [IRA-400(HCO_3)] for the decomposition of alkaloids by a "columnar" technique. This technique

(1) First conceived and tested in Professor Carl Djerassi's laboratory at Wayne State University.
(2) (a) L. Kofler and F. A. Müller, *Mikrochemie*, **22**, 43 (1937); (b) A. Oliverio and F. S. Trucco, *Atti accad. Gioenia sci. nat. Catania*, [6] **4**, (1939); *Chem. Abstr.*, **35**, 7115 (1941); (c) C. Massatsch, *Pharm. Ztg.*, **83**, 210, (1947).
(3) A. Burger, *J. Am. Chem. Soc.*, **67**, 1615 (1945).
(4) I. A. Kaye, I. C. Kogon, and W. Burlant, *J. Am. Chem. Soc.*, **72**, 5752 (1950).
(5) N. Weiner and I. A. Kaye, *J. Org. Chem.*, **14**, 868 (1949).
(6) H. Müller, *Hoppe-Seyler's Z. physiol. Chem.*, **209**, 207 (1932).
(7) D. Taber and A. I. Kosak, *J. Org. Chem.*, **21**, 257 (1956).
(8) L. Saunders, *J. Pharm. Pharmacol.*, **5**, 569 (1953).
(9) E. E. van Tamelen, Patricia Barth, and F. Lornitzo, *J. Am. Chem. Soc.*, **78**, 5442 (1956).

TABLE I[a]

RECOVERY OF ALKALOIDS FROM PICRATE SALTS WITH IRA-400(HCO_3)

Alkaloid	*p*Kb	Picrate m.p., °C.	Recovery, %	Recovered Base M.P., °C.[b]	Resin Needed, G./M. Eq. Base[c]
Cinchonidine[d]	5.80 10.03	207-209° (208-209°)	95.9[e]	205–206° (210°)	5.4
Cinchonine[d]	5.85 9.92	222–225° (212–215°)[2b,f]	96.9	261–262° (265°)	5.8
Codeine	6.05	196–197° (196–197°)[11]	100.0[g]	154–157° (154-156°)[11]	5.1
Morphine	6.13	164–167° (163–165°)[11]	86.4[h]	249–253° (254°)	7.2[h]
Reserpine	7.40[12]	180–183° (183-186°)[13]	98.8	256–258° (277°)[13]	5.9
Narcotine	7.80	174–176° (175°)	98.0	176–178° (176°)	4.6
Papaverine	8.07	186–189° (183°)	100.0[g]	148-150° (147°)	3.6

[a] Melting points were taken on a Kofler apparatus. Recorded melting points are given in parentheses. Unless noted, physical constants are taken from *The Merck Index*, 6th Ed., Merck & Co. Inc., Rahway, 1952. [b] Melting points of recovered alkaloids were identical with those of starting material. Mixture melting points were undepressed. [c] Estimated from amount of red "spent" resin formed. Density of wet resin was 0.52. [d] Form di-picrates. [e] Salted out with aqueous sodium chloride. [f] Also rec. 194° and 198–210°.[2a] [g] Isolated by "freeze-drying." [h] Flow rate, 100 ml. in 20 min. Only 75% recovery at rate of 100 ml. in 60 min.

has been briefly described[10] and used for the decomposition of the picrates of 6-methoxy-, 6,7-dimethoxy-, 6-methoxy-7-ethoxy-, 6,7-dimethoxy-8-hydroxy-, and 6,7,8-trimethoxy-1-isobutyl-2-methyl-1,2,3,4-tetrahydroisoquinolines in reference to the structure proof of the cactus alkaloid, pilocereine. This method has now been applied to the picrates of seven alkaloids of varying structures and base strengths (*p*Kb, 5.8–10.03). Results are given in Table I. A study of flow rate over the resin, solvent ratios, and the amount of resin used yielded the data in Table II.

TABLE II

EFFECT OF FLOW RATE AND SOLVENT VARIATION ON AMOUNT OF RESIN USED[a]

Flow Rate Ml./Hr.	Solvent,[b] % Water in Acetone	Resin Needed, G./M. Eq. Base
160	10	16.0
75	10	7.4
15	10	5.8
9	10	2.9
40	0[c]	No picrate decomposition
40	1	28.9
40	5	7.4
40	10	6.6

[a] Decomposition of 0.2 g. of codeine picrate in 40 ml. of solvent. [b] Resin was pre-washed with the solvent used. Resin was washed with acetone and air-dried before use.

Satisfactory results were obtained with all of the alkaloids except morphine and no decomposition was noted in any case. The relatively low recovery (86%) of morphine is presumably due to partial retention on the resin through its phenolic group. Lower yields of morphine were obtained at slower flow rates, however, in other cases the flow rate over the resin was not crucial. At least 2–7% of water in the solvent was mandatory. The nearly neutral character of Amberlite IRA-400(HCO_3) allowed the use of acetone, an excellent solvent for picrates. On strongly basic resins, acetone condenses with itself.[14] A "batch" technique was not successful because of the hydrolysis of Amberlite IRA-400 (picrate). The resin could be effectively regenerated after use.

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Alkaloids. Except for reserpine which was donated by the Upjohn Co. of Kalamazoo, Mich., the alkaloids used were commercial samples obtained through the School of Pharmacy of The University of Connecticut.

Preparation of picrates. One g. of alkaloid in 50 ml. of hot 95% ethanol was combined with a slight excess of picric acid in 50 ml. of hot 95% ethanol. The solution was allowed to cool and the precipitate was filtered and dried.

Preparation of resin.[15] Two hundred g. of Amberlite IRA-400(Cl)[16] in an appropriate column were washed with 3–4 l. of 10% sodium bicarbonate solution until the eluate gave no chloride test (silver nitrate). It was then washed with 4–5 l. of distilled water and stored under distilled water.

Decomposition of picrates. (Table I) A column of resin (28 × 1.2 cm.) was washed with 100 ml. of 10% aqueous acetone

(10) C. Djerassi, S. K. Figdor, J. M. Bobbitt, and F. X. Markley, *J. Am. Chem. Soc.*, 78, 3861 (1956); 79, 2203 (1957).

(11) K. W. Bentley, *The Chemistry of the Morphine Alkaloids*, Oxford University Press, London, 1954, pp. 81, 30.

(12) N. Neuss, H. E. Boaz, and J. W. Forbes, *J. Am. Chem. Soc.*, 75, 4870 (1953).

(13) L. Dorfman, A. Furlenmeier, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. M. Mueller, E. Schlittler, R. Schwyzer, and A. F. St. André, *Helv. Chim. Acta*, 37, 59 (1954).

(14) R. Pallaud and G. V. Austerweil, *Compt. rend.*, 240, 1218 (1955); C. J. Schmidle and R. C. Mansfield, *Ind. Eng. Chem.*, 44, 1388 (1952).

(15) Different from and much superior to the method previously presented.[10]

(16) Provided by the Rohm & Hass Co., Philadelphia, Pa.

and agitated by inversion to remove gas bubbles (10% resin shrinkage occurred). One half g. of picrate in 100 ml. of 10% aqueous acetone was allowed to flow over the resin at a rate of 30–60 ml./hr. The column was washed with 100 ml. of solvent, the washings and eluate were combined, and the acetone was removed under vacuum. The resulting aqueous phase was filtered, salted out (sodium chloride) and filtered, or "freeze-dried" to obtain pure crystalline alkaloid.

Regeneration of resin. The bright red "spent" resin was transformed *immediately after use* back into Amberlite IRA-400(Cl) by washing with a solution of 50 ml. of concentrated hydrochloric acid in 200 ml. of acetone until no more yellow color was eluted.

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1-Hydroxy-2,4-Di-*t*-butylphenazine

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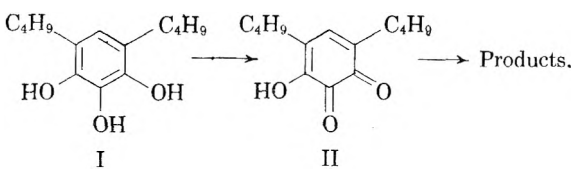
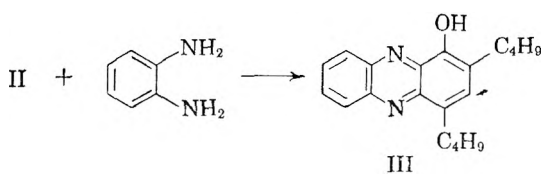
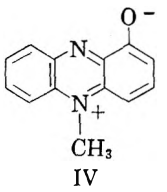
It has been proposed[2] that the oxidation of 4,6-di-*t*-butylpyrogallol in alkaline solution proceeds *via* a highly colored intermediate hydroxy-*o*-quinone:



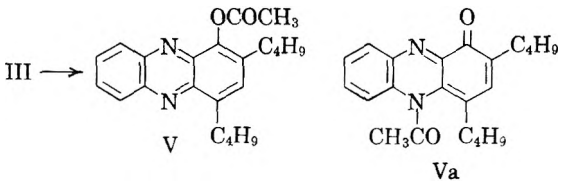
Evidence for such an intermediate *o*-quinone has been obtained by oxidation of di-*t*-butylpyrogallol to an intermediate purple compound, either by air oxidation in alkali or by bromine oxidation in buffered acetic acid solution. The intermediate purple compound coupled with *o*-phenylenediamine to give 1-hydroxy-2,4-di-*t*-butylphenazine (III).



This phenazine could not be methylated with dimethylsulfate to a pyocyanine-type (IV) derivative.[3,4] It was recovered unchanged from ethereal



diazomethane. Acetic anhydride gave an acetyl derivative, V, which from the infrared spectrum had the indicated structure rather than the alternate (Va).



EXPERIMENTAL

2,4-Di-t-butyl-1-hydroxyphenazine. Ten grams of dibutylpyrogallol[2] was dissolved in 150 ml. of acetic acid containing 15 g. of sodium acetate. To this solution was added 6.5 g. of bromine in 50 ml. of acetic acid. The solution at once developed a brilliant purple color. The mixture was allowed to stand for 15 min. after which 5 g. (10% excess) of *o*-phenylenediamine dissolved in 50 ml. of acetic acid was added. The purple color changed instantly to a brown-orange color. This mixture was allowed to stand for 48 hr. and the acetic acid was evaporated under nitrogen on a steam bath. The solid residue was extracted with 50 ml. of methyl alcohol containing a little concentrated hydrochloric acid. This dissolved most of the brownish orange solid. The product which remained undissolved was then treated with water to remove potassium bromide and the bright orange crystalline residue was dried. This crystalline residue was dissolved in chloroform and the chloroform solution was washed repeatedly with water. The bright orange chloroform layer was retained and the aqueous washings were discarded. Evaporation of the dried chloroform solution gave an orange crystalline solid which was recrystallized from chloroform-methanol mixture. The product was obtained in a yield of 3.2 g. (21%) with a melting point of 170.5°. A deep blue solution resulted when the product was dissolved in alcoholic alkali.

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.9; H, 7.9; N, 9.1. Found: C, 77.4, 77.5; H, 7.76, 7.8; N, 9.1, 9.4.

The same product was obtained by the air oxidation of a mixture of di-*t*-butylpyrogallol and *o*-phenylenediamine. However, the yield was lower and the product difficult to isolate.

2,4-Di-t-butyl-1-hydroxyphenazine acetate. Two hundred milligrams of 2,4-di-*t*-butyl-1-hydroxyphenazine was mixed with 3 cc. of acetic anhydride plus 5 cc. of pyridine. The mixture was boiled 0.5 hr., then cooled and allowed to stand for 48 hr. No crystallization had occurred so the mixture was diluted with water. The gummy material which precipitated was rubbed with a stirring rod to induce crystallization. The solid so obtained was filtered and recrystallized from aqueous methanol. The pale yellow crystalline powder had a melting point of 160.5–162°.

Anal. Calcd. for $C_{22}H_{26}O_2N_2$: N, 8.0. Found: N, 8.3, 8.2.

In alkaline methanol, a blue color developed slowly, indicating slow hydrolysis to the parent compound.

Infrared spectra of the phenazine and its acetate. The spectrum of the parent phenazine showed a relatively sharp —OH band, shifted to 2.95 μ. This indicates internal H-bonding to the adjacent nitrogen. The acetyl derivative showed an ester band at 5.65 μ, and no indication of amide groups. No —OH band was present.

(1) Present address: E. I. du Pont de Nemours & Company, Wilmington, Del.

(2) T. W. Campbell, *J. Am. Chem. Soc.*, **73**, 4190 (1951).

(3) A. R. Surrey, *Org. Syntheses*, **26**, 86 (1946).

(4) Wrede and Strack, *Ber.*, **62**, 2053 (1929); *Z. physiol. Chem.*, **74**, 181, 184, 185 (1929).

Attempted methylation with diazomethane. Diazomethane was made by adding 2.0 g. of *N*-nitro-*N*-methyl-*N'*-nitroguanidine in portions to 20 g. of 50% potassium hydroxide solution covered by 50 ml. of ether at 0°. The ether layer was removed, washed with water, and placed in a 200-ml. Erlenmeyer flask. Two hundred and fifty mg. of 1-hydroxy-2,4-di-*t*-butylphenazine was added and the solution was allowed to stand overnight. The ether was evaporated and the orange crystalline residue melted without further purification at 169.5 to 170.5°. This material was recrystallized from a chloroform-methanol mixture. It melted sharply at 170.5°. A mixture melting point with 1-hydroxy-2,4-di-*t*-butylphenazine showed no depression.

Methylation with methyl sulfate. Using the method described in *Organic Syntheses*[3] for the preparation of pyocyanine, 200 mg. of the phenazine was warmed at about 110° with 2.0 g. of methyl sulfate for 1 hr. The reaction mixture was poured into a mixture of 10 cc. H_2O, 10 cc. methanol, and 1.5 ml. of 6*N* potassium hydroxide. The resulting dark solid was removed, and dissolved in alkaline methanol to a blue solution, as contrasted to the purple of the starting phenazine. The blue solution was extracted with ether; the color transferred to the ether phase. Gradually the color changed, through green to yellow. The yellow solution gave a faint olive green solution in alkali, and a more intense red in acid. Evaporation of the yellow ethereal solution gave a gum which solidified on standing. This was taken up in boiling methanol, filtered through charcoal, and allowed to crystallize at −10°. An orange, crystalline product was obtained, m.p. 168–169°, which was starting material (20 mg.). The bulk of the product, obtained on dilution with water, was a yellow gum which could not be crystallized.

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An Observation on Chlorination of Normal Hexane with Iodine Monochloride[1]

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Normal hexane is usually considered to be a rather stable solvent, not easily susceptible to halogenations. According to the literature,[2] it acts as a typical "purple" solvent for halogen solutions and the solutions of iodine monochloride in this solvent should have a red-brown color with an absorption maximum in the vicinity of 460 mμ.

In the course of study of iodine monochloride complexes with various Lewis bases, it was decided to use normal hexane as the reaction medium. It was immediately discovered that contrary to the expectations, dilute solutions of iodine monochloride in this solvent had a distinct purple color. Absorption spectra of these solutions were obtained and the resulting absorption curves showed a maximum of 520 mμ which is characteristic of iodine solutions in nonpolar solvents. Although it has become evident that *n*-hexane was not a suitable solvent for the study of iodine monochloride complexes, it was of interest to the authors to establish if the reaction actually occurred between iodine monochloride and *n*-hexane rather than with a reactive impurity in the solvent.

When iodine monochloride is added to the purified *n*-hexane, it dissolved rapidly in the solvent, but the process of dissolution is accompanied by the evolution of a small quantity of a gaseous product, presumably, hydrogen chloride. Although in some instances, the resulting solutions did have, originally, a reddish-brown color, the latter very rapidly turned to purple and showed the characteristic iodine absorption band.

In order to see if we have a photochemical halogenation reaction, iodine monochloride solutions were prepared in a photographic dark room and the absorption spectra were obtained without any previous exposure of the solutions to illumination. In all cases the absorption maxima were shifted toward the iodine peak.

The disappearance of halogen in the *n*-hexane solutions was followed by preparing standard solutions of iodine monochloride in this solvent and titrating the total halogen iodometrically in aliquots of the solutions withdrawn after definite intervals of time. The results of this study are shown in Table I. Since it has been shown that the reaction between iodine monochloride and *n*-hexane can occur in the dark, this series of experiments was done under ordinary illumination.

TABLE I
TITRATION OF IODINE MONOCHLORIDE IN NORMAL HEXANE

Experiment 1		Experiment 2		Experiment 3	
Time, hr.	Normality × 10^3	Time, hr.	Normality × 10^3	Time, hr.	Normality × 10^3
0	3.26	0	5.20	0.3	5.57
1	2.64	1	4.66	1.2	3.68
3	2.12	2	4.09	19.2	2.81
5.5	1.75	18	2.68	44.7	2.75
23.5	1.66	45	2.45	98.5	2.60
100	1.66	69	2.37	260.	2.56
	1.65[a]	90	2.35		2.44[a]
			2.30[a]		

[a] Normality as calculated from absorbance data assuming only I_2 remaining.

It is interesting to note that the limiting concentration of the titratable halogen is either equal to half, or less than half of the original halogen present. After the solutions reached an apparent equilibrium, their adsorption spectra were obtained. In all cases the remaining halogen was the iodine and the calculation of the final concentration from the absorption data agrees well with the titration value.

Since there still remained a possibility that notwithstanding an apparently careful purification of

(1) Paper XII in the series "Studies on the Chemistry of Halogens and of Polyhalides." Previous paper, *J. Am. Chem. Soc.*, **77**, 4622 (1957).

(2) N. N. Greenwood, *Rev. Pure and Appl. Chem.*, **1**, 89 (1951).

the solvent, some trace impurities may have remained and were responsible for the halogenation reaction, a large quantity (approx. 50 g./liter) of iodine monochloride was added to previously purified *n*-hexane. The mixture was allowed to stand for several days, the remaining iodine monochloride was destroyed with stannous chloride, and the solvent was dried and fractionated. This solvent was used to prepare new solutions of iodine monochloride; however, no change in the behavior of the system was observed. These results indicate that the presence of an impurity is not responsible for the halogenation reaction.

Another portion of purified *n*-hexane was treated with a large amount of iodine monochloride for several days after which excess halogen was destroyed as described above. The resulting solution was concentrated by fractional distillation and an infrared spectrum was obtained of the residue. There was a weak but a definite indication of the carbon-chlorine stretching vibration at 700 cm.$^{-1}$ Unfortunately, this band was largely masked by the carbon-hydrogen rocking vibration at 720 cm.$^{-1}$

A solution of chlorine was prepared in *n*-hexane and the change in the halogen content was followed iodometrically. Although a loss of chlorine was observed, the rate of this loss was much slower than for iodine monochloride. About 50% of chlorine still remained in solution after a 12-hr. period. On the other hand, iodine solutions in this solvent appear to be perfectly stable.

Solutions of iodine monochloride were likewise prepared in purified *n*-pentane, *n*-heptane, isooctane, and cyclohexane. While the first three solvents behaved similarly to the *n*-hexane, it was found that iodine monochloride solutions in cyclohexane appeared to be considerably more stable, although in general one would expect a cyclic hydrocarbon to be more reactive than an aliphatic one.

These results agree with the observations of Buckles and Mills[3] who found it possible to obtain the absorption curve of iodine monochloride in cyclohexane, provided that fresh solutions are used. These authors report an absorption maximum of 466 mμ with a molar absorbancy index of 165.

The experimental evidence obtained in this investigation indicates that iodine monochloride is a very active chlorinating agent for saturated aliphatic hydrocarbons. It seems to react much faster than elemental chlorine and it would consequently seem rather unlikely that the chlorination is preceded by the dissociation of iodine monochloride into molecular iodine and chlorine. It is also interesting to note that iodine is often used as a catalyst in the chlorinations of saturated hydrocarbons. It appears to be quite likely that this catalytic action is due to the intermediate formation of iodine monochloride.

A more detailed investigation of the iodine monochloride reactions with saturated aliphatic hydrocarbons would be of interest. However, such an investigation is not contemplated by the present authors as it is beyond their immediate interests.

(3) R. E. Buckles and J. F. Mills, *J. Am. Chem. Soc.*, **76**, 4845 (1954).

EXPERIMENTAL

Iodine monochloride. Iodine monochloride was prepared by the method of Cornog and Karges.[4] It was first purified by sublimation in a desiccator over phosphorus pentoxide and the obtained product was transferred, in a dry box, to a glass apparatus consisting of a series of bulbs attached to a manifold. The apparatus was evacuated and sealed and the iodine monochloride was fractionally crystallized at least five times. The purified product was transferred to a series of glass bulbs which were sealed until use. The m.p. was 27.2° (lit.[4] 27.2°).

n-Hexane. *n*-Hexane was a Mateson, Coleman, and Bell product and was originally purified by vigorously shaking it with 10% by volume portions of fuming sulfuric acid until the acid layer remained colorless. The solvent was then repeatedly washed with dilute sulfuric acid and with water. This treatment was followed by repeated washing with alkaline permanganate, with water, and drying with barium oxide. The solvent was finally refluxed over phosphorus pentoxide and fractionally distilled through a 1-meter helices-packed column. The purified product had an absorbance of less than 0.01 units, when measured in 5.00-cm. silica cells at 220 mμ, which was superior to the best commercial grade of "research" grade *n*-hexane. The absorption measurements were done on a Cary recording spectrophotometer, Model 11 in the ultraviolet and visible regions of the spectra, and on a Perkin-Elmer infrared spectrometer, Model 13.

Acknowledgment. The authors are indebted to the Research Corp. for the support of this work and to Drs. R. E. Buckles and W. B. Person of this laboratory for many helpful discussions.

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(4) J. Cornog and R. A. Karges, *Inorganic Syntheses*, vol. I, McGraw Hill, New York, N. Y., 1939, p. 165.

Detection of Flavanones by Reduction with Sodium Borohydride[1]

ROBERT M. HOROWITZ

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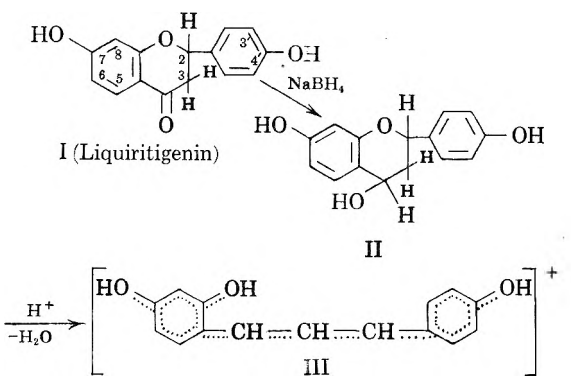
Flavanones may be conveniently reduced under mild conditions by sodium borohydride in aqueous or alcoholic solution. Thus, Pew[2] has reported the

(1) (a) Presented in part before the 131st Meeting of the American Chemical Society, Miami, Fla., April 1957; abstracts p. 58 L. (b) A method which is closely similar has since been reported by E. Eigen, M. Blitz, and E. Gunsberg. *Arch. Biochem. and Biophysics*, 68, 501 (1957).

(2) J. C. Pew, *J. Am. Chem. Soc.*, **77**, 2831 (1955).

reduction of 6-allyl-8-methoxyflavanone and 6-allyl-3′,4′,8-trimethoxyflavanone to their corresponding 4-hydroxyflavanes by sodium borohydride in alcohol. This reaction may be applied, either in solutions or on paper chromatograms, to the detection of most of the naturally occurring flavanones, since the 4-hydroxyflavanes formed in the reduction give a brilliant purple or blue-red color upon treatment with strong acids. The particular shade of color depends upon the type of hydroxylic substitution, and it is often sufficiently characteristic to be of some use in identification. The following flavanones, most of which are naturally occurring, gave a purple or blue-red color when examined by this method: hesperidin, hesperetin, neohesperidin, naringin, naringenin, isosakuranetin, eriodictyol, homoeriodictyol, butin, liquiritigenin, and liquiritigenin 4′-methyl ether. All of the foregoing compounds have hydroxyl or methoxyl substituents in both the A and B rings. Pinocembrin (5,7-dihydroxyflavanone) and 7-hydroxyflavanone gave a red-orange rather than a purple or blue-red color. 3′,4′-Dihydroxyflavanone and 3′-methoxy-4′-hydroxyflavanone yielded blue colors which were not intense enough to be easily visible on paper chromatograms. It is apparent from this series that the flavanone must have at least one hydroxyl or methoxyl substituent in both the A and B rings in order to yield the maximum development of color.

The probable course of the reaction may be represented as follows:[3]



Because of the close relationship it bears to a flavylium salt, it is certain that an ion of the type III would be deeply colored.

The chalcones, flavones, flavonols, isoflavones, and aurones which were examined were not reduced by the sodium borohydride and failed without exception to give the colors characteristic of the flavanones.[4] Many of them did, however, form bright yellow complexes with the sodium borohydride or its decomposition products and these could be readily observed in ultraviolet light or occasionally in daylight. It is thus possible, by applying this procedure alone, to estimate the number of flavonoids on a chromatogram and to differentiate the flavanones from other types.

Dihydroquercetin (3,3′,4′,5,7-pentahydroxyflavanone), the only 3-hydroxyflavanone which was tested, failed to give a pronounced color either on chromatograms or in solution under the usual conditions for the reaction. When a solution of the substance was boiled with the reducing agent for at least ten minutes before acidifying, a red-orange color was obtained. It has been reported that sodium borohydride reduces dihydroquercetin to a leucoanthocyanidin (conditions not specified) which is converted to cyanidin by air and hydrochloric acid.[5]

As an illustration of the use of this method in the study of plant extracts, a chromatographic examination was made of the products obtained from Douglas fir bark. Dihydroquercetin has been previously reported as the principal flavonoid of this species.[6] Paper chromatograms of an extract of Douglas fir bark, when treated with sodium borohydride and hydrogen chloride, exhibited a small purple spot which had the same R_f value as eriodictyol (3′,4′,5,7-tetrahydroxyflavanone) in 10% acetic acid. In addition, both the substance from Douglas fir bark and eriodictyol reduced ammoniacal silver nitrate, a reaction given by compounds containing an *ortho* dihydroxy group. From this evidence it may be concluded that Douglas fir bark contains as a minor component a flavanone which has been provisionally identified as eriodictyol.[7]

The procedure described here should be of value in detecting the presence of flavanones in plant extracts and should aid in the identification of these compounds from abundant sources such as citrus. It is clear that the method could be adapted to quantitative estimations.

EXPERIMENTAL

A freshly prepared 2% solution of sodium borohydride in methanol was used, although wide variations of concentration are permissible.

Paper chromatograms. The dried chromatogram, hung in a fume hood, is sprayed lightly with the borohydride reagent. After about 1 min. it is placed in a closed container (such as a desiccator) and is fumed with hydrogen chloride gas. (Spraying with aqueous hydrochloric acid is not satisfactory.) A bright, easily visible color develops within a few seconds if the concentration of hydrogen chloride is high and it is usually completely developed in 5–10 minutes. There is a perceptible fading of the color within a few hours.

Solutions. An alcoholic solution (0.1 ml.) of the flavanone or crude extract is treated with an equal volume of the boro-

(3) This scheme is essentially that of T. A. Geissman and R. O. Clinton, *J. Am. Chem. Soc.*, **68**, 700 (1946), for the catalytic reduction of flavanones.

(4) Flavonols and, undoubtedly, other flavonoids can be reduced by lithium aluminum hydride; R. Mirza and R. Robinson, *Nature*, **166**, 997 (1950).

(5) T. Swain, *Chemistry and Industry*, 1144 (1954).

(6) J. C. Pew, *J. Am. Chem. Soc.*, **70**, 3031 (1948).

(7) Pew, (ref. 6) mentions that some samples of Douglas fir wood appear to contain a small amount of naringenin. This would not reduce ammoniacal silver nitrate, however.

hydride reagent. After about 1 min. at room temperature several drops of concentrated hydrochloric or sulfuric acid are added. The color develops at once or after very brief warming. Plant extracts containing leucoanthocyanins give similar colors on addition of hydrochloric acid without the use of sodium borohydride.

Extraction of Douglas fir bark. The powdered bark (50 g.) was extracted in a Soxhlet apparatus first with ether and then with methanol. The methanolic extract was treated with lead acetate; the precipitated lead salts were washed with methanol and decomposed with hydrogen sulfide in methanol. Filtration followed by evaporation of the filtrate yielded a crude crystalline material which was used for paper chromatography.

Chromatography of Douglas fir bark flavonoids. Ascending chromatograms were prepared using 10% acetic acid on Whatman No. 1 paper. After treatment with sodium borohydride and hydrogen chloride three spots were observed: a small purple spot (R_f = 0.29), a large tan spot (R_f = 0.48) (dihydroquercetin) and a bright yellow spot near the origin (R_f = 0.04) (probably quercetin and other flavones). All the spots gave intense reduction of ammoniacal silver nitrate. Eriodictyol had R_f = 0.29 when run simultaneously.

Acknowledgment. I should like to thank Prof. H. Erdtman for a gift of pinocembrin and Mr. Bruno Gentili for the preparation of several of the compounds.

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Solvation of Stilbene and Azobenzene Metal Adducts

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The addition of alkali metals to unsaturated compounds is facilitated by inclusion of ether in which the adducts are soluble. Little is known about the chemical effects of these ethers. In one instance stable etherates are reported[1] and in another instance an optically active ether has conferred activity to the product from an adduct.[2] Now we have studied the etherates of stilbene and azobenzene metal adducts, which remain after evaporation of dioxahexane solutions.

The sparingly-soluble azobenzene dilithium adduct in 2,5-dioxahexane has been shown to undergo a variety of alkylation reactions.[3] We have confirmed the behavior by preparation from 1-chlorobutane of *N,N'*-di-*n*-butylhydrazobenzene. In order to ascertain the role of the dioxahexane in these metal-adducts systems we have heated the azobenzene-dilithium suspension both at 50° (30 mm.) and also at 100° (5 mm.). In either instance the dry residue has the same yellow color it displays in the suspension. When a weighed amount of this dry diadduct is hydrolyzed by water and then is analyzed for lithium content, the calculated formula weight indicates that 2 molecules of dioxahexane are coordinated with 1 molecule of azobenzene dilithium. Indeed, we have isolated 95% of the 2,5-dioxahexane expected if each lithium atom were coordinated with both oxygens of such a diether. Of interest is the further observation that the azobenzene disodium adduct also is coordinated with 2 molecules of dioxahexane.

If the rate of alkylation of the dimetal adducts is dependent on coordination interchange between the ether and the alkylating agent, then the more reactive stilbene-disodium ought to be less firmly solvated than its azobenzene analogue. But experiment shows that vacuum-evaporation of the stilbene-disodium system at 25° leaves a red residue in which 2 molecules of dioxahexane are included. However, the similarity with the azobenzene disodium adduct no longer prevails when the stilbene-disodium adduct is heated under vacuum at 50° or 100°. Then the ratio is found by titration for alkali to correspond with 2 molecules of adduct per one molecule of dioxahexane.

This evidence that solvation is less firm to the carbon-sodium linkage than it is to the nitrogen-sodium linkage is exemplified further by the observation that the stilbene-disodium containing only one ether-oxygen per two atoms of metal is more active than disodium adduct in which one atom of metal is coordinated with two ether-oxygen atoms. Thus it reacts more rapidly with alkylation agents.

It is of further interest to discover whether the diastereomeric ratio of dialkylation products from stilbene-disodium adducts is altered by the extent of solvation. An alkylation agent must be chosen for which the reaction rate is sufficiently slow that interphase reactivity is minimized in the heterogeneous systems comprising the several solvated species. We have chosen diethyl sulfate which is known to react slowly with the solution of stilbene-disodium adduct in dioxahexane to give 13% of *meso* and 26% of *dd,ll*-3,4-diphenylhexane besides regenerated stilbene.[2]

By contrast the *meso* diastereomer predominates in reactions of the red residues with diethyl sulfate. However, the extent of solvation seems to make little difference in the diastereomeric ratio, although the *meso* to *dd,ll* ratio is slightly higher (35% vs. 14%) from the solvate comprising 1 diadduct per 2 dioxahexane than the ratio (39% vs. 19%) from the 2 diadduct: 1 dioxahexane solvate. While this difference may not be highly significant, it may be

(1) B. M. Mikhailov and N. G. Chernova, *Doklady Akad. Nauk S.S.S.R.*, 74, 939 (1950), *Chem. Abstr.*, 45, 4698 (1951).
(2) A. G. Brook, H. L. Cohen, and G. F Wright, *J. Org. Chem.*, 18, 447 (1953).
(3) J. W. B. Reesor and G. F Wright, *J. Org. Chem.*, 22, 385 (1957).

noted that it corresponds with a greater regeneration of stilbene (41% *vs.* 33%) from the solvate yielding the lesser amount of *dd,ll* diastereomer. The correspondence indicates a steric effect, especially since the over-all yields of diastereomeric products are higher than was observed in the homogeneous alkylation.[2] Steric effects dependent on solvation have been suspected previously.[3]

It seemed to be of interest to examine the extent of solvation in the so-called stilbene-monosodium adduct,[4] but this examination proved to be impossible by the techniques which we employed. When a dioxahexane solution containing one molecule of stilbene per atom of sodium is evaporated at 25° its greenish brown color is displaced by a red color as the solution becomes more concentrated, until finally a red residue comprising equal amounts of diadduct and stilbene remains. When the residue is vacuum-evaporated at 100° and then is extracted with hexane to remove the stilbene the diadduct containing one half molecule of dioxahexane remains. Alkylation of the residue gives the same ratio (*ca.* 2.1) of diastereomeric 3,4-diphenylhexanes which were obtained from the authentic diadduct, which was prepared at 100°.

EXPERIMENTAL[5]

Azobenzene-dilithium adduct: 2,5-dioxahexane, 1:2. The solid-liquid 2-phase system from 1.82 g. (0.01 mole) of azobenzene and lithium in 40 ml. of dioxahexane after 72 hours of agitation was drained from the Schlenk tube to remove excess metal and then was evaporated for 4 hr. under nitrogen at 50° and 30 mm. Some of the yellow powder (0.3521 g.) was hydrolyzed with water. The organic portion was destroyed by boiling with nitric and sulfuric acid. The evaporated residue was ignited as lithium sulfate to redness and then weighed in absence of water: 0.1041 g., corresponding to a formula weight of 372 for the yellow powder.

A repetition in which the dioxahexane was removed at 100° under 1–5 mm. and the hydrolyzed residue was titrated with standard acid showed a formula weight of 376, identical with that calculated as 1 adduct plus 2 dioxahexane.

Another sample of yellow powder (0.01 mole) obtained after 100° at 30 mm. for four hours was hydrolyzed with 0.5 ml of water. The hydrolyzate was evaporated under 30 mm. at 50°–60° through a Drierite tower and then a trap chilled to −80°, the system finally having been flushed with nitrogen. In the trap was found 1.709 g. of dioxahexane, N_D^{20} 1.3799, b.p. 84° or 95% of that required for the 1:2 ratio specified above. The amount of dioxahexane obtained from the equivalent amount of red azobenzene-disodium adduct heated at 50° (30 mm.) was identical.

Finally a sample of the yellow powder which had been heated for 4 hr. at 100° (1 mm.) was treated with pure methyl sulfate in the manner described previously. A 75% yield of *N,N'*-dimethylhydrazobenzene, m.p. 33–34°, was obtained as well as a 20% yield of hydrazobenzene. Both products were characterized by mixture melting points.

N,N'-dibutylhydrazobenzene. A red solution prepared during 16 hr. from 1.82 g. (0.01 mole) of azobenzene, and a 5 mm.[3] piece of sodium in 40 ml. of dioxahexane was chilled to 0° and stored while 2.02 g. (0.022 mole) of 1-chlorobutane in 5 ml. of dioxahexane was added during 5 min. Then the green solution was warmed to 25° during 30 min., and was stirred while bleaching to orange, and finally a very light red color, occurred. The dioxahexane was vacuum-evaporated and the residue was dissolved in water and diethyl ether. The water-washed non-aqueous layer was evaporated and the residue was dissolved in 3 ml. of hexane. Chromatography by hexane elution through a 10 cm. × 1 cm. column of silicic acid (Mallinckrodt as received) yielded first the dibutylhydrazobenzene (m.p. 54–55°, 1.38 g.) in 40% yield. Two crystallizations from 4 ml. of absolute ethanol raised the m.p. to 57.2–57.7°.

Anal. Calcd. for $C_{20}H_{28}N_2$: C, 81.0; H, 9.53; N, 9.45. Found: C, 81.2; H, 9.90; N, 9.44.

Stilbene-disodium adduct: 2,5-dioxahexane, 1:2. A diadduct solution prepared from 0.9 g. (0.005 mole) of stilbene and an excess of sodium in 40 ml. of dioxahexane contained in a modified Schenk tube[4] was dropped during 3 hr. into a tared flask containing glass helices, which was maintained at 25° with a water bath and was continuously evacuated under 1 mm. This flask had been filled originally with nitrogen, and back-diffusion of air into it was prevented by introduction of a small amount of nitrogen into the exhaustion system.

After 0.71 g. of red residue had been collected in this manner it was treated with 50 ml of water-saturated diethyl ether. The water extract of the hydrolyzate was titrated with standard acid, showing that 75.2 mg. of sodium was present. The formula weight of 432 thus determined is 6% greater than that (406) of 1 stilbene-disodium adduct plus 2 moles of 2,5-dioxahexane.

Stilbene-disodium adduct: 2,5-dioxahexane, 2:1. (*a*) *From the diadduct.* A red residue prepared as described above was subsequently heated under vacuum at 100° for 40 min. Subsequent hydrolysis and titration showed that the formula weight of the residue was 285 or 5% greater than that (271) of 2 moles of stilbene-disodium adduct plus 1 mole of 2,5-dioxahexane.

(*b*) *From the monoadduct.* A brownish-green solution of stilbene-monosodium adduct prepared from 1.804 g. of stilbene and 0.23 g. of sodium in 40 ml. of dioxahexane was vacuum-evaporated at 100° as was described above. The light red residue was shaken with glass rods and commercial hexane (distilled into the system from sodium ketyl) until all of the solid was detached from the walls. The light red solution was decanted off. This extraction was repeated twice. The combined decantates (75 ml.) were washed with water. This aqueous extract contained 2.7% of the sodium originally introduced into the system. The non-aqueous layer upon evaporation yielded 0.895 g. (49.5%) of the stilbene originally introduced. This evidence that the diadduct was regenerated upon vacuum evaporation was confirmed by the red solution found in dioxahexane from an aliquot of the hexane-insoluble residue. By contrast a portion of the residue before hexane extraction redissolved in dioxahexane to give a greenish-brown solution.

The formula weight of the hexane-extracted red residue was not determined. Isolation of dioxahexane after the red residue was bleached by carbon dioxide indicated a diadduct to dioxahexane ratio of 1:1 but this value must be questioned either because of the intractable behavior of the evaporating system or else because the metallic carboxylate may have retained dioxahexane of solvation.

3,4-Diphenylhexanes. Each of the diadducts from stilbene described above, in 0.005 mole quantity, was treated with an excess (5 ml.) of pure diethyl sulfate. After 4 hr. of agitation the disappearance of red color showed that reaction was complete. The system was extracted with commercial hexane and water containing 1 g. of sodium iodide for at least 3 min., in order to decompose excess ethyl sulfate. The hexane layer was evaporated to a small volume and then was chromatographed on a 30 cm. × 1 cm. column containing 150–170 mesh alumina (the narrow screen cut minimizes "coning")

(4) J. W. B. Reesor, J. G. Smith, and G. F Wright, *J. Org. Chem.*, 19, 940 (1954).

(5) Melting points have been corrected against reliable standards.

activated at 200° for one day. Elution with hexane yielded successively the *meso* diastereomer and then the *dd, ll*, isomer. Finally the column was eluted with methanol to remove stilbene. The yields for diadduct-dioxahexane, 1:2 were 0.33 g. (35%) *meso*, 0.13 g. (14%) *dd, ll*, characterized by the absorption peak at 280 mμ and 0.39 g. (41%) of stilbene characterized by mixture melting point. The yields from diadduct–dioxahexane 2:1 were 0.37 g. (39%) *meso*, 0.18 g. (19%) *dd, ll*, and 0.31 g. (33%) of stilbene. The *meso*-3,4-diphenylhexane was characterized by mixture melting point.[4]

A comparable experiment with diethyl sulfate and the red residue from the monoadduct after hexane extraction to remove stilbene yielded *meso* and *dd, ll*-3,4-diphenylhexane in a ratio of 2.1:1.

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2-Pyrones. XXVIII. 4,7,7-Trimethyl-7,8-dihydro-(2*H*,5*H*)-pyrano-[4,3-b]-pyran-2,5-dione

RICHARD H. WILEY, J. G. ESTERLE, K. F. HUSSUNG, C. L. DE SILVA, AND S. C. SLAYMAKER

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On numerous occasions over the past several years we have observed the formation of a solid by-product during the preparation of β-methylglutaconic anhydride. This solid, m.p. 154–155°, is best prepared by distillation of β-methylglutaconic acid at atmospheric pressure—a process that sometimes gives the anhydride and sometimes gives the by-product. Its empirical composition, $C_{11}H_{12}O_4$, and molecular weight of 204 correspond to the combination of two molecules of β-methylglutaconic acid with the loss of one molecule of carbon dioxide. At various times we have considered several different structural possibilities for this material based on various types of condensations of two molecules of the anhydride. Of these only that of 4,7,7-trimethyl-7,8-dihydro-(2*H*,5*H*)-pyrano[4,3-b]pyran-2,5-dione[1] (I) is in accord with all of the physical and chemical data now available to characterize this product. We now have confirmatory evidence for this structure which establishes it with reasonable assurance.

Most structural possibilities, such as those based on Diels-Alder condensations, can be eliminated at once as the dimer shows no acidic, enolic, or ketonic properties and does not react readily with bromine. Although the dimer does not dissolve in cold alkali and cannot be saponified with aqueous or alcoholic alkali, it does react quantitatively with three moles of potassium hydroxide on refluxing in ethylene glycol to give a saponification equivalent of 69. Two moles of alkali are required by formula I for opening the rings and one for decarboxylation of the resultant isodehydroacetic acid analog. Phorone has been isolated as the product of this alkaline hydrolysis. Formation of phorone requires opening of both rings, decarboxylation at both carboxyl groups, and isomerization of the double bond. The carbon chain in the dimer is established by the isolation of this degradation product.

The spectral data for the dimer also confirm the structure I. Spectral analogies would be expected with the related open chain isopropyl isodehydroacetate (II). There is a remarkable parallel in the data for these two materials. The dimer absorbs in the ultraviolet at 254 mμ, log ε 3.984; 294 mμ, log ε 3.698. Isopropyl isodehydroacetate absorbs at 248 mμ, log ε 3.80; 295 mμ, log ε 3.78. The principal and characteristic infrared absorption bands occur at 1745 and 1718 cm.$^{-1}$ (2-pyrone and unsaturated delta lactone carbonyl stretching vibrations respectively); 1071 cm.$^{-1}$ (C=O stretching); and at 850 cm.$^{-1}$ (ethylenic C—H rocking vibration band characteristic of 2-pyrones). The related absorption bands for ethyl isodehydroacetate occur at 1754, 1727, 1080, and 850 cm.$^{-1}$ The dimer differs from the ethyl ester in having a relatively strong absorption band at 1406 cm.$^{-1}$, assignable to the C—H bending vibration of the conjugated methylene group. In both structures the 2-pyrone carbonyl absorption is shifted to higher frequencies, a phenomenon previously noticed with 2-pyrones having carbonyl substituents in the 5-position.[2]

The pyrolysis of the dimer is a most interesting reaction. The pyrolysis product, formed by heating the dimer to 350° in the presence of copper, is 4-methyl-6-(2′-methylpropenyl)-2-pyrone[3] (III) obtained by decarboxylative rearrangement of the acyl glutaconic anhydride obtained in turn from senecioyl chloride and β-methylglutaconic anhydride. The infrared absorption characteristics of the products obtained by the two processes are identical. The great diminution of the very strong band at 1080 cm.$^{-1}$, characteristic of the C—O stretching vibration in the unsaturated delta lactone structure of the dimer and one of the most prominent in its spectra, can be used to assess the purity of the 2-pyrone in which this band is very weak. It has been noted previously[4] that δ,δ-dimethyl-δ-valerolactone is converted to isoheptanoic acid at 216° in a similar reaction.

This conversion of β-methylglutaconic anhydride in two pyrolytic steps to 4-methyl-6-(2′-methylpropenyl)-2-pyrone has suggested the combination of these two steps into one as a more di-

(1) The product, ultimately identified as (I) will be referred to as the dimer in this discussion in the interests of brevity.

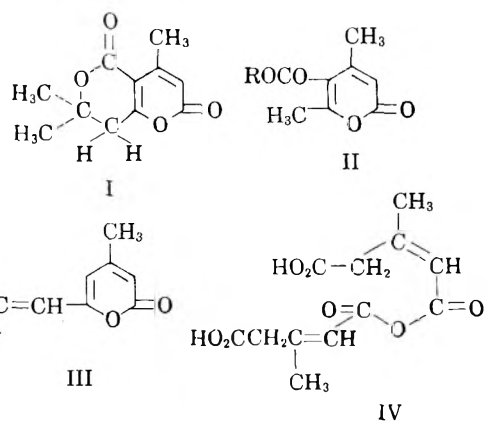
(2) Richard H. Wiley, and S. C. Slaymaker, *J. Am. Chem. Soc.*, **78**, 2393 (1956).

(3) Richard H. Wiley, and J. G. Esterle, *J. Org. Chem.*, **21**, 1335 (1956).

(4) R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 580 (1933).

rect route to this pyrone which is of interest as a possible intermediate or inhibitor in the biosynthesis of cholesterol. This direct synthesis has been achieved to give 35% yield of the pyrone from the acid. The acid is first heated to 250° at atmospheric pressure for one hour and then, after addition of copper, to 300° for an additional hour during which time the pyrone distills from the reaction mixture.

The formation of the dimer can be accounted for assuming a condensation in the linear anhydride (IV) between a methylene group and anhydride carbonyl followed by lactonization and decarboxylation or by a self-acylation of the anhydride and its decarboxylated product followed by a rearrangement in which the intermediate is lactonized rather than decarboxylated as in previously observed[5] reactions of this type. There may be no fundamental difference in these two possibilities. In each the anhydride, or acid, carbonyl condenses at the methylene carbon as a means of providing the carbon—carbon bond required to form the 2-pyrone ring. Both have, however, been previously observed only as base-catalyzed reactions. The dimer has been obtained from the senecioyl chloride acylation of the anhydride which indicated the feasibility of the later reaction sequence.



I II III IV

EXPERIMENTAL[6]

Preparation of the dimer (I). Fifty grams (0.35 mole) of β-methylglutaconic acid was placed in a 125-ml. Claisen flask with a receiver, an ebulator, and a thermometer. The pressure was reduced to 3 mm. The flask was heated to 185° over a 0.5-hr. period. The temperature was held constant until the pressure which suddenly rises to 60 mm. dropped to 10 mm. The temperature was then again raised slowly and the material distilling between 180 and 210° was collected. Upon recrystallization from methanol 15 g. of material, m.p. 154–155°, was obtained.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; sapon. equiv. 69.4; mol. wt. 208.4. Found: C, 63.36; H, 6.09; sapon. equiv., 69 (in ethylene glycol); mol. wt. 204 (Rast).

Conversion of dimer to phorone. One gram (0.0048 mole) of the dimer was dissolved in 20 ml. of 1N potassium hydroxide in ethylene glycol. The solution was heated slowly to 130° over a period of 30 min. and held at this temperature for 15 min. Ten ml. of water was added to the cooled solution. The acidified solution was extracted with ether. The ether extracts were washed with aqueous sodium carbonate, dried, and evaporated to give a residue. Distillation of this residue gave 0.2 g. of material which gave a positive ketone test. The infrared spectra of this product was identical with that of an authentic sample of phorone. The dinitrophenylhydrazone, m.p. 109°, was prepared and gave no depression in melting point when a mixed melting point was run with an authentic sample.

4-Methyl-6-(2′-methylpropenyl)-2-pyrone by pyrolysis of the dimer. A mixture of 5.0 g. (0.024 mole) of the high boiling fraction and 1 0 g. of copper powder was heated on a Wood's metal bath at 270–290° for 1.5 hr. After the initial heating period the temperature of the bath was gradually raised to 350°. There was collected as distillate 1.7 g. (43%) of 4-methyl-6-(2′-methylpropenyl)-2-pyrone. Refractionation gave a fraction b.p. 109°/1 mm., which was recrystallized from ether to give the pyrone, m.p. 45–46°. The infrared spectrum of the product was identical with that of an authentic sample of the pyrone prepared as previously described.

4-Methyl-6-(2′-methylpropenyl)-2-pyrone by pyrolysis of β-methylglutaconic acid. In a 25-ml. distilling flask was placed 15.0 g. (0.104 mole) of crude β-methylglutaconic acid. The flask was immersed in a Wood's metal bath previously heated to 250°. The crude acid melted and evolved carbon dioxide vigorously. A small amount of low boiling material was collected as distillate. After this initial reaction had subsided, the flask was heated for 1 hr. at 250° and then, after adding 1.0 g. of copper powder, at 300° for 1 hr. The temperature of the bath was then gradually raised to 360° during which time 3.1 g. (38%) of 4-methyl-6-(2′-methylpropenyl)-2-pyrone was collected. The infrared spectrum of the product was identical with that of an authentic sample of the pyrone prepared as previously described.

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(5) Richard H. Wiley and N. R. Smith, *J. Am. Chem. Soc.*, **74**, 3893 (1952).

(6) Analyses by Micro Tech Laboratories, Skokie, Ill.

Some 1,3-Dinitrophenanthrene Derivatives

CHARLES K. BRADSHER AND DOROTHY J. BEAVERS

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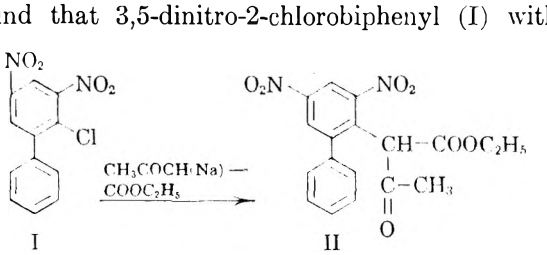
In earlier experiments,[1] directed toward the synthesis of dinitrophenanthrene derivatives, it was found that 3,5-dinitro-2-chlorobiphenyl (I) with

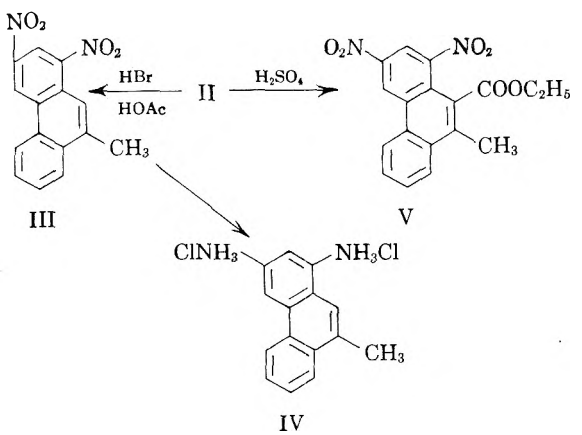


I II

(1) C. K. Bradsher and S. T. Amore, *J. Am. Chem. Soc.*, **66**, 1283 (1944).

sodio-acetoacetic ester in ethanol merely underwent ethoxylation, while in inert solvents such as benzene, xylene, or dioxane, no reaction was apparent. Subsequently, Zaheer and Kacker[2] observed that, in ether the reaction (I–II) is very slow (2–3% yield after 58 hours)[3] but found that sodioacetoacetic ester and the halide (I) could be made to react more completely if heated *without solvent* at 100–110°. More recently Zaheer and Kacker[4] have published a warning that carrying out the reaction on a scale larger than five to six grams of the diphenyl compound may lead to explosion.

It has been our own experience that violent decomposition occurred frequently (two runs out of seven) even on a 5.5 g. scale. It has also been found that an easily controlled reaction, leading to cleaner products, can be obtained at a moderate temperature by use of a large excess of acetoacetic ester as the solvent. As had been anticipated,[1] the dinitrobiphenylyl ester (II) may be cyclized in a boiling hydrobromic–acetic acid medium, affording 1,3-dinitro-9-methylphenanthrene (III) in 54% yield. Reduction of the dinitrophenanthrene (III) yielded 1,3-diamino-9-methylphenanthrene, isolated as the dihydrochloride (IV).



The two nitro groups have a strong deactivating influence on all of the rings of the phenanthrene skeleton of III, as evidenced by its resistance to nitration.

Cyclization of the keto ester II in concentrated sulfuric acid appeared to occur without decarboxylation, yielding a mixture consisting chiefly of ethyl 1,3-dinitro-9-methyl-10-phenanthrenecarboxylate (V) contaminated with some of the free acid.

EXPERIMENTAL

Ethyl α-(3,5-dinitrobiphenylyl-2)acetoacetate (II). Sodium metal (0.25 g.) was allowed to react with 7 g. of dry ethyl acetoacetate and the mixture was heated for 15.5 hr. at 60° with 1.5 g. of 3,5-dinitro-2-chlorobiphenyl.[1] The mixture was dissolved in 3% sodium hydroxide solution, and the product was precipitated by acidification with nitric acid. Recrystallization from ethanol yielded 0.9 g. (45%) of yellow prisms, approximate m.p. 105–107.5°. The analytical sample was obtained by recrystallization from ethanol, m.p. 104–106° (lit.[4] m.p. 102–103°); λ_{max}[5] (log ϵ) 250 (4.34) and 327 mμ (broad, 3.30); λ_{min} 298 mμ (3.10).

Anal. Calcd. for $C_{18}H_{16}N_2O_7$: C, 58.06; H, 4.33. Found: C, 58.33; H, 4.41.

Essentially the same yield (42% of slightly less pure material, m.p. 100–107°) was obtained when the condensation was carried out as above except that the reaction was allowed to proceed for 12 days at 20°. Essentially the same results were obtained when 3,5-dinitro-2-bromobiphenyl[2] was allowed to react for 16 hr. at 60° (45%) or for one month at 20° (43.5%).

1,3-Dinitro-9-methylphenanthrene (III). One gram of the dinitrobiphenylylacetoacetic ester (II) was dissolved in 20 ml. of acetic acid, 12 ml. of 48% hydrobromic acid was added, and the mixture was refluxed for 8 hr. The product was collected and recrystallized from benzene affording 0.41 g. (54%) of a grey powder, m.p. 215–217°. An analytical sample obtained by recrystallization from ethanol consisted of yellow needles, m.p. 221–222.5°; λ_{max} (log ϵ) 239 (4.58), 307 (inflection, 383) 355 mμ (broad, 3.97); λ_{min} 301 mμ (3.69).

Anal. Calcd. for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57. Found: C, 63.76; H, 3.53.

Samples of the dinitromethylphenanthrene (III), crystallized from benzene, appeared to be solvated and could not be freed from benzene even by drying for 24 hr. at 80° (1 mm.).

A 0.5-gram sample of III was dissolved in glacial acetic acid (75 ml.) and heated with 10 ml. of fuming nitric acid at 90° for 1 hr. The starting material was recovered unchanged.

1,3-Diamino-9-methylphenanthrene dihydrochloride (IV). One-half gram of the dinitromethylphenanthrene (III) was suspended in 150 ml. of absolute ethanol, 0.1 g. of Adams' catalyst was added, and the mixture was hydrogenated with stirring at room temperature. After slightly more than the theoretical quantity of hydrogen had been absorbed, the solution was filtered and poured into water. The resulting mixture was extracted with ether four times, and the ethereal extract washed with water and then saturated with hydrogen chloride, affording a pale pink solid. Recrystallization from ethanol-concentrated hydrochloric acid yielded cream-colored prisms shrinking at 310° before decomposing at 315–317°.

Anal. Calcd. for $C_{15}H_{15}Cl_2N_2 \cdot {}^1/_2H_2O$: C, 59.41; H, 5.32. Found: C, 59.64; H, 5.58.

1,3-Dinitro-9-methyl-10-carbethoxyphenanthrene (V). (*a*) *By cyclization of the keto ester* II. Three grams of the keto ester II was dissolved in 125 ml. of concentrated sulfuric acid at room temperature, and the purple solution stirred occasionally during the course of 0.5 hr. The mixture was then poured on ice and the flocculent precipitate was collected, washed with water, and dried, yielding 2.63 g. of a tan solid. The solid was suspended in 200 ml. of a 15% ammonia solution and the mixture heated at 60° with stirring. Filtration of the red solution yielded a quantity of solid

(2) S. H. Zaheer and I. K. Kacker, *J. Indian Chem. Soc.*, **23**, 380 (1946).

(3) This very slow rate of reaction can best be attributed to steric factors. Zaheer and Kacker[2] have rejected the explanation of Bradsher and Amore[1] that steric hindrance about the activated halogen atom makes the size of the approaching anions of paramount importance. On the other hand they have offered no explanation for the fact that an ethanol solution of ethyl sodioacetoacetate with 2,4-dinitrochlorobenzene (unhindered) yields an acetoacetic ester derivative, while the same solution with 3,5-dinitro-2-chlorobiphenyl (hindered) yields the 2-ethoxy derivative.

(4) S. H. Zaheer and I. K. Kacker, *J. Indian Chem. Soc.*, **32**, 491 (1955).

(5) All spectra were determined in 95% ethanol using 1-cm. silica cells.

which was again suspended in 200 ml. of 15% ammonia solution and stirred overnight. Filtration yielded 1.76 g. of crude undissolved ester as a tan solid, m.p. 230–235°.

(*b*) *From the acid via the silver salt.* The ammonia extract obtained above (400 ml.) was added with stirring to a solution formed by dissolving 2 g. of silver nitrate in 40 ml. of concentrated ammonium hydroxide. The solution was heated in the steam bath for 2.5 hr. and then stirred overnight at room temperature. The chocolate powder was collected and dried; yield 0.56 g. The silver salt was suspended in 60 ml. of methanol containing 1 g. of ethyl iodide and the mixture refluxed for 4 hr. After removal of the silver iodide by filtration, the ester was isolated and recrystallized from ethanol, yielding 0.2 g. of long yellow needles, m.p. 230–234°. The analytical sample (procedure b) melted at 237–239°.

Anal. Calcd. for $C_{18}H_{14}N_2O_6$: C, 61.01; H, 3.98. Found: C, 61.11; H, 4.28.

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Photodimerization of Acridizinium Salts

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Crystalline acridizinium bromide monohydrate[2] (I) when exposed to irradiation by sunlight or from a sun lamp is converted to a higher melting, less soluble compound lacking the yellow color and the fluorescence characteristic of the starting material. The ultraviolet absorption spectrum of the new compound (Fig. 1) makes it clear that the irradiation has destroyed the conjugation characteristic of the acridizinium system. The possibility that photooxidation has taken place is easily eliminated by the observation that there is no change in weight during irradiation. Analysis indicates that the new product (II) has approximately the same composition as the starting material.

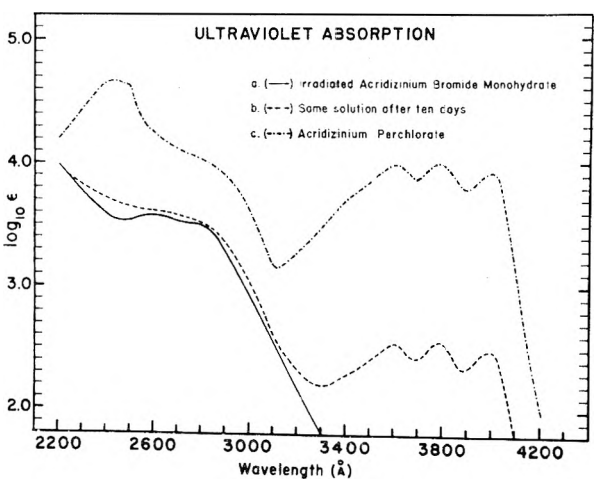
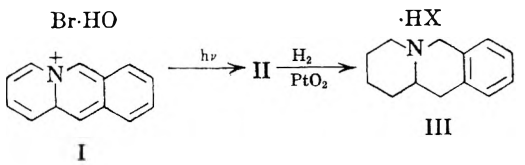


FIGURE 1.

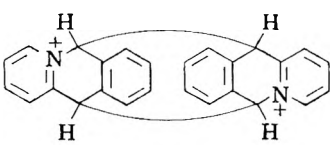
The irradiation product is a salt and can be converted to a picrate and a perchlorate having the composition expected for the acridizinium analog. The bromide (II) was unaffected by refluxing for two hours in 48% hydrobromic acid and when heated at 100° with 6*N* nitric acid it was merely converted to the nitrate salt. When the bromide II



was reduced catalytically in the presence of platinum oxide the only product identified was a salt of benzo[c]azabicyclo[4.4.0]decane (III).

An interesting observation was that a solution of the nonfluorescent irradiated bromide (II), in 95% ethanol, after standing at room temperature for ten days became faintly fluorescent. Spectroscopic examination of the solution showed a definite indication of the presence of a small quantity of the acridizinium ion. When the irradiation product (II) in 95% ethanol solution was refluxed for 18 hours it afforded acridizinium bromide in 82% yield. If this is a simple thermal dissociation it occurs more readily in solution since a sample of crystalline irradiated bromide II was unchanged after heating in a drying oven at 75° for 24 hours.

Analogy between the acridizinium ion and anthracene[3] suggested that the new product might be a photodimer. Anthracene[4] and many of its derivatives[5] dimerize when irradiated in *solution*, and the dimers are known to dissociate[5] on heating. Since the acridizinium ion is unsymmetrical, several isomeric forms of the meso-connected ion are theoretically possible. Structure II seems most likely[6] in that it permits maximum separation between the like charges.



II

Observations concerning boiling point elevation of ethanol solutions, although complicated by the

(1) Public Health Service Research Fellow of the National Institutes of Health, 1952–1954. This investigation was supported in part by a research grant (G-2364) of the National Science Foundation.

(2) C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **77**, 4812 (1955).

(3) A subsequent communication will describe another anthracene-type reaction of the acridizinium ion.

(4) J. Fritzsche, *J. Prakt. Chem.*, 101, 333 (1867).

(5) F. D. Greene, S. L. Misrock, and J. R. Wolfe, Jr., *J. Am. Chem. Soc.*, **77**, 3852 (1955).

(6) It is possible that a detailed picture of the structure of II will be provided by the methods of x-ray crystallography. Professor J. M. Robertson has indicated his interest in the problem.

possibility for ionization, make it clear that II is not an isomer of I and afford a strong indication that it is a dimer.

EXPERIMENTAL[7]

Photodimerization of acridizinium bromide. One gram of crystalline acridizinium bromide monohydrate I was irradiated under a General Electric sunlamp for about 5.5 hr. with occasional stirring to ensure complete exposure. As the reaction progressed, the color of the material changed from yellow to light tan and the crystals disintegrated. Recrystallization from ethanol-ether yielded .96 g. (93%) of colorless prisms, m.p. 260–263°.

Similar results may be obtained by the use of direct sunlight. In one experiment it was demonstrated that irradiation in a stoppered glass vial for a total of 16 hr. produced no detectable change in weight although conversion was practically complete.

An analytical sample was prepared by recrystallization from ethanol-ether, m.p. 260–264°.[8]

Anal. Calcd. for $(C_{13}H_{10}NBr \cdot 3/2\ H_2O)_2$: C, 54.51; H, 4.22; N, 4.89. Found: C, 54.86; H, 4.03; N, 4.70.

Properties of irradiated acridizinium bromide. The new product (II) is less soluble in water and ethanol than is the starting material I, and the solutions lack the fluorescence characteristic of the acridizinium ion.

The irradiation product was unaffected by drying at 75° for 24 hr. or refluxing in 48% hydrobromic acid for 2 hr.

When 0.23 g. of the irradiation product (II) was refluxed for 18 hr. in 15 ml. of 95% ethanol it yielded 0.19 g. (82.5%) of acridizinium bromide, m.p. 236–237° (lit.[2] 239–240°). The identity of the product was established by means of the ultraviolet absorption spectrum.

Hydrogenolysis of the irradiation product. Hydrogenation of 0.5 g. of irradiated acridizinium bromide was carried out in about 50 ml. of ethanol using Adams' catalyst, a little more than eight molar equivalents of hydrogen being absorbed. The solution was filtered and concentrated yielding 0.3 g. of fine white crystals m.p. 200–228°. These were converted to the picrate in ethanol yielding yellow needles m.p. 160° (lit.[9] 161–162°) of benzo[c]azabicyclo[4.4.0]decane picrate (III) identified by a mixed melting point determination with an authentic sample.

Boiling-point elevation in ethanol. The boiling point elevation caused by solution of 0.300 g. of the bromide in 10 ml. of absolute ethanol was observed and compared with a value calculated on the assumption that no ionization had occurred, and using 1.2° as the molal boiling point elevation constant for ethanol.

Acridizinium bromide (278). Observed, 0.180°; Calcd. 0.162°. Irradiated acridizinium bromide (574). Observed 0.068°, 0.078°. Calcd. 0.078°.

In the first of the two determinations on irradiated acridizinium bromide (II), refluxing in the molecular weight apparatus was continued for 3 hr., during which the boiling-point elevation rose to 0.133°. There was no indication that a maximum in boiling-point had been reached.

The picrate of the irradiation product II was prepared in ethanol as yellow crystals, m.p. 280–283°.

Anal. Calcd. for $(C_{19}H_{12}N_4O_7 \cdot 1/2\ H_2O)_2$: C, 54.71; H, 3.14; N, 13.42. Found: C, 54.65; H, 3.06; N, 13.21.

The nitrate of the irradiation product II was formed when a small quantity of II was heated on the steam bath for 15 min with 6*N* nitric acid in an attempt to bring about oxidation. The salt, recovered by pouring the solution on ice, was recrystallized from alcohol-ether as colorless needles, m.p. 228–230°.

Anal. Calcd. for $C_{26}H_{20}N_4O_6 \cdot 3/2\ H_2O$: C, 61.00; H, 4.53; N, 10.84. Found: C. 60.84; H, 4.28; N, 10.55.

The perchlorate of the irradiation product II was prepared by addition of perchloric acid to a water solution of the bromide and recrystallized from water as colorless needles, m.p. 294°.

Anal. Calcd. for $(C_{13}H_{10}NClO_4)_2$: C, 55.79; H, 3.60; N, 5.01. Found: C, 55.66; H, 3.85; N, 4.97.

A 0.15 g. sample of the perchlorate (m.p. 290°) was refluxed overnight in 95% ethanol. The solution was concentrated and cooled yielding 0.1 g. (67%) of yellow needles, m.p. 205°. This was identified as acridizinium perchlorate (lit.[2] 205–206.2°) by means of the ultraviolet absorption spectrum.

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(7) All melting points were taken on a Fisher-Johns apparatus and are uncorrected. Ultraviolet absorption spectra were measured in 95% ethanol (1 cm. silica cells). Analyses are by Micro-Tech Laboratories, Skokie, Ill.

(8) Melting point obtained with fairly rapid heating. If the compound is heated very slowly it turns yellow, melting at 238°. It is noteworthy that acridizinium bromide melts at 239–240° (ref. 2).

(9) N. J. Leonard, S. Swann, Jr., and G. Fuller, *J. Am. Chem. Soc.*, **76**, 3193 (1954).

Base-Catalyzed Cleavage of β-Hydroxy Acids and Their Esters

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The cleavage of a β-hydroxy acid or ester, in the manner indicated *below*, has been described frequently in the literature.[3]

The effect of molecular structure on base-catalyzed decomposition of β-hydroxy acids and esters was investigated rather extensively by Ivanov and coworkers.[4] All of the β,β-disubstituted α-aryl-β-hydroxypropionic acids studied by them were decomposed readily into arylacetic acids and ketones.

(1) This paper represents part of a dissertation submitted by R. H. Cox in partial fulfillment of the requirements for for the Ph.D. degree in the University of Michigan, 1954.

(2) Sterling-Winthrop Fellow.

(3) In 1880, H. Schnapp [*Ann.*, 201, 62 (1880)] observed that α,α-diethyl-β-hydroxybutyric acid decomposed, under the influence of heat, into diethylacetic acid and acetaldehyde. Subsequently, a number of similar decompositions have been reported; in most instances the cleavage was catalyzed by a base. Of practical interest is the cleavage of β,β-disubstituted α-phenyl-β-hydroxypropionic acids which has been observed in several instances during the attempted preparation of basic esters of these acids [A. W. Weston and R. W. DeNet, *J. Am. Chem. Soc.*, **73**, 4221 (1951); F. F. Blicke and H. Raffelson, *J. Am. Chem. Soc.*, **74**, 1730 (1952); F. F. Blicke and R. H. Cox, *J. Am. Chem. Soc.*, **77**, 5401 (1955)].

$$\begin{matrix} R^1R^2CCOOR \\ | \\ R^3R^4COH \end{matrix} \longrightarrow R^1R^2CHCOOR + R^3R^4CO$$

R is hydrogen or alkyl
R^3R^4CO is an aldehyde or ketone

(4) D. Ivanov and J. Popov, *Bull. soc. chim.*, [5] 49, 1547 (1931); D. Ivanov, M. Mihova, and T. Christova, *Bull. soc. chim.*, [4] 51, 1321 (1932).

Cleavage of β-monosubstituted α-aryl-β-hydroxypropionic acids took place less readily.[5] In all instances it appeared that the presence of a β-aryl group facilitated the decomposition. Of the α-alkyl- and α,α-dialkyl-β-hydroxypropionic acids studied,[6] only those acids which contained two substituents in the β-position, at least one of which was aromatic, were cleaved; those acids which contained only an aryl substituent, or one or two alkyl substituents, in the β-position were not decomposed under the experimental conditions.

During this investigation of the decomposition of β-hydroxy acids, the required acid was refluxed with two molecular equivalents of 3.2% aqueous sodium hydroxide for sixteen hours.

In the case of the following six β,β-disubstituted α-phenyl-β-hydroxypropionic acids, at least 96% of the calculated amount of phenylacetic acid was isolated after alkaline treatment: α-phenyl-β-methyl-β-hydroxybutyric, α-phenyl-β-propyl-β-hydroxycaproic, α-phenyl-α-(1-hydroxycyclohexyl)-acetic, α-phenyl-α-(1-hydroxycyclooctyl)acetic, α-phenyl-β-cyclohexyl-β-hydroxybutyric, and α,β-diphenyl-β-hydroxybutyric acid. The one acid in this group which contained an aryl substituent in the β-position, α,β-diphenyl-β-hydroxybutyric acid, decomposed very rapidly. Quantitative observations clearly indicated that the β-cyclohexyl analog, α-phenyl-β-cyclohexyl-β-hydroxybutyric acid, decomposed more slowly. It is interesting to note that we obtained practically complete decomposition of α-phenyl-α-(1-hydroxycyclohexyl)acetic acid into phenylacetic acid and cyclohexanone under relatively mild conditions while Linstead[7] found that a solution of 1-hydroxycyclohexylacetic acid, when refluxed for twenty-four hours with a tenfold excess of 10% aqueous potassium hydroxide, yielded only a trace of cyclohexanone; only when a tenfold excess of 60% aqueous potassium hydroxide was employed was substantial cleavage of the acid noted.

In order to investigate the possible influence of an α-hydrogen atom in the cleavage of a β-substituted α-phenyl-β-hydroxypropionic acid, we studied α-phenyl-α-(1-hydroxycyclohexyl)butyric acid, a compound which does not contain such an atom. This compound was cleaved almost quantitatively into α-phenylbutyric acid and cyclohexanone.

In the case of the following three β-monosubstituted α-phenyl-β-hydroxypropionic acids, the first-mentioned acid underwent the most decomposition and the last-mentioned acid the least: α-phenyl-β-hydroxybutyric, α-phenyl-β-cyclohexyl-β-hydroxypropionic and α-phenyl-β-hydroxypelargonic acid.

α-Phenyl-β-hydroxypropionic (tropic) acid has been shown[8,9] to undergo dehydration readily when treated with alkali. In our experiments we also obtained dehydration of this acid; however, to some extent the acid decomposed with the evolution of formaldehyde which was identified by its odor and by a Schiff test.

After alkaline treatment, the following α-cyclohexyl-β-hydroxy acids were recovered unchanged in at least 96% yield: α-cyclohexyl-β-hydroxypropionic, α-cyclohexyl-β-hydroxybutyric, α-cyclohexyl-β-methyl-β-hydroxybutyric, α-cyclohexyl-β-propyl-β-hydroxycaproic, α-cyclohexyl-α-(1-hydroxycyclohexyl)acetic, α,β-dicyclohexyl-β-hydroxypropionic, α,β-dicyclohexyl-β-hydroxybutyric, α-cyclohexyl-β-hydroxypelargonic, and α-cyclohexyl-α-(1-hydroxycyclooctyl)acetic acid. However, the last two compounds especially were observed to undergo slight decomposition which was established by the isolation and identification of the carbonyl compound and by the lowered melting point of the recovered acid.

β,β-Diphenyl-β-hydroxypropionic acid (m.p. 212°), after alkaline treatment, was recovered in practically quantitative yield but the recovered acid melted at 202–207° which indicated some decomposition. β,β-Dicyclohexyl-β-hydroxypropionic acid was unaffected by the alkaline treatment.

When we heated the methyl esters of α-phenyl-β-hydroxypropionic acid and α-cyclohexyl-β-hydroxypropionic acid with excess hydrazine monohydrate, the corresponding hydrazides were obtained. However, the methyl esters of α-phenyl-α-(1-hydroxycyclohexyl)acetic, α-phenyl-α-(1-hydroxy-4-methylcyclohexyl)acetic and α-phenyl-α-(1-hydroxycyclooctyl)acetic acid, when treated similarly at room temperature, were converted quantitatively into phenylacethydrazide.

Methyl α-phenyl-α-(1-hydroxycyclooctyl)acetate, when treated with excess liquid ammonia, was partially (25%) decomposed into phenylacetamide and cyclooctanone.

Subsequent to our investigation, Rondestvedt and Rowley[10] obtained quantitative data on the base-catalyzed cleavage of β-hydroxy acids which permit generalizations regarding the mechanism of cleavage.

EXPERIMENTAL

α-Phenyl-β-cyclohexyl-β-hydroxypropionic,[11] α-phenyl-β-hydroxybutyric acid, and the other acids employed, with the exception of the one reported below, have been described.[12,13]

α-Phenyl-α-(1-hydroxycyclohexyl)butyric Acid. This acid was prepared by a variation of the general procedure.[14] Ap-

(5) D. Ivanov, *Bull. soc. chim.*, [4] **53**, 321 (1933).
(6) D. Ivanov, *Bull. soc. chim.*, [5] **7**, 569 (1940).
(7) R. P. Linstead, *J. Chem. Soc.*, 362 (1927).
(8) K. Kraut, *Ann.*, **148**, 236 (1868).
(9) H. S. Raper, *J. Chem. Soc.*, **123**, 2558 (1923).
(10) C. S. Rondestvedt and M. E. Rowley, *J. Am. Chem. Soc.*, **78**, 3804 (1956).
(11) F. F. Blicke and H. Zinnes, *J. Am. Chem. Soc.*, **77**, 6247 (1955).
(12) F. F. Blicke and H. Raffelson, *J. Am. Chem. Soc.*, **74**, 1730 (1952).
(13) F. F. Blicke and R. H. Cox, *J. Am. Chem. Soc.*, **77**, 5401, 5403 (1955).
(14) D. Ivanov and A. Spassov, *Bull. soc. chim.* [4] **49**, 19 (1931).

proximately 2 moles of isopropylmagnesium chloride was allowed to react with 0.5 mole of α-phenylbutyric acid. To the mixture there was added 1.6 moles of cyclohexanone. The yield was 62%; m.p. 125–128° after recrystallization from benzene-petroleum ether (60–70°).

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.26; H, 8.45; neut. equiv., 262.2. Found: C, 73.12; H, 8.68; neut. equiv., 261.8.

The following esters were obtained by the use of diazomethane.

Methyl α-phenyl-α-(1-hydroxycyclohexyl)acetate. The yield was 81%; m.p. 84° after recrystallization from petroleum ether (60–70°).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.29; H, 8.08.

Methyl α-phenyl-α-(1-hydroxy-4-methylcyclohexyl)acetate. The yield was 77%; m.p. 113–114° after recrystallization from petroleum ether (90–100°).

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.26; H, 8.45. Found: C, 73.60; H, 8.89.

Methyl α-phenyl-α-(1-hydroxycyclooctyl)acetate. The ester was obtained in 74% yield; m.p. 93–95° after recrystallization from petroleum ether (60–70°).

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.85; H, 8.53.

The following hydrazides were prepared by heating the required methyl esters with a fourfold excess of hydrazine monohydrate on a steam bath until a homogeneous solution was obtained.

α-Phenyl-β-hydroxypropionhydrazide. The yield was 81%; m.p. 169–171° after recrystallization from water.

Anal. Calcd. for $C_9H_{12}O_2N_2$: C, 59.98; H, 6.71. Found: C, 60.14; H, 6.75.

α-Cyclohexyl-β-hydroxypropionhydrazide. This compound melted at 213–214° (dec.) after recrystallization from water; yield 60%.

Anal. Calcd. for $C_9H_{18}O_2N_2$: C, 58.04; H, 9.74. Found: C, 58.33; H, 9.76.

Base-catalyzed cleavage. The required acid (0.02 mole) was dissolved in 50 cc. of aqueous sodium hydroxide solution which contained 1.6 g. (0.04 mole) of sodium hydroxide, the solution was refluxed for 16 hours and then extracted with ether (nonacidic fraction). The alkaline solution was then acidified and the precipitate (acidic fraction) was filtered; ether extraction of the filtrate yielded an additional amount of acidic fraction.

The acidic fraction was composed of the acid formed by cleavage, the original acid, or a mixture of the two acids. Each acid was characterized by a mixed melting point and by a neutralization equivalent.

In those instances in which cleavage occurred, the carbonyl compound, found in the nonacidic fraction, was identified by its boiling point and/or the melting point of a known derivative.

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Aromatic Nucleophilic Substitution Reaction in Qualitative Organic Chemistry: The Reaction of 2,4-Dinitrofluorobenzene with Phenols

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The preparation of derivatives of phenols, for identification purposes, by reactions of the corresponding sodium phenoxides with 2,4-dinitrochlorobenzene is described or mentioned in several texts and laboratory manuals[2–6] for organic qualitative analysis. The procedure, based upon work of Bost and Nicholson,[7] appears to be simple but the products obtained are frequently oils rather than crystalline solids. The 2,4-dinitrophenyl ether has therefore not found favor as a derivative in the identification of phenols.

The reason for the formation of the oils lies in the choice of solvent for this reaction. In the alcohol water solvent used, there are generally three nucleophilic ions present, hydroxide, phenoxide, and ethoxide.[8] Since the nucleophilic attacking power of these ions is in the order ethoxide > phenoxide > hydroxide,[8] one generally obtains two ethers, 2,4-dinitrophenetole as well as the expected substituted diphenyl ether. Any phenol formed by the reaction with an excess of hydroxide ion is readily removed from the desired derivative by washing with dilute base. However, the two ethers cannot be separated by this simple washing, so that an oil results. If Bost and Nicholson's procedure is carefully followed so that equimolar amounts of NaOH, phenol, and 2,4-dinitrochlorobenzene are used, little ethoxide ion is present and only one ether, a crystalline derivative, is obtained. A more promising method of obtaining crystalline derivatives is to use a solvent which does not give nucleophilic ions by reacting with hydroxide ion, or to use an aqueous solvent and remove the 2,4-dinitrophenol which is the by-product.

The change in solvent to water was not practical with the solid 2,4-dinitrochlorobenzene for the heterogeneous reaction at room temperature is slow. However, the liquid, 2,4-dinitrofluorobenzene, contains the more highly activated fluorine atom,[9] so that a Schotten-Bauman reaction at room temperature was possible. Fifteen ml. of 5% NaOH (an excess), 0.005 mole of phenol, and 0.005 mole of 2,4-

(1) From the independent study theses submitted to the College of Wooster in partial fulfillment of the degree of Bachelor of Arts, of James P. Douglas, 1954, Howard Leister, 1955, and Martha B. Voelkel, 1956.

(2) J. W. Chittum, *Laboratory Manual of Organic Chemistry*, 6th Edition, Edwards Brothers, Ann Arbor, Mich. (1947), p. 36–38.

(3) N. D. Cheronis and J. B. Entriken, *Semimicro Qualitative Organic Analysis*, Crowell, New York (1947), p. 221 and 381–385.

(4) F. Wild, *Characterization of Organic Compounds*, Cambridge Press, Cambridge (1948), p. 70–71 and 34–37.

(5) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, Inc., 4th ed., New York (1956), pp. 262 ff.

(6) Staff of Hopkin and Williams Research Laboratory, *Organic Reagents for Organic Analysis*, Chemical Publishing Co., Inc., Brooklyn (1946), p. 52.

(7) R. W. Bost and F. Nicholson, *J. Am. Chem. Soc.*, **57**, 2368 (1935).

(8) J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, **76**, 3011 (1954).

(9) A. L. Beckwith, J. Miller, and G. D. Leahy, *J. Chem. Soc.*, 3552 (1952).

TABLE I

NEW 2,4-DINITROPHENYL ETHERS OF PHENOLS

Phenol Used	Derivative[a] M.P., ° C.	Yield, %	Formula	Analytical Data[b] % N Obsvd.	% N Calcd.	% C Obsvd.	% C Calcd.	% H Obsvd.	% H Calcd.
2,4-Dimethylphenol	101.5–102.5	92	$C_{14}H_{12}O_3N_2$	9.50	9.72	58.2	58.3	4.38	4.20
Resorcinol monomethyl ether	87–88.5	95	$C_{13}H_{10}O_6N_2$	9.78	9.65	54.0	53.8	3.41	3.47
Resorcinol monoethyl ether	113.5–115.0	92	$C_{14}H_{12}O_6N_2$	9.20	9.21	55.5	55.3	3.84	3.98
o-Hydroxy diphenyl	113.0–114.0	90	$C_{18}H_{12}O_5N_2$	8.45	8.33	64.5	64.3	3.60	3.60
3,4-Dimethylphenol	105.0–105.5	96	$C_{14}H_{12}O_5N_2$	9.90	9.72	58.4	58.3	4.03	4.20
o-Cyclohexylphenol	76.0–77.0	94	$C_{18}H_{18}O_5N_2$	8.25	8.18	63.5	63.2	5.57	5.30
3,5-Dimethylphenol	100.0–100.5	95	$C_{14}H_{12}O_5N_2$	9.86	9.71	58.4	58.3	4.24	4.20
8-Hydroxy quinoline	165–165.5 d.p.	90	$C_{15}H_9O_5N_3$	13.40	13.50	58.3	57.9	3.21	2.91
p-Benzylphenol	74.5–75.0	96	$C_{19}H_{14}O_5N_2$	7.83	8.00	65.1	65.0	4.10	4.03
p-*t*-Butylphenol	108.5–110.0	90	$C_{16}H_{16}O_5N_2$	9.04	8.86	61.1	60.8	4.98	5.10
Catechol	136.0–138.0	72	$C_{18}H_{10}O_{10}N_4$	12.6	12.7	48.8	48.9	2.36	2.28
Orcinol	152.7–153.9	92	$C_{19}H_{12}O_{10}N_4$	11.1	12.3	49.9	50.0	3.07	2.63
Hydroquinone monobenzyl ether	129.0–130.0	95	$C_{19}H_{14}O_6N_2$	7.42	7.65	62.6	62.3	3.71	3.85
p-Cyclohexylphenol	100.0–101.0	94	$C_{18}H_{18}O_5N_2$	8.14	8.18	63.5	63.2	5.20	5.30

[a] All melting points taken with a calibrated thermometer. [b] Analyses by C. Weiler and F. B. Strauss.

dinitrofluorobenzene were shaken for 5 min. in a glass-stoppered bottle. Crystalline precipitates which gave literature melting points after one or two recrystallizations were obtained. The drawback with this simple, rapid procedure was that the more acidic phenols gave low yields. This procedure was not applied to dihydric phenols.

The second change in solvent used was to replace alcohol with acetone, and to use triethyl amine as the reaction catalyst. This procedure, using 2,4-dinitrofluorobenzene, gave high yields (80–95%) with most monohydric phenols and good yields (60–80%) with the dihydric phenols used. The crude products crystallized immediately when the acetone was removed. Those phenols whose derivatives crystallized more slowly were: *p*-cyclohexyl phenol, 15 min.; resorcinolmonomethyl ether and *o*-cyclohexylphenol, 1 hr.; thymol, overnight; while carvacrol and pyrogallol did not crystallize. It should be noted that the last phenols used were of technical or practical grades. The reaction procedure was used on 41 phenols with satisfactory results in 38 cases. The data for the reaction is summarized in Tables I and II.

The substituted 2,4-dinitrophenyl ethers are recommended as good derivatives of phenols since: (1) the reagent is available, (2) the yield of derivative is high and the procedure is simple, (3) the melting points of the ethers formed are high, (4) phenols which melt at nearly the same temperatures give derivatives which have different melting points, (5) the ethers are pure so that constant melting points are obtained after one or two recrystallizations.

TABLE II

2,4-DINITROPHENYL ETHERS OF PHENOLS

Phenol Used	Derivative, M.P., °C. Obsvd.	Lit., ref.	No Recryst.	Yield, %
m-Cresol	73–74	74[4]	2	...
o-Chlorophenol	99–100	100[4]	2	79
o-Bromophenol	87–88	89[4]	1	82
o-Cresol	88–89	90[4]	2	94
m-Chlorophenol	73.5–75.5	75[3]	2	93
p-Cresol	93–93.5	93[4]	2	71
Guaicol	92.5–94.0	97[3]	3	100
2,4-Dibromophenol	135–135.5	135[4]	1	76
p-Chlorophenol	125–125.5	126[4]	2	68
Phenol	70.0–71.5	69[4]	2	62
2,4-Dichlorophenol	118–118.5	119[3]	2	81
o-Iodophenol	93.5–94.0	95[4]	1	88
o-Nitrophenol	139–140.5	142[4]	2	82
Eugenol	114–115.5	115[4]	2	94
Thymol	64.5–66.5	67[3]	2	84
Hydroquinone monomethyl ether	111–112.0	110[10]	2	94
p-Bromophenol	140–141.5	141[4]	2	89
2,4,6-Trichlorophenol	134.5–135	135[4]	2	75
α-Naphthol	127–128.0	128[4]	2	80
m-Nitrophenol	135–135.5	138[4]	2	95
2,4,6-Tribromophenol	137.5–138	138[3]	2	75
p-Nitrophenol	118–119.0	120[3]	2	90
Resorcinol	191–192.0	194[4]	1	60
β-Naphthol	94–94.5	95[4]	2	94
Hydroquinone	243–246 (d.p.)	240[11]	...	84
Isoeugenol	127.5–128	130[4]	2	97

EXPERIMENTAL

Whalley[12] used a similar procedure for the reaction of alcohols and 2,4-dinitrofluorobenzene. He used no solvent

(10) E. T. Burrows, J. C. Clayton, B. E. Hems, A. G. Long, *J. Chem. Soc.*, Suppl. Issue, 1, 198 (1949).

(11) Beilstein, *"Handbuch der Organischen Chemie,"* 4th ed., Julius Springer, Berlin, 1923, Vol. 6, 845.

(12) W. B. Whalley, *J. Chem. Soc.*, 2241 (1950).

for liquid alcohols, but ether or benzene was used to dissolve solid alcohols.

Procedure. The phenol, 0.005 mole (±10 mg.) was dissolved in 5 ml. of acetone, and 0.50 ml. of triethyl amine was pipetted into the reaction flask. The 2,4-dinitrofluorobenzene (0.005 mole, ± 10 mg.) was dissolved in 5 ml. of acetone. The two solutions were mixed at room temperature, then refluxed for 0.5 hr. in a water bath. The acetone was removed by evaporation, followed by the addition of 10 ml. of 5% HCl. The derivative crystallized and was filtered and washed several times with water. The precipitate was then ground under 15 ml. of 5% NaOH in a mortar, filtered, and washed several times with water. The crude product was dried for 24 hr. in a vacuum desiccator over "drierite". The best solvent for recrystallization of derivatives melting below 120° was ethanol or ethanol-water, while acetic acid or acetic acid–water was preferred for those melting above 120°.

The reaction procedures failed with 2,4-dinitrophenol because of low yield, while pyrogallol and carvacrol gave oils which did not crystallize.

The samples of phenols were either technical, practical, or purified grades. The technical and practical grades were not further purified before use.

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Reactions of *O*-Benzoyl-9-*aci*-nitrofluorene[1]

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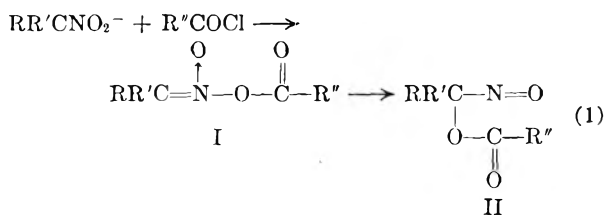
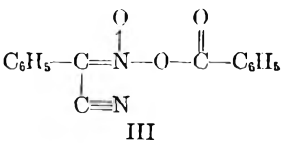
Salts of secondary alkyl nitroparaffins react with acid chlorides to yield the products shown in equation one.[3] In the alkyl series, the nitronic anhydrides I are relatively unstable and at temperatures



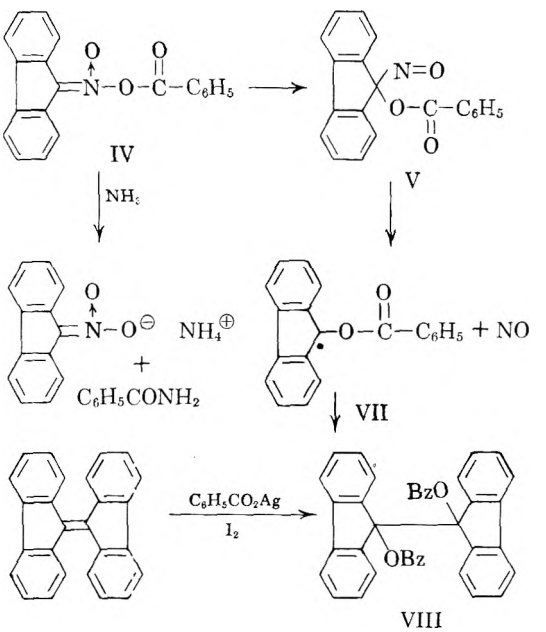
well below 0°[3] they rearrange to the nitroso derivatives II. The nitronic anhydrides of more highly conjugated nitroparaffins are relatively stable, on the other hand, presumably because a rearrangement to II would result in a decrease in resonance energy. Two compounds of this type are known.[4] The first, *O*-benzoyl-*aci*-nitrophenylacetonitrile (III), was synthesized by Thurston and Shriner[5]



and its structure was proved by the same authors. The second, *O*-benzoyl-9-*aci*-nitrofluorene (IV), was first synthesized by Nenitzescu and Isacescu.[6] In this paper we present evidence for its structure and list several of its reactions.

O-Benzoyl-9-*aci*-nitrofluorene was prepared by the reaction of benzoyl chloride with sodium 9-fluorenenitronate. The infrared spectrum of IV had intense absorption bands at 5.67 and 6.16 μ; this set of bands in the double bond stretching region of the spectrum is characteristic of nitronic anhydrides.[3] The isolation of benzamide and ammonium 9-fluorenenitronate from the ammonolysis of IV further confirms the structure assigned.

When a solution of IV in carbon tetrachloride was refluxed, nitric oxide was evolved and 9,9′-dibenzoyloxy-9,9′-bifluorenyl (VIII) was formed. The



first step in this reaction is probably the formation of the nitroso compound V, since this is the sequence that has been established for the corresponding alkyl nitronic anhydrides.[3] Homolysis of the carbon-nitrogen bond of V would yield nitric oxide and the relatively stable radical VII, the dimerization of which would yield VIII. The last

(1) Taken in part from a thesis submitted by William J. Considine to the faculty of the Graduate School of Yale University in partial fulfillment of the requirements for the Ph.D. degree. Presented before the Division of Organic Chemistry at the 130th Meeting of the AMERICAN CHEMICAL SOCIETY, Atlantic City, New Jersey, September 21, 1956.

(2) Author to whom inquiries are to be sent (The Johns Hopkins University, Baltimore 18, Md.).

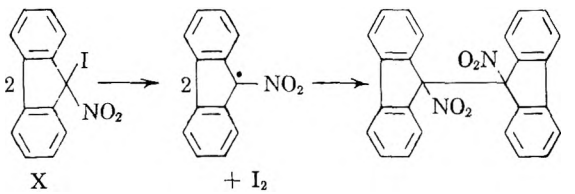
(3) E. H. White and W. J. Considine, *J. Am. Chem. Soc.*, in press.

(4) A compound isolated from the reaction of benzoyl chloride with the potassium salt of 3-nitroindene may be a third example [W. Wislicenus and K. Pfeilsticker, *Ann.*, **463**, 40 (1924)]. The authors proposed that the product was 1-benzoyl-3-nitroindene, but in view of the oxygen acylation observed with the related nitrofluorene, the product is probably *O*-benzoyl-3-*aci*-nitroindene.

(5) J. Thurston and R. Shriner, *J. Org. Chem.*, **2**, 183 (1937).

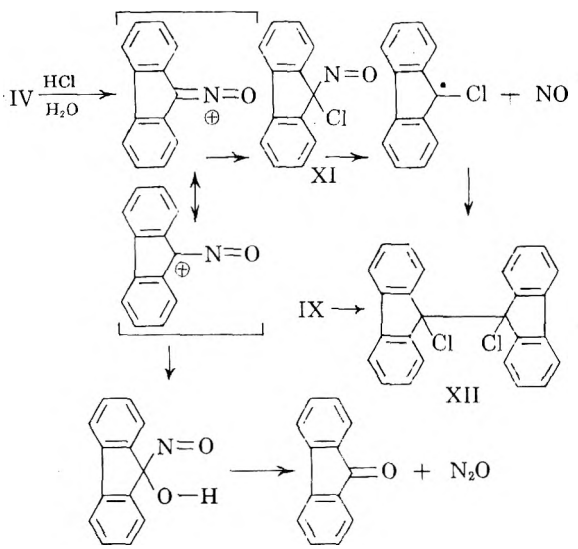
(6) C. D. Nenitzescu and D. A. Isacescu, *Bull. Soc. Chim. Romania*, **14**, 53 (1932); *Chem. Abstr.*, **27**, 964 (1934).

mentioned compound was synthesized independently from bifluorenyl (IX) by means of the Prevost reaction. A pyrolysis reaction similar to the one discussed has been reported for 9-iodo-9-nitrofluorene (X) by Nenitzescu and Isacescu.[7]

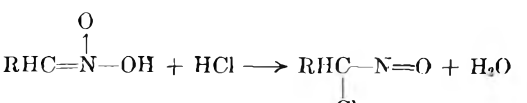


X + I_2

The acid hydrolysis of IV also led to a dimeric product, 9,9′-dichloro-9,9′-bifluorenyl (XII). Fluorenone is another product of this reaction. The formation of these products can be accounted for by the following analogous sequence of reactions.



The reaction leading to XI is very similar to one reported by Steinkopf and Jürgens,[8]



whereas the formation of fluorenone is probably an example of the Nef reaction.[9]

O-Benzoyl-*aci*-nitrophenylacetonitrile (III) also proved to be thermally labile. The reaction products in this case were rather complex, however, and they were not investigated further.

EXPERIMENTAL

Salts of 9-nitrofluorene. The potassium salt was prepared from fluorene and ethyl nitrate by essentially the method of Wislicenus and Waldmuller,[10] except that potassium *t*-butoxide in *t*-butanol was used as the base. A 72% yield of the salt was obtained. The sodium and ammonium salts were prepared from the potassium salt by the methods of Wislicenus and Waldmuller.[10]

O-Benzoyl-9-aci-nitrofluorene (IV). *Modification of the method of Nenitzescu and Isacescu.*[6] Benzoyl chloride (0.75 g., 5.4 mmoles) was added to a suspension of sodium 9-fluorenenitronate (1.40 g., 6.0 mmoles) in 50 ml. of methylene chloride. The mixture was stirred for 24 hr., then filtered. The solvent was removed *in vacuo* and the product was recrystallized from acetone to yield 0.745 g. of IV (2.4 mmoles, 45% based on the benzoyl chloride), m.p. 134–135° dec. (lit[6]. 134–136°). Infrared spectrum, $\lambda_{max}^{CHCl_3}$ 5.67 μ and 6.16 μ.

Anal. Calcd. for $C_{20}H_{13}O_3N$: C, 76.18; H, 4.16; N, 4.44. Found: C, 76.47; H, 4.03; N, 4.28.

Ammonolysis of O-benzoyl-9-aci-nitrofluorene. O-Benzoyl-9-*aci*-nitrofluorene (0.190 g., 0.60 mmole) was dissolved in 10 ml. of absolute ether and the solution was saturated with anhydrous ammonia gas. While protected from the atmosphere with a sodium hydroxide tube, the solution was stirred for 24 hr. The reaction mixture was filtered and the precipitate was washed with 100 ml. of anhydrous ether in small portions. A yellow powder, (0.12 g., 0.54 mmole, 87%) was obtained, m.p. 139–140° dec. (lit.[10] 146–148). The infrared spectrum of this material was identical with that of an authentic specimen of ammonium 9-fluorenenitronate.

The yellow filtrate and washes were combined and washed with 5% sodium hydroxide solution and then with water. The ether phase was dried over anhydrous magnesium sulfate. Evaporation of the ether yielded 0.042 g. (0.35 mmole, 58%) of faintly yellow plates. A comparison of the infrared spectrum of this material with that of an authentic sample of benzamide indicated clearly that the product was rather pure benzamide; every absorption band coincided with corresponding bands in the spectrum of the authentic benzamide.

Pyrolysis of O-benzoyl-9-aci-nitrofluorene. A solution of *O*-benzoyl-9-*aci*-nitrofluorene (1.0 g., 3.2 mmoles) in 50 ml. of carbon tetrachloride was refluxed for 24 hr. in a flask previously flushed with nitrogen and connected to a gas buret filled with mercury. Forty-three ml. of a colorless gas was collected in the buret at 24° and 766 Hg, or 34 ml. at STP (1.52 mmoles, 48%). The infrared spectrum of the gas was identical with that of a mixture of nitric oxide and carbon tetrachloride. When the gas infrared cell was opened to admit atmospheric oxygen, the gas turned brown and the infrared spectrum now obtained was that of nitrogen dioxide mixed with carbon tetrachloride.

When the carbon tetrachloride solution cooled, needles were deposited. This material was redissolved and the volume of the solution adjusted so as just to keep the material in solution at the boiling point. The solution was then allowed to cool. Tan needles were obtained which after one recrystallization from acetone gave 650 mg. of white prisms, m.p. 288.5–289.5°, undepressed when mixed with authentic 9,9′-dibenzoyloxy-9,9′-bifluorenyl. An additional 101 mg. was obtained from the mother liquor. A total of 0.75 g. of product was obtained (1.3 mmoles, 83%). The infrared spectrum of this material was identical with that of authentic 9,9′-dibenzoyloxy-9,9′-bifluorenyl.

Bifluorylidene (IX). *Modification of the method of Graebe and Stindt.*[11] A mixture of fluorene (25 g., 0.15 mole) and plumbous oxide (100 g., 0.45 mole) in a flask was immersed in an oil bath at a temperature of 250°. Over the course of 1 hr. the temperature was raised to 310° and it was held at 310°–320° for 1.5 hr. The reaction mass was cooled and extracted with boiling benzene. The hot benzene solution was filtered and the volume of the boiling solvent was adjusted so as just to keep the material in solution. Picric acid (15 g., 0.065 mole) was added and the solution was set aside to cool. A black crystalline mass was isolated by filtration. It was dissolved in ether and the ether was put

(7) C. D. Nenitzescu and D. A. Isacescu, *Ber.*, **63**, 2489 (1930).

(8) W. Steinkopf and B. Jürgens, *J. prakt. Chem.*, [2] **84**, 689, 711 (1911).

(9) W. E. Noland, *Chem. Revs.*, **55**, 137 (1955).

(10) W. Wislicenus and M. Waldmuller, *Ber.*, **41**, 3334 (1908).

(11) C. Graebe and H. Stindt, *Ann.*, **291**, 1 (1896).

onto a column of alumina. The column was washed with additional ether until no further colored material was eluted. The red ether solution was evaporated and the residue was recrystallized from benzene to give 1.74 g. (0.0053 mole, 7%) of red needles, m.p. 187–189° (lit.[11] 188°).

9,9'-Dibenzoyloxy-9,9'-bifluorenyl[12] (VIII). A mixture of bifluorylidene (0.332 g., 10 mmole), silver benzoate (0.458 g., 2 mmoles), and iodine (0.254 g., 1 mmole) was refluxed in 50 ml. of dry benzene until the initial red color of the mixture was discharged. The yellow solution was filtered hot and evaporated. The residue was extracted with boiling acetone and the resulting material was crystallized from the same solvent to yield 0.400 g. (0.7 mmole, 70%) of yellow rods, m.p. 281–284°. Clarification of a solution in acetone with Norite and further recrystallizations from acetone gave white prisms melting at 288–289.5°. Infrared spectrum, λ_{max}^{KBr} 5.80 μ.

Anal. Calcd. for $C_{40}H_{26}O_4$: C, 84.19; H, 4.59. Found: C, 84.19; H, 4.80.

Acid hydrolysis of O-benzoyl-9-aci-nitrofluorene. A solution of *O*-benzoyl-9-*aci*-nitrofluorene (0.125 g., 0.4 mmole) in 25 ml. of 90% aqueous dioxane 0.1*N* in HCl was kept at room temperature overnight. The solution was poured into 375 ml. of ether and the ether phase was washed with five 125-ml. portions of water. The ether was washed with two 125-ml. portions of a 5% sodium bicarbonate solution and then it was dried over magnesium sulfate. The sodium bicarbonate extract was acidified with 6*N* HCl and extracted successively with 250 ml. and 125 ml. of ether. The ether extracts were dried over magnesium sulfate and evaporated to give 0.042 g. (0.34 mmole, 87%) of white needles of benzoic acid, m.p. 116–118° (lit. 121.4°). The infrared spectrum of this material was essentially identical with that of authentic benzoic acid.

The first ether solution was evaporated to give 79 mg. of a yellow oil which was chromatographed on alumina. Two fractions were eluted with a 5% benzene–95% hexane mixture. The first fraction consisted of yellowish white crystals. Recrystallization from benzene-hexane and then benzene gave 0.040 g. (0.10 mmole, 0.20 meq., 50%) of white prisms, m.p. 238–241° dec. (lit.[13] 236°), undepressed when mixed with authentic 9,9'-dichloro-9,9'-bifluorenyl of m.p. 238–241°. The infrared spectrum in KBr was identical with that of an authentic specimen of 9,9'-dichloro-9,9'-bifluorenyl.

The second fraction consisted of 0.018 g. (0.10 mole, 25%) of yellow crystals of fluorenone. Sublimation of this material yellow plates, m.p. 67–69° (lit.[14] 83–84). The infrared spectrum was identical with that of an authentic specimen of fluorenone.

9,9'-Dichloro-9,9'-bifluorenyl (XII). *Modification of the method of Graebe and Mantz.*[15] Dry chlorine gas was passed through a solution of bifluorylidene (0.50 g., 1.5 mmoles) in 25 ml. of chloroform until the deep red color was discharged. The resulting yellow solution was evaporated to dryness. The crystalline residue was recrystallized twice from a benzene-hexane mixture and twice, after clarification with Norite, from hexane to give 0.149 g. (0.37 mmole, 24%) of white prisms of XII, m.p. 239–242° dec. (lit. 234°;[16] 235–236[13]).

O-Benzoyl-aci-nitrophenylacetonitrile (III). *Modification of the method of Thurston and Shriner.*[4] Benzoyl chloride (1.50 g., 10.5 mmoles) was added to a stirred suspension of sodium phenylcyanomethanenitronate (3.00 g., 16.3 mmoles) in 30 ml. of dry methylene chloride at room temperature. During five days of stirring in darkness, the benzoyl chloride reacted completely. The reaction mixture was then poured into water and the organic phase was washed with a sodium bicarbonate solution. The methylene chloride solution was dried and then evaporated in vacuum to yield 2.74 g. (10.3 mmoles, 96%) of III, m.p. 108–109° dec. Recrystallization from a methylene chloride-pentane mixture yielded 2.30 g. (8.65 mmoles, 82% based on benzoyl chloride) of pure O-benzoyl-*aci*-nitrophenylacetonitrile, m.p. 115–116° dec. (lit.[4] 116° dec.), infrared spectrum, $\lambda_{max}^{CHCl_3}$ at 4.50 μ, 5.67 μ, and 6.18 μ.

Pyrolysis of O-benzoyl-aci-nitrophenylacetonitrile. A solution of III (1.06 g., 3.98 mmoles) in CCl_4 (18.6 ml.) was refluxed for one day in a system free of oxygen. Fifty ml. (STP) of nitric oxide were evolved. The solvent was removed and the residue subjected to molecular distillation at 0.1 mm. Hg. A small volatile fraction was obtained with an odor reminiscent of benzoyl chloride. A second fraction was obtained at *ca.* 100°. Treatment with pentane yielded crystalline material, m.p. 129–131°, $\lambda_{max}^{CCl_4}$ 5.62 μ.

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.20. Found: C, 71.76; H, 3.96; N, 11.06.

The nonvolatile residue was a viscous oil with an absorption band at 5.74 μ. It may possibly be the dimer corresponding to VIII.

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(12) Method of C. Prevost, *Compt. rend.*, **196**, 1129 (1933).

(13) J. Schmidt and H. Wagner, *Ann.*, **387**, 147 (1912).

(14) E. Huntress, E. Hershberg, and J. Cliff, *J. Am. Chem. Soc.*, **53**, 2720 (1931).

(15) C. Graebe and B. Mantz, *Ann.*, **290**, 238 (1896).

Preparation of Some Substituted Allyl Hydroperoxides from Bromides[1]

JOSEPH HOFFMAN

Received March 12, 1957

The preparation of allyl hydroperoxide from allyl alcohol by way of the methanesulfonate has been described.[2] In the case of substituted allyl hydroperoxides, often the required alcohol is not available. It has now been found that such hydroperoxides may be prepared conveniently from substituted allyl bromides. These bromides are readily prepared by reaction of the appropriate olefin with *N*-bromosuccinimide,[3] and treatment of them with potassium hydroxide–hydrogen peroxide in an aqueous methanol medium at room temperature gives the hydroperoxides. These hydroperoxides can be extracted with benzene and purified through their sodium salts and subsequent distillation.

By this procedure, α- and β-diisobutylene hydroperoxides were prepared: 2-neopentylallyl hydroperoxide from 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentenyl hydroperoxide from 2,4,4-trimethyl-2-pentene. The method was extended to

(1) This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under contract No. AF 18(600)787.

(2) H. S. Mosher and S. Dykstra, *J. Am. Chem. Soc.*, **79**, 3474 (1957).

(3) K. Ziegler, A. Spaeth, E. Schaaf, W. Shumann, and E. Winkelmann, *Ann.* **551**, 80 (1942).

TABLE I

OPTIMUM CONDITIONS IN THE PREPARATION OF HYDROPEROXIDES

Brominated[a] Product	Methanol,[b] Ml.	Time, Hours	Hydroperoxide Yield, %[c]	Hydroperoxide Wt., g.[d]
I	450	40	50	7.0
II	450	40	35	5.5
III	375	20	65	7.8

[a] 1 mole of olefin and 0.5 mole of NBS were refluxed for 1–2 hr. in the presence of 0.1 g. of benzoyl peroxide and 200 ml. of carbon tetrachloride. NOTE: Occasionally these bromination reactions are very vigorous. The reflux condenser should be efficiently cooled and should lead into a Dry Ice-acetone trap in all cases. I, B.p. 47.5–49.5° (10 mm.), n_D^{20} 1.4744, yield 79%. II, B.p. 47–49° (10 mm.), n_D^{20} 1.4754, yield 75%. III, B.p. 39–40° (10 mm.), n_D^{20} 1.4736, yield 70%. [b] In addition, each reaction mixture consisted of 0.125 mole of bromide, 87 g. (0.75 mole) of 30% hydrogen peroxide and 40 g. (0.14 mole) of 20% potassium hydroxide. [c] Determined by iodometric titration of active oxygen in benzene extract. [d] Final distilled product.

(NBS), 0.1 g. of benzoyl-peroxide and 200 ml. of carbon tetrachloride was refluxed for about 2 hr. The product was worked up in the usual manner to give a 79% yield based on NBS.

A mixture of 24.0 g. (0.125 mole) of bromide, 450 ml. of methanol, 40 g. of 20% potassium hydroxide (0.14 mole) and 87 g. (0.75 mole) of 30% hydrogen peroxide was allowed to stand in a flask resting in a water bath at approximately 25° for 40 hr. The methanolic solution was then added to two volumes of water and saturated with ammonium sulfate. The hydroperoxide was extracted with four 200-ml. portions of benzene. The benzene extracts were washed with a saturated ammonium sulfate solution and then let stand over anhydrous magnesium sulfate. Iodometric titration[4] of an aliquot portion of the benzene solution indicated a yield of 9.0 g. of hydroperoxide (calculated as diisobutylene hydroperoxide) or 50%. The benzene solution was transferred to a separatory funnel and cooled to 12°. Sodium hydroxide (100% excess of stoichiometric in 40% concentration) was added at once and the separatory funnel was shaken vigorously for 3–5 min. The temperature rose to about 20° during shaking. After the formation of a precipitate, the mixture was cooled to 10° and washed, by decantation, with several fresh portions of cold benzene, then peroxide-free ether. After most of the final portion of ether had been removed, the mixture was cooled to 5–10° and the hydroperoxide was recovered by adding glacial acetic acid (equivalent to the sodium hydroxide used) dissolved in ether. This was added in several portions with vigorous shaking after each addition. The excess acetic acid was removed by washing with saturated aqueous sodium bicarbonate. Finally, the ethereal solution was dried over anhydrous magnesium sulfate, the ether was removed and the hydroperoxide was distilled on a small modified Claisen flask at a bath temperature of 65–70°.

TABLE II

PROPERTIES OF HYDROPEROXIDES

Hydroperoxide	B.P. °C.	B.P. Mm.	n_D^{20}	Formula	Analyses C Calcd.	C Found	H Calcd.	H Found
t-BuCH$_2$C(CH$_2$OOH)=CH$_2$[a]	58.5–59.5	5	1.4482	$C_8H_{16}O_2$	66.63	66.73	11.18	11.38
t-BuCH(CH$_2$OOH)=CCH$_3$[b]	58.5–59.5	5	1.4523	$C_8H_{16}O_2$	66.63	66.25	11.18	11.45
t-BuC(CH$_2$OOH)=CH$_2$[c]	48–49	5	1.4464	$C_7H_{14}O_2$	64.58	64.63	10.84	10.61

Significant infrared absorption bands (μ): [a] 3.00, 3.28, 6.09 and 11.90. [b] 2.95, 6.01 and 11.92. [c] 2.95, 3.21, 6.09 and 11.82.

the preparation of 2-*t*-butylallyl hydroperoxide from 2,3,3-trimethyl-1-butene.

In the bromination of 2,4,4-trimethyl-2-pentene, evidence was obtained for a shift of the double bond to the α-position with attachment of the bromine to the neopentyl carbon atom. The shift appeared to occur to the extent of 85–90%; this conclusion was drawn by a comparison of the infrared spectrogram of the bromide with those of α- and β-diisobutylene. Moreover, during the reaction of this bromide with alkaline hydrogen peroxide, there was a shift of the double bond back to the β position to give mainly β-diisobutylene hydroperoxide. Bromination of 2,4,4-trimethyl-1-pentene gave a product whose infrared spectrogram indicated little if any rearrangement of the double bond. This bromide on reaction with alkaline hydrogen peroxide gave α-diisobutylene hydroperoxide. Further evidence for the position of the double bonds in these two hydroperoxides is given below.

EXPERIMENTAL

2-Neopentylallyl hydroperoxide. A mixture of 1.0 mole of 2,4,4-trimethyl-1-pentene, 0.5 mole of *N*-bromosuccinimide

Evidence in proof of structure of α- and β-diisobutylene hydroperoxides. A 1% solution of the hydroperoxides in benzene was decomposed at 100° in an evacuated glass bomb. The unsaturated aldehydes thus formed were precipitated as 2,4-dinitrophenylhydrazones. The two aldehydes have been shown to form this derivative without migration of the double bond.[5] The dinitrophenylhydrazones were submitted to silicic acid chromatography: in the case of the α-diisobutylene hydroperoxide, the C_8-carbonyl derivatives consisted of about 97% 2-formyl-4,4-dimethyl-1-pentene and 3% 2-formyl-4,4-dimethyl-2-pentene; the β-hydroperoxide gave about 10% of the former and 90% of the latter. These

(4) V. R. Kokatnur and M. Jelling, *J. Am. Chem. Soc.*, **63**, 1432 (1941).

(5) D. J. Hadley, R. H. Hall, R. Heap, and D. I. H. Jacobs, *J. Chem. Soc.*, 1416 (1954).

derivatives were identified by comparison of their infrared spectrograms with those of authentic samples. Further evidence was shown by their ultraviolet spectra maxima in 95% ethanol: 2,4-dinitrophenylhydrazone of 2-formyl-4,4-dimethyl-1-pentene, 3720 Å (lit.[5] 3720 Å); 2,4-dinitrophenylhydrazone of 2-formyl-4,4-dimethyl-2-pentene, 3775 Å (lit.[5] 3780 Å).

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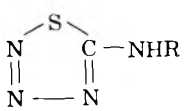
Communications TO THE EDITOR

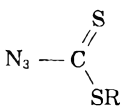
Assignment of Thiatriazole Structure to So-Called Azidodithiocarbonates

Sir:

Recent studies[1-3] on the chemistry of 5-substituted amino-1,2,3,4-thiatriazoles, I, has led to a reexamination of the structures of the products obtained by the condensation of azide ion with carbon disulfide previously designated in the literature[4] as *azidodithiocarbonates*, II.



I



II
III (R = H)
IV (R = C_6H_5CO—)

The reaction of sodium azide with carbon disulfide by the method of Smith, Wilcoxon, and Browne[5] followed by acidification of the concentrated aqueous solution led to the precipitation of pale yellow crystals which, after drying over phosphorus pentoxide, displayed all of the thermal and chemical properties for the compound designated[5] as *azidodithiocarbonic acid*, III. In a similar manner, *benzoylazidodithiocarbonate*, IV, was prepared by the method of Audrieth, Johnson, and Browne[6] which showed all of the thermal and chemical properties previously described[6] for that designation. The infrared spectra of III and IV were taken in saturated chloroform solutions, against chloroform, using a Perkin-Elmer Model 21-A Double-Beam Infrared Spectrophotometer. Table I summarizes the absorption frequencies obtained.

The most important observation arising from this study is the *complete absence* of the azido group, $-N_3$, absorbance in the infrared spectra of III and IV. Recent studies[8] have confirmed the strong absorbance for the azido group which occurs with great consistency close to 2130 cm.$^{-1}$ This intense N≡N asymmetric stretching absorption is so strong and so little altered by environmental groups as to make its absence in an infrared spectrum a guarantee that the compound under scrutiny is free of this structural group. For this reason the ideas previously presented in the literature[4-6] for the so-called *azidodithiocarbonates*, II, III, and IV, are in need of revision.

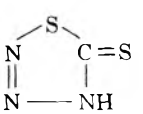
TABLE I

SUMMARY AND ASSIGNMENTS OF INFRARED ABSORPTIONS

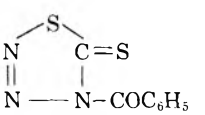
Frequency (Cm.$^{-1}$)		
Azidodithiocarbonic acid (III)	Benzoylazidodithiocarbonate (IV)	Assignments[a]
3030	Absent	NH
3005	Absent	NH
2533	Absent	N . . . . H
Absent	1680	=N—CO—
1590	1590[b]	—N=N—
		—C=C—C_6H_5
1470	1450	>N—C=S
1333	1333	C=S
Absent	1180[c]	C_6H_5CO
1100	1100	C—N
Absent	1000	C_6H_5
900	900	—N—S—C—[d]

[a] Based on data summarized by Bellamy.[7] [b] This is exhibited as a doublet. [c] This is exhibited as a very broad doublet with strong absorption. [d] Heterocyclic ring configuration.

An analysis of the infrared spectral data, Table I, coupled with the chemical properties of III and IV previously reported[5,6] suggests that these compounds *are derivatives of 1,2,3,4-thiatriazole.* On this basis we have assigned structure V, 4*H*,1,2,3,4-thiatriazoline-5-thione (which may be abbreviated to thiatriazolinethione), and VI, 4-benzoyl-1,2,3,4-thiatriazoline-5-thione (which may be abbreviated to 4-benzoylthiatriazolinethione), to the products previously designated as III and IV, respectively:

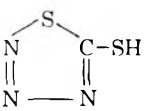


V

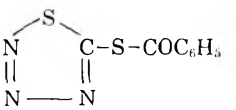


VI

The choice of structures V and VI over the alternate tautomeric *thiol* forms, VII and VIII, were



VII

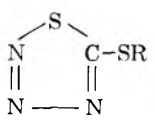


VIII

dictated by the spectra and, especially in the choice

(1) E. Lieber, E. Oftedahl, C. N. Pillai, and R. D. Hites, *J. Org. Chem.*, **22**, 441 (1957).
(2) E. Lieber, C. N. Pillai, and R. D Hites, *Can. J. Chem.*, **35**, 832 (1957).
(3) E. Lieber and C. N. Pillai, *J. Org. Chem.*, **22**, 1054 (1957).
(4) L. F. Audrieth, *Chem. Revs.*, **15**, 169 (1934).
(5) G. B. L. Smith, F. Wilcoxon, and A. W. Browne, *J. Am. Chem. Soc.*, **45**, 2604 (1923).
(6) L. F. Audrieth, J. R. Johnson, and A. W. Browne, *J. Am. Chem. Soc.*, **52**, 1928 (1930).
(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen and Company, Ltd., London, 1954.
(8) E. Lieber, C. N. R. Rao, T. S. Chao, and C. W. W. Hoffman, *Anal. Chem.*, **29**, 916 (1957).

of VI, by degradative and kinetic evidence.[6,9,10] The chemical and kinetic evidence[6] further indicates a widely disparate structural alteration for the so-called *alkyl azidodithiocarbonates* over that of the so-called acyl *azidodithiocarbonates*. This evidence points to the structure, IX, for the *alkyl azidodithiocarbonates:*



IX

X · R = CH_3)

These structures easily explain the fact that the *alkyl azidodithiocarbonates* invariably formed *normal thiocyanates* while the *acyl azidodithiocarbonates* yield *isothiocyanates:*

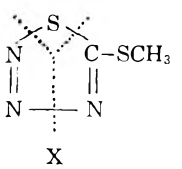
$$RSCSN_3 \longrightarrow RSCN + N_2 + S$$

$$RCOSCSN_3 \longrightarrow RNCS + N_2 + S$$

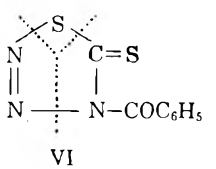
Audrieth, Johnson, and Browne[6] suggested that in the case of the acyl derivative ($R = C_6H_5$) the *normal thiocyanate* is first formed as an intermediate and immediately undergoes rearrangement to the *isothiocyanate:*

$$RCOSCN \longrightarrow RCONCS$$

Unfortunately not much is known about the above interconversion. However, the literature[11] indicates that this is not an easy process. On the other hand, by the assignment of structures X and VI, the mode of ring rupture indicated



X



VI

produces all of the degradation products without the need of postulating a rearrangement of *normal-* to an *iso-thiocyanate* in the case of the benzoyl derivative. The indicated mode of ring rupture is exactly the same as described for the 5-substituted amino-1,2,3,4-thiatriazoles,[2,3] I.

(9) It is interesting to note that as early as 1922, Oliveri-Mandala, *Gazz. chim. ital.*, **52**, II, 139 (1922) in a general discussion on the addition of hydrazoic acid to systems containing adjacent double bonds had postulated that the addition of HN_3 to CS_2 could lead to structures III, V, and VII but rejected V and VII in favor of III on the basis of degradative evidence.

(10) The absence of the SH stretching vibration between 2600–2500 cm.$^{-1}$ coupled with the strong absorbancies for C=S; —N—C=S; and —N—C(=O)— (Table I) were decisive. Studies in this laboratory show that the very strong absorbance at 900 cm.$^{-1}$ can be taken as indicative of a heterocyclic —N—S—C— grouping.

(11) H. E. Williams, *Cyanogen Compounds*, Edward Arnold and Co., London, 2nd ed. 1948, p. 321.

These studies are continuing and will subsequently be reported upon in detail.

Acknowledgment. The authors are indebted to the Research Corp. and the Eli Lilly Co. for research grants which made these studies possible.

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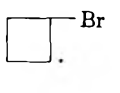
Received July 30, 1957

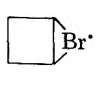
The Hunsdiecker Reaction of Optically Active Silver *trans*-Cyclobutane-1,2-dicarboxylate

Sir:

In view of recent interest in the mechanism of the brominative decarboxylation (Hunsdiecker reaction) of cyclic 1,2-dicarboxylates,[1] we wish to make a preliminary report of an experiment which further elucidates the stereochemistry of that reaction. It has been shown that brominative decarboxylations of *cis-* and *trans*-cyclobutanedicarboxylate[2] and of *cis-* and *trans*-cyclohexanedicarboxylate[1] lead to the corresponding *trans*-1,2-dibromocycloalkanes. Abell[1] had pointed out that these results may be explained in terms of the usual free-radical mechanism ($RCO_2Ag \rightarrow RCO_2Br \rightarrow R\cdot \rightarrow RBr$)[3] either by a steric effect in the addition of a bromine atom to radical I or by the intermediacy of a bridged radical, II, which would yield *trans*-dibromide if the ring opened with inversion of configuration. A third possibility is that radical III,



I



II

III IV

formed in the first phase of the decomposition of the bishypobromite, might decompose to the cycloolefin, IV, which could then add bromine by an ionic mechanism.

Reaction paths involving II or IV would almost necessarily give racemic *trans*-dibromocycloalkane, whereas a stepwise, sterically controlled, stereospecific introduction of bromines by way of III and I could give optically active product from optically active *trans*-dicarboxylate.

(1) P. I. Abell, *J. Org. Chem.*, **22**, 769 (1957).

(2) E. R. Buchman, J. C. Conly, and D. R. Howton, N6onr-244/XI Tech. Rept., California Institute of Technology, 1951, p. 90; *cf.* E. Vogel, *Fortschr. chem. Forsch.*, **3**, 430 (1955).

(3) R. G. Johnson and R. K. Ingham, *Chem. Revs.*, **56**, 219 (1956).

Addition of the silver salt of (−)-*trans*-cyclobutane-1,2-dicarboxylic acid[4] having $[\alpha]_D^{25}$ −83.4° (water) (about 46% racemic) to the theoretical amount of bromine in refluxing carbon tetrachloride[2] gave as 32% of the neutral product *trans*-1,2-dibromocyclobutane, distilled through a semimicro column at 20 mm. with a pot temperature of 120°. The purest fraction contained 4% (by vapor chromatographic analysis) of a higher boiling, unsaturated, unidentified contaminant, and had $[\alpha]_D^{27}$ −6.0° (carbon tetrachloride), m.p. −38 to −22°, and n_D^{25} 1.5358. *Anal.* Calcd. for $C_4H_6Br_2$: C, 22.46; H, 2.83. Found: C, 22.74; H, 2.87. (Buchman[2] had shown that the dibromide product from racemic *trans*-dicarboxylate was identical with that from addition of bromine to cyclobutene, and reported for the dibromide b.p. 72–4°/20mm., n_D^{25} 1.5343, m.p. −1° to +1°.) It was shown that the unknown contaminant was not responsible for the optical activity of the dibromide, since a higher boiling fraction of the reaction product (5 mm., pot temp. 150°) contained about 55% of the unknown and yet possessed $[\alpha]_D^{27}$ −3.3° (carbon tetrachloride).

It may be concluded that the reaction does not proceed entirely, if at all, through symmetrical intermediates such as II or IV, if we assume that neither asymmetric addition of bromine atoms to these intermediates nor asymmetric destruction of racemic dibromide in the reaction mixture occurs. These reasonable assumptions will be checked by further experiments, which should also reveal the optical yield and stereochemistry (double retention or double inversion) of the reaction.

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Adrian S. Fox

Received August 12, 1957

(4) L. J. Goldsworthy, *J. Chem. Soc.*, 125, 2012 (1924).

Ortho Alkylation of Aniline with Styrene

Sir:

Recent publications[1,2] on the *ortho* alkylation of aromatic amines in the presence of aluminum anilide type catalysts prompt us to report some unusual results which were obtained during a reinvestigation of the Hofmann-Martius[3] and Reilly-Hickinbottom[4] rearrangements. Hickinbottom[5] discovered that a mixture of aniline and its hydrochloride reacted with styrene at 200–240° (sealed tube) in 6 hr. to give a 28.4% yield of α-phenethylated anilines, 7.5% *ortho*, 17.7% *para* and 3.2% N, by isolation. Under what presumably were identical conditions, we consistently obtained an 82–85% yield of monoalkylated aniline which promptly crystallized to give a 74–77% isolated yield of *ortho-α-phenethylaniline*, m.p. and mixed m.p. 58.5–59.0°. Infrared analysis showed only 5–10% of the *para* isomer in the crude product; *N*-α-phenethylaniline was apparent (infrared) after 1 but not 6 hr. Aniline and α-phenethyl chloride gave similar, but not identical results; no alkylation of aniline by styrene was observed without the hydrochloride being present. But *N*-α-phenethylanilinium chloride, under essentially identical conditions, gave only 19–24% of mono-C-alkylate, 60–70% the *para* isomer.

We have no explanation at present for the discrepancy between our results and those of Hickinbottom. Complete details, and a rationalization of the different isomer distributions obtained by direct alkylation and by rearrangement of the anilinium salt, will be published shortly. The scope of this *ortho* alkylation is being investigated further.

This work was supported in part by a grant from the Research Corporation, for which we are grateful.

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(1) G. G. Ecke, J. P. Napolitano and A. J. Kolka, *J. Org. Chem.*, 21, 711 (1956).

(2) G. G. Ecke, J. P. Napolitano, A. H. Filbey and A. J. Kolka, *J. Org. Chem.*, 22, 639 (1957).

(3) A. W. Hofmann and C. A. Martius, *Ber.*, 4, 742 (1871).

(4) J. Reilly and W. J. Hickinbottom, *J. Chem. Soc.*, 117, 103 (1920).

(5) W. J. Hickinbottom, *J. Chem. Soc.*, 319 (1934).

Synthesis of 2-Heptafluorobutyrylthiophene

Sir:

The preparation of 2-heptafluorobutyrylthiophene has been accomplished by the Grignard method after previous failures using other synthetic techniques. Although aliphatic acids have been successfully condensed with thiophene using P_2O_5 as the condensation agent,[1,2] the use of a totally fluorinated acid such as heptafluorobutyric acid resulted only in its conversion to the acid anhydride by the condensation agent. The use of the anhydride was also unsuccessful. It has also been found that the acylation of thiophene with organic

(1) H. D. Hartough and A. I. Kosak, *J. Am. Chem. Soc.*, 69, 3098 (1947).

(2) H. Wynberg and A. Logothetis, *J. Am. Chem. Soc.*, 78, 1958 (1956).

acid anhydrides may be effected by the use of catalytic amounts of substances such as iodine or hydriodic acid,[3] zinc chloride,[4] phosphorus pentoxide,[5] and stannic chloride or BF_3-etherate.[6] As in the previous case, the use of a fluorinated anhydride, such as heptafluorobutyric anhydride, in the acylation reaction with the above catalysts, gave no product or produced only tars. Similar results were encountered by a Friedel-Crafts type reaction in the presence of aluminum chloride.[7] This reaction was carried out at low temperature using the acid chloride as the acylating agent without the use of solvent and also in the presence of nitrobenzene.

We now wish to describe the synthesis of 2-heptafluorobutyrylthiophene which may be generally applicable to condensation reactions involving a fluoro-alkyl group and a cyclic-type compound. Thiophene magnesium bromide was first prepared from 2-bromothiophene and magnesium by the standard Grignard method. The volatile heptafluorobutyryl chloride was then prepared by the slow addition of heptafluorobutyric acid to phosphorus pentachloride using a Dry Ice–alcohol trap. The Grignard was added slowly to a mixture of the acid chloride and ether over a period of 90 min. and then refluxed for several hours. The contents were added to a 10% ice–NH_4Cl solution. The separated ether layer was neutralized with 10% K_2CO_3 and finally dried over anhydrous sodium sulfate. Distillation gave a 32% yield of ketone, b.p. 91.5–92.1° at 32 mm.

Anal. Calcd. for $C_8H_3OF_7S$: C, 34.29; H, 1.08; F, 47.47. Found: C, 34.13; H, 1.25; F, 46.85.

The compound was characterized by the 2,4-dinitrophenylhydrazone, m.p. 90.2–90.8°.

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(3) H. D. Hartough and A. I. Kosak, *J. Am. Chem. Soc.*, **68**, 2639 (1946).

(4) H. D. Hartough and A. I. Kosak, *J. Am. Chem. Soc.*, **69**, 1012 (1947).

(5) T. Steinkopf, *Ann.*, 413, 346 (1917).

(6) M. W. Farrar and R. Levine, *J. Am. Chem. Soc.*, **72**, 4433 (1950).

(7) J. H. Simons, W. T. Black, and R. F. Clark, *J. Am. Chem. Soc.*, **75**, 5621 (1953).

Additions and Corrections

VOL. 21, 1956

F. Shafizadeh and A. Thompson: An Evaluation of the Factors Influencing the Hydrolysis of the Aldosides.

Page 1061. In Table I, columns 4 and 5, the 3rd and 4th entries from the bottom (3.8 and 5.5; 9.0 and 13.1) should be interchanged. A. THOMPSON, MAY 16, 1957.

VOL. 22, 1957

Normal Allentoff and G. F Wright: Grignard Synthesis of 2-Phenyl-2-butanol in Optically Active Solvents.

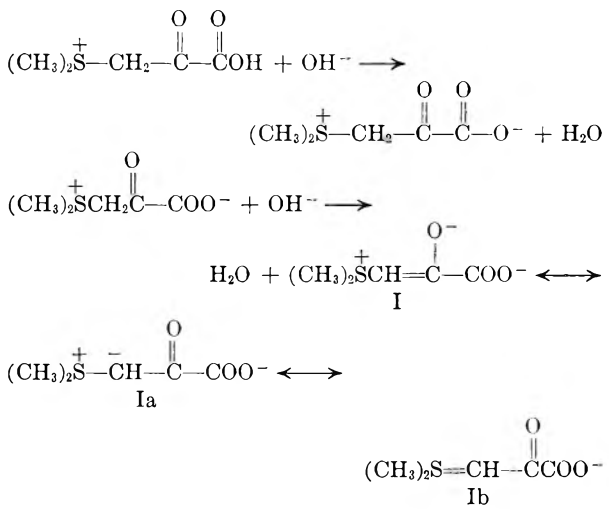
Page 1. The name of the first author should read Norman Allentoff. G. F WRIGHT, MARCH 21, 1957.

Mark D. Baelor and George Gorin: Ester Derivatives of Mucic Acid.

Page 65. The name of the first author should read Mark D. Bealor. MARK D. BEALOR, MAY 7, 1957.

N. F. Blau and C. G. Stuckwisch: The Conjugative Effect of the Dimethylsulfonio Group in an Aliphatic System.

Page 82. In paragraph 1, correct equations are



In paragraph 2, line 6, for conjugative read conjugative. N. F. BLAU, October 25, 1957.

Harold Kwart and Lewis G. Kirk: Steric Considerations in the Darzens Condensation.

Page 116. A recent communication we have received from Professor M. Ballester of the University of Barcelona directs attention to an article which he published in 1954; [*Anales real soc. espan. fis. y quim.*, Madrid, **50B**, 759, (1954)]. This article was not available to us in the Spanish original when we submitted our publication in 1956. The *Chemical Abstracts* version which we read does not disclose the claim that Professor Ballester makes to having given earlier consideration to the possibility of two diastereomerically related transition states in the Darzens condensation.

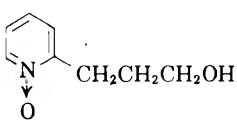
This difficulty in international communications is sincerely regretted. HAROLD KWART, JUNE 25, 1957.

H. J. V. Krishna and B. N. Joshi: A Note on the Preparation of β-Ionone.

Page 224. We wish to correct the statement that Y. R. Naves and co-workers had not studied the preparation of β-ionone by cyclization of pseudoionone by means of a mixture of 175 g. of concd. H_2SO_4 (95%) and 75 g. of glacial acetic acid. Prof. Naves has drawn our attention to a publication of his [Y. R. Naves and P. Ardizio, *Bull. soc. chim. France*, **21**, 661–6 (1954)] wherein he reported that he had repeated the experiment of Royals [*Ind. Eng. Chem.*, **38**, 546 (1946)] using the above mentioned reagent and reached a conclusion similar to ours. H. J. V. KRISHNA AND B. N. JOSHI, AUGUST 20, 1957.

V. Boekelheide and Wayne Feely: A Convenient Synthesis of Pyrrocoline.

Page 589. Formula I should be



V. BOEKELHEIDE

Carl Tabb Bahner, Joan Wilson, Mary West, George Browder, J. C. Goan, Clarence Cook, John Fain, Edgar Franklin, and Albert Myers: Isoquinoline Analogs of 4-(*p*-Dimethylaminostyryl)quinoline.

Page 684. In col. 2, line 1 of paragraph 5, for *4-(p-Dimethylaminostyryl)quinoline* read *4-(p-Dimethylaminostyryl)-quinazoline.* CARL TABB BAHNER, November 18, 1957.

H. Gilman and R. D. Gorsich: An Improved Metalation Procedure for Dibenzofuran.

Page 687. In col. 2, lines 2 and 3 from bottom, for "derived" read "derivatized." HENRY GILMAN, AUGUST 6, 1957.

A. H. Blatt and Norma Gross: Replacement of Halogen by Hydrogen in Nitro Aryl Halides.

Page 1047. In paragraph 3, line 4, "0.56*M*" should read "0.056*M*." A. H. BLATT, November 13, 1957.

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Subject Index 1957 VOLUME 22