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Isomer Distribution in the Aluminum Chloride–Catalyzed Benzoylation of Toluene in Nitrobenzene[1-3]

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Pure samples of *o*-, *m*-, and *p*-methylbenzophenone were synthesized and a procedure developed for the infrared analysis of mixtures of these three components. The method was applied to the product obtained in the aluminum chloride-catalyzed reaction of benzoyl chloride with toluene at 25° in nitrobenzene solution. The results indicate the following isomer distribution: *ortho*-, 7.2%; *meta*-, 1.1%; *para*-, 91.7%. The presence of the *ortho*- isomer was confirmed by the preparation and isolation of solid derivatives. It was demonstrated that the reaction products do not undergo isomerization under the conditions of the benzoylation reaction. Consequently, the observed isomer distribution can be taken as a measure of the relative rates of reaction at the *ortho*-, *meta*-, and *para*- positions. The low yield of the *ortho*- isomer suggests that the substituting species must have large steric requirements. The large *para*-/*meta*- ratio indicates that the benzoylation reaction must be one of high selectivity.

The Friedel-Crafts acylation of simple monosubstituted benzene derivatives is commonly considered to result only in *para*-substitution.[5] Early reports exist of the formation of small amounts of the *ortho*- isomer during the benzoylation of toluene.[6,7] However, more recently it has been claimed that the acetylation and benzoylation of toluene result in the exclusive formation of the *para*- isomer.[8,9] No reports exist of the formation of the *meta*- isomer in the acylation of toluene,[10] although it has been reported recently that the acetylation of *t*-butylbenzene at 0° results in the formation of 1.8% of the *meta*- and 98.2% of the *para*- acetyl derivatives.[11]

Recently a quantitative relationship was proposed between the "activity" of a substituting agent, as measured by log ($k_{\text{toluene}}/k_{\text{benzene}}$) or log p_f, and its "selectivity," as measured by log (*para*-/*meta*-) or log (p_f/m_f).[12,13] In the acetylation reaction, toluene has been reported to react 8.35 and 13.3 times as fast as benzene.[14,15] On the basis of the proposed relationship, a yield of approximately 5% of the *meta*- isomer would be expected for a toluene/benzene ratio of this magnitude.

In view of the failure of numerous workers to observe any *meta*- isomer, a careful examination of this reaction appeared desirable. Accordingly, we undertook to establish the isomer distribution and the toluene/benzene rate ratio with high precision

(1) Directive Effects in Aromatic Substitution. XVI.

(2) Supported in part by the Petroleum Research Fund of the AMERICAN CHEMICAL SOCIETY.

(3) Based upon a thesis submitted by Herbert L. Young in 1956 in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(4) Standard Oil Co. (Indiana) Fellow at Purdue University, 1953–1955.

(5) C. A. Thomas, *Anhydrous Aluminum Chloride in Organic Chemistry*, Reinhold Publishing Corp., New York, N. Y., 1941, p. 206.

(6) E. Elbs, *J. prakt. Chem.* [2], **35**, 466 (1887).

(7) W. D. Cohen, *Rec. trav. chim.*, **38**, 113 (1919).

(8) R. Pajeau, *Bull. soc. chim.* [5], **13**, 544 (1946).

(9) E. Koike and K. Okawa, *J. Chem. Soc. Japan*, **75**, 85 (1954).

(10) A number of examples of *meta* orientation have been described in the acylation of *alpha* substituted toluenes in which the *alpha* substituents are *meta* directing. W. Borsche and F. Simm, *Ann.*, **553**, 260 (1942); F. Kunckell, *Ber.*, **39**, 3145 (1906); D. Papa, E. Schwenk, and A. Klingsberg, *J. Am. Chem. Soc.*, **68**, 2133 (1946).

(11) J. C. Butler, L. L. Ferstandig, and R. D. Clark, *J. Am. Chem. Soc.*, **76**, 1906 (1954).

(12) H. C. Brown and K. L. Nelson, *J. Am. Chem. Soc.*, **75**, 6292 (1953).

(13) H. C. Brown and C. W. McGary, *J. Am. Chem. Soc.*, **77**, 2300 (1955).

(14) Y. Ogata and R. Oda, *Bull. Inst. Phys. Chem. Res. (Tokyo)*, **21**, 728 (1942).

(15) H. F. McDuffie and G. Dougherty, *J. Am. Chem. Soc.*, **64**, 297 (1942).

in order to test whether the acylation reaction constitutes a possible exception to the proposed quantitative treatment. In view of the higher volatility and lower stability of acetyl chloride as compared to benzoyl chloride, we selected the latter acylating agent for study.

RESULTS

Infrared spectroscopy was used for the analysis of the isomeric methylbenzophenones in the reaction product. This procedure required the synthesis of the three isomeric ketones in high purity for use as infrared standards. The physical properties of these derivatives are summarized in Table I.

TABLE I

PHYSICAL CONSTANTS OF *o*-, *m*- AND *p*-METHYLBENZOPHENONES

	Methylbenzophenones		
	ortho	*meta*	*para*
Freezing point, obsd., °C.[a]	11.81	glass	56.94
Freezing point, calcd., °C.[a,b]	11.84		57.00
Purity, mole %[a]	99.9		99.9
M.p., °C.		0–2	
B.p., °C. (mm.)	162.2(10)	172.6(10)	177.4(10)
	185.5(25)	195.8(25)	199.9(25)
	205.0(50)	214.9(50)	218.6(50)
n_D^{20}	1.5949[c]	1.5993[d]	
d_4^{25} g./ml.	1.0829	1.0832[e]	
M.p. of 2,4-dinitrophenylhydrazone	198.5–199.5[f]	221–222[g]	236–237[h]
M.p. of oxime	108–109[i]		

[a] Cooling curve data; mean value of two determinations. [b] Freezing point corrected to 0% impurity. [c] E. Koike and K. Okawa, *J. Chem. Soc. Japan*, **75**, 85 (1954) report n_D^{20} 1.5895. [d] E. Koike and K. Okawa, *loc. cit.*, report n_D^{20} 1.5982; J. W. Melton and H. R. Henze, *J. Am. Chem. Soc.*, **69**, 2018 (1947) report n_D^{20} 1.5970. [e] J. W. Melton and H. R. Henze, *loc. cit.*, report d_4^{20} 1.095. [f] M. S. Newman and C. D. McCleary, *J. Am. Chem. Soc.*, **63**, 1537 (1941) report m.p. 184–190°. [g] M. S. Newman and C. D. McCleary, *loc. cit.*, report m.p. 220.4–221.4°. [h] W. S. Grieve and D. H. Hey, *J. Chem. Soc.*, 1797 (1934) report m.p. 199–200°. [i] I. I. Lapkin and A. V. Lyubimova, *J. Gen. Chem.* (*U.S.S.R.*), **19**, 707 (1949) report m.p. 104–105°.

The infrared spectra of the individual methylbenzophenones indicated differences sufficiently characteristic to be promising for the analysis of isomeric mixtures. Synthetic mixtures were prepared and analyzed successfully.

Nitrobenzene has frequently been utilized to provide homogeneous conditions for acylation reactions. Accordingly, the benzoylation of toluene was carried out at 25° in this solvent employing benzoyl chloride and aluminum chloride. The higher boiling methylbenzophenones were separated from the nitrobenzene solvent by fractional distillation. Yields of 87–96% of the isomeric methylbenzophenones were obtained in reaction times of 2.5–5.5 hr.

There is some evidence for the isomerization of aromatic ketones in the presence of hydrogen chloride and excess aluminum chloride.[16] It was therefore necessary to test the possibility of isomerization under the conditions adopted for the acylation reaction. Accordingly, pure samples of the methylbenzophenones were dissolved in nitrobenzene together with aluminum chloride, benzoyl chloride, and hydrogen chloride to give a solution related in composition to the acylation reaction mixtures. After reaction periods of 6.5–25 hours at 25°, the products were isolated and analyzed by infrared spectrophotometry. As far as could be ascertained, the spectra were identical with those of the materials introduced. It was concluded that isomerization is not a factor under the reaction conditions.

Infrared analyses pointed to the presence of approximately 92% of the *p*- and 8% of the *o*-, with but traces of *m*-methylbenzophenone indicated. Upon balancing out the absorption of the *ortho*- and *para*- isomers by means of a suitable standard mixture in the reference cell of the double-beam spectrophotometer, small but definite absorption bands appeared at 8.3, 10.5, 12.9 and 14.0μ. Since these are characteristic absorption bands for the *meta*- isomer, its presence in the reaction mixture was thereby established. However, the compound was evidently present in quite small amounts. After considerable experimentation, it became apparent that a precise analysis of the minor components, especially the *meta*- isomer, would require the separation of a considerable portion of the predominant *para*- isomer.

Fractional distillation was examined. A typical benzoylation reaction product was carefully distilled under reduced pressure in a column rated at 100 theoretical plates. There was obtained a small fraction (~5%) which distilled at a lower temperature than that of the *para*- isomer. The identity of this fraction as *o*-methylbenzophenone was confirmed by the preparation of its oxime and 2,4-dinitrophenylhydrazone (Table I) and mixed melting points of the derivatives with authentic samples. Unfortunately, the distillation proved difficult and we were unable to achieve clear-cut separation into definite plateaus. Consequently, this approach was abandoned.

p-Methylbenzophenone melts at 57°, considerably higher than the other isomers. It proved possible to utilize a series of repeated fractional crystallizations to achieve the separation of 75–85% of the material as the pure *para*- isomer. The mother liquor, now greatly enriched in the *ortho*- and *meta*- isomers, could now be successfully analyzed for the three isomers by infrared. The results of five individual preparations and analyses are presented in Table II.

The isomer distributions were determined for reaction mixtures containing aluminum chloride

(16) G. Baddeley, *Quarterly Reviews*, **8**, 355 (1954) and references there cited.

TABLE II

ISOMER DISTRIBUTION IN THE ALUMINUM CHLORIDE-CATALYZED REACTION OF BENZOYL CHLORIDE WITH TOLUENE AT 25° IN NITROBENZENE SOLUTION

Initial Concentration of Reactants, *M*			Methylbenzophenone Product			
Benzoyl chloride	Aluminum chloride	Toluene	*Ortho-*	*Meta-*	*Para-*	Yield, %
0.66	1.3	1.3	8.0	1.0	91.0	96.0
1.0	1.0	1.0	7.4	1.2	91.4	87.0[a]
0.57	1.1	1.1	6.8	1.1	92.1	89.5
0.95	0.95	1.4	7.4	1.2	91.4	88.0
0.24	0.47	0.47	6.6	1.1	92.3	90.0
		Mean	7.2 ± 0.4	1.1 ± 0.1	91.7 ± 0.5	

[a] Additional 4.9% of benzoyl chloride accounted for (recovered as benzoic acid).

($AlCl_3$) and benzoyl chloride in a molar ratio of 1.0 and 2.0. Since the isomer distribution appeared to be independent of this ratio, all of the values obtained were utilized to calculate a mean product composition (Table II).

DISCUSSION

The identification of 7.2% of *o*- and 1.1% of *m*-methylbenzophenone in the product demonstrates that the acylation reaction is predominantly, but not exclusively, *para* substituting.

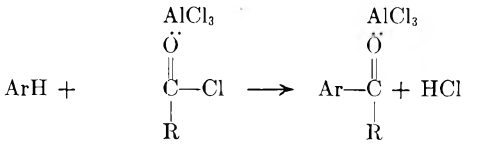
The small amount of *ortho* isomer suggests that the substituting species must be one of large steric requirements. It has been suggested frequently that the function of the aluminum chloride in the acylation reaction is to ionize the acyl halide, followed by an attack of the acylonium ion on the aromatic.[17,18]

$$RCOCl + AlCl_3 \longrightarrow RCO^+ + AlCl_4^-$$

$$RCO^+ + ArH \longrightarrow RCOAr + H^+$$

The large steric requirements exhibited by the reaction suggests that the attacking species cannot be the simple acylonium ion. The steric requirements of such an ion would be expected to be no greater than those of the isopropyl cation. Yet isopropylation of toluene results in the formation of 26.2% of the *ortho*-isomer.[19]

The addition compounds of aluminum chloride with acid chlorides are now believed to have the metal halide coordinated with oxygen atom of the carbonyl group.[20] A direct attack of this addition compound on the aromatic would be far more consistent with the observed large steric factor.[21]



The high *para-*/*meta-* ratio indicates that the benzoylation reaction must be a highly selective one. The yield of 98.2% of *para-* and 1.8% of *meta-* in the acetylation of *t*-butylbenzene[11] suggests that acetylation must also be highly selective, although somewhat less so than benzoylation.[22] These conclusions are not in accord with the relatively low toluene/benzene rate ratios previously noted.[14,15] However, distributions and rate ratios are for different conditions and, for that reason, are not strictly comparable.

A procedure was recently proposed for calculating the partial rate factors (o_f, m_f, p_f) and relative rate of reaction (k_T/k_B) for any electrophilic substitution reaction of toluene solely from the isomer distribution.[19] The following relationships are used:

$$\log m_f = 0.309 S_f$$

$$\log o_f^{2.3} = 1.310 S_f + \log\left(\frac{\%\ ortho\text{-}}{2 \times \%\ para\text{-}}\right)$$

$$\log (k_T/k_B) = 1.310 S_f - \log\left(\frac{6 \times \%\ para\text{-}}{100}\right)$$

The selectivity factor, S_f, is defined as $\log p_f/m_f$, but may be calculated directly from the isomer distribution,

$$S_f = \log\left(\frac{2 \times \%\ para\text{-}}{\%\ meta\text{-}}\right)$$

Using these relationships, the partial rate factors and the relative rate of benzoylation of toluene to benzene may be calculated from the observed isomer distribution (Table II):

$$o_f = 32.0$$
$$m_f = 4.9$$
$$p_f = 817$$
$$k_T/k_B = 149$$

The predicted relative rates of benzoylation differ markedly from the observed acetylation rates.[14,15] Recently, the rates of benzoylation of benzene and toluene in bromobenzene as solvent were measured.[24] The rate ratio at 40°, $k_T/k_B = 53$, is in better agreement, but still differs considerably from the predicted value of 149. A rate study under conditions identical with those utilized for the isomer

(17) H. Meerwein, *Ann.*, **455**, 227 (1927).

(18) E. R. Alexander, *Ionic Organic Reactions*, John Wiley and Sons, New York, N. Y., 1950, p. 260.

(19) H. C. Brown and C. R. Smoot, *J. Am. Chem. Soc.*, **78**, 6255 (1956).

(20) N. N. Lebedev, *J. Gen. Chem. U.S.S.R.*, **21**, 1788 (1951). B. P. Surz and I. Cooke, *Helv. Chim. Acta*, **37**, 1273 (1954). I. Cooke, B. P. Surz, and C. Herschmann, *Helv. Chim. Acta*, **37**, 1280 (1954).

(21) A detailed examination of the mechanism of the acylation reaction has been completed by Dr. Frederick R. Jensen and will be prepared for publication shortly.

(22) The *para-*/*meta-* ratios in the nitration of toluene (8.45) and *t*-butylbenzene (6.32) are quite similar. K. L. Nelson and H. C. Brown, *J. Am. Chem. Soc.*, **73**, 5605 (1951).

(23) When steric effects are not important, the alternative relationship, $\log o_f = 1.215 S_f$, can be used.

(24) F. Smeets and J. Verhulst, *Bull. soc. chim. Belg.*, **63**, 439 (1954).

TABLE III

DATA FOR ISOMER DISTRIBUTION RUNS

Benzoyl Chloride		Aluminum Chloride		Toluene		Nitrobenzene,	Time,
Wt. (g)	Moles	Wt. (g).	Moles	Wt. (g.)	Moles	Ml.	Hr.
77.9	0.554	146.7	1.10	101.6	1.10	600	2.5
422.3	3.00	400.3	3.00	276.3	3.00	2170	3.5
111.3	0.792	201.1	1.58	145.9	1.58	1030	3.0
146.0	1.04	138.7	1.04	144.9	1.57	760	5.5
62.8	0.446	118.8	0.892	82.2	0.892	1670	4.7

distribution appeared desirable to test the accuracy of the predictions. Such a study is reported in the following paper.

EXPERIMENTAL

Materials. The bromotoluenes were the purest available commercial products. They were fractionated in a column rated at 50 theoretical plates. Center fractions which exhibited constant b.p. and n_D^{20} were utilized. The purities were established by cooling curves. The following constants and purities were observed: *ortho-* n_D^{20} 1.5562, 99.6 mole %; *meta-*, n_D^{20} 1.5528, 99.3 mole %; *para-*, m.p. 26.6°, 99.9 mole %.

Benzoyl chloride was fractionated at reduced pressure in an all-glass system: b.p. 74–76° (7.5 mm.), n_D^{20} 1.5333. Toluene was distilled over calcium hydride, b.p. 110°, n_D^{20} 1.4964. Nitrobenzene was distilled twice at atmospheric pressure, the center 75% cut being retained, b.p. 209–210°, n_D^{20} 1.5525, purity 99.8–99.9 mole % by cooling curve. Carbon disulfide, used for the infrared spectra, was purified by distillation over mercuric chloride.

Aluminum chloride (Baker's Analyzed Grade, Anhydrous) was sublimed several times in an all glass apparatus at reduced pressure (30–50 mm.). The sublimate was obtained as a pure white crystalline product, and was stored as loose plugs in sealed ampules.

The tolyl cadmium derivatives were prepared from the corresponding Grignard reagents and anhydrous cadmium chloride and were treated with benzoyl chloride following the procedure of Cason and Prout.[25] The reactions were carried out on a 1.0 mole scale. After hydrolysis, the crude products were recovered by distillation under reduced pressure in yields of 60–70%. The ketones were carefully purified by fractional distillation (and fractional crystallization for the *para-* isomer) until all fractions exhibited constant b.p., constant n_D^{20} (±0.0001), and identical infrared spectra. The physical properties are summarized in Table I.

Cooling curves. The melts were quite viscous and crystallization relatively slow. By utilizing a small temperature differential, 25–30°, a satisfactory curve was readily obtained for the *para-* isomer. However, both the *ortho-* and *meta-* isomers tended to solidify to glasses and to crystallize only with great difficulty. The existence of true crystalline phases with sharp melting points could be observed on small samples. Satisfactory cooling curves were finally realized for the *ortho-* isomer by employing a very slow cooling rate, extending the cooling curve over a period of 8 hr. Even this expedient did not help in the case of the *meta-* derivative. However, the three isomers were prepared by identical procedures, and in view of the high purities realized for the other isomers, we believe that the *meta-* derivative must be of comparable purity.

Derivatives. The 2,4-dinitrophenylhydrazones were prepared by a standard procedure.[26] In view of the discrepancies with literature values for the melting points, elementary analyses were made. These agreed closely with the calculated values. It is possible that we isolated different geometrical isomers than those obtained by the earlier workers (Table I).

The oxime of the *ortho-* isomer was readily prepared[26] and melted sharply. The *meta-* and *para-* derivatives did not give satisfactory melting points—they presumably consist of a mixture of the two geometric isomers.

Procedure for the benzoylation of toluene. Consideraleb experimentation was required to develop a procedure which yielded consistent results. Accordingly, the general procedure which was developed and used will be described in detail.

A 2-l., three-necked flask, equipped with a sealed (Trubore) stirrer and a nitrogen inlet, was thoroughly dried by heating with a flame in a stream of dry nitrogen. Sealed ampoules of aluminum chloride, encircled at one end with a file scratch, were touched with a hot rod in such a way as to crack, but not break, the ampoule. The end of the ampoule was placed in the open neck of the flask, the top broken off, and the loose plug of aluminum chloride transferred into the flask. Nitrobenzene (over calcium hydride) was siphoned through a glass filter stick into the flask. When the aluminum chloride had largely dissolved, benzoyl chloride was added. The flask was then immersed in a water bath (25 ± 1°) and the orange-yellow solution brought to reaction temperature. The reaction flask was equipped with an addition funnel having an equilizer side arm and the reaction was initiated by the rapid addition (8–15 min.) with stirring of toluene. The reaction mixture changed in color from the original orange-yellow to an orange-red. After 10 min., the funnel was replaced by a thermometer well and thermometer. In all cases the temperature remained at 25°. All operations were carried out with a constant dry nitrogen atmosphere.

The data of the various runs are summarized in Table III.

After an appropriate reaction period, the reaction mixture was poured into excess 4*N* sodium hydroxide and the mixture was heated under reflux for 2.5 hr. Two clear phases resulted. (Without this precaution, some derivative of benzoyl chloride, probably benzoic anhydride, contaminated the methylbenzophenone product and interfered with the subsequent infrared analysis.) The nitrobenzene layer was separated and washed with 500 ml. of water, which was added to the basic aqueous phase. The aqueous phase was then extracted with three 500-ml. portions of ether. The original nitrobenzene phase, to which was added 500 ml. of ether, and the combined ether extracts were washed (in that order) with 250 ml. portions of 3*N* hydrochloric acid, water, and saturated sodium chloride solution, and finally dried over anhydrous magnesium sulfate. The bulk of the ether was removed by distillation and the residue fractionated through a 50-cm. heated column. The nitrobenzene and ketone fractions were taken off at reduced pressure. Infrared examination of the last nitrobenzene fractions insured that none of the product was being lost in these fractions. A small intermediate fraction containing both nitrobenzene and ketone was saved for infrared analysis. Small aliquots of the product were removed and stored.

(25) J. Cason and F. Prout, *Org. Syntheses*, **28**, 75 (1948).

(26) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, 3rd ed., John Wiley and Sons, Inc., New York, 1948.

The products were melted and placed in a constant temperature bath at 45 ± 0.3°, seeded with the *para-* isomer, and allowed to crystallize slowly (10–35 hr.). The mother liquor was then decanted and the crystalline material remelted and recrystallized at 48°. The operation was repeated at 51°, 54°, and 55.5°. The final crystalline material was stored and the combined mother liquors were melted and subjected to another series of such crystallizations. With each succeeding series of crystallizations, the initial crystallization temperature was lowered and the quantity of the final crystalline phase sharply decreased. The sixth and final series of crystallizations was carried out at 35°, 40°, 45°, 50°, 54° and 55.5°.

The *para-* isomer was obtained as large, translucent prisms, m.p. 56–57°, indistinguishable by infrared spectrophotometry from the 99.9% material. The mother liquors were distilled at reduced pressure through a small 10-cm. column, and the minute residue recovered for infrared analysis. Losses in this series of operation were quite low, usually less than 2%.

Infrared analyses. The infrared spectra (7–15μ region) were obtained with a double beam Perkin-Elmer recording spectrophotometer, Model 21. All samples were dissolved in carbon disulfide. Matched cells (thickness: 0.10 mm.) were used with carbon disulfide in the reference cell. When the "differential" method was used for the analysis of the *meta-* isomer, a suitable standard mixture, dissolved in carbon disulfide, was placed in the reference cell. The intensities were measured in terms of % transmission: the "base line" technique was used to determine the value of T_0. The spectra of a set of standard mixtures were determined along with each group of unknown samples. Calibration curves were then constructed and used to determine the concentrations of the components in the unknown mixtures.[27]

The compositions of the intermediate fractions were determined by use of two standard mixtures of *o-* and *p-*methylbenzophenone containing 10–20% nitrobenzene. The residues were shown to be the *para-* isomer by their infrared spectra. The concentrations of the *ortho-* and *para-* isomers in the mother liquors were determined by the use of three standard mixtures, total concentration 0.5 gm./5 ml., containing about 3.5% (0.017–0.019 gm./5 ml.) of the *meta-*isomer. The following absorption bands were used: *ortho-*, 13.2μ and *para-*, 12.0μ. Both bands are of strong intensity and are essentially free of interference from the other isomers.

The concentration of the *meta-* isomer in the mother liquors was determined by the "differential" procedure, in which the absorptions of the *ortho-* and *para-* isomers were balanced out by means of a suitable standard mixture in the reference cell.

A second procedure was also used. The spectra of the series of standard mixtures and unknown samples were redetermined with pure carbon disulfide in the reference cell. The absorption band at 8.3μ is of medium intensity and is characteristics of the *meta-* isomer. However, at the high concentrations used in the analysis the *para-* isomer also has an appreciable absorption at this wave length. The optical density of the 8.3μ band was therefore corrected for the *para-* contribution and then used for the analysis of the *meta-* isomer. The correction was simply the optical density at 8.3μ of the special reference sample, since the concentration of the *para-* isomer was the same in all the standard and unknown mixtures.

Both types of analyses were repeated with a second series of standard mixtures. In all, seven determinations of the *meta-* isomer were made for each of the last three runs.[28] The percentage of the *meta-* isomer was calculated from its estimated concentration and the actual total concentration of the sample. The precision realized is indicated by the data in Table IV.

TABLE IV

SUMMARY OF *Meta-* ISOMER DETERMINATIONS

Band (μ)	Procedure	% Meta Detn. 3	% Meta Detn. 4	% Meta Detn. 5
8.3	Differential	3.0	3.9	3.1
12.9	Differential	3.8	4.4	3.6
14.0	Differential	3.5	4.3	2.7
12.9	Differential	3.5	4.1	3.5
14.0	Differential	2.9	4.1	2.6
8.3	*Para-* isomer correction	2.9	4.3	2.8
8.3	*Para-* isomer correction	2.9	4.0	2.8
Mean values		3.2 ± 0.3	4.2± 0.2	3.0 ± 0.3

TABLE V

COMPOSITION OF METHYLBENZOPHENONE PRODUCTS

Fractions	Weight (g.) Detn. 3 *Ortho-*	Detn. 3 *Meta-*	Detn. 3 *Para-*	Detn. 4 *Ortho-*	Detn. 4 *Meta-*	Detn. 4 *Para-*	Detn. 5 *Ortho-*	Detn. 5 *Meta-*	Detn. 5 *Para-*
Intermediate	1.16	...	4.6	3.06	...	8.2	1.09	...	3.6
Main	8.35	1.58	122.0	10.2	2.24	155.0	4.10	0.845	67.9
Residue	...	...	1.4	...	...	0.9	...	...	1.3
Total	9.51	1.58	128.0	13.3	2.24	164.1	5.19	0.845	72.8
Total ketone			139.1			179.6			78.8
Theoretical yield			155.4			204.0			87.5
% Yield			89.5			88.0			90.0

The mean values of the *meta-* percentage and the *ortho-* and *para-* percentages were totaled and normalized to a basis of 100%. These results provided the compositions of the mother liquors. The compositions of the main product fractions were then calculated from the compositions of the mother liquors and the enrichment factors from the fractional crystallizations. From these results and the weights of the isomers present in the intermediate fraction the complete compositions of the products could be calculated. The distribution in the last three runs is shown in Table V.

The results for the complete analyses are summarized in Table II.

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(27) For a more complete description of the infrared analyses consult the Ph.D. thesis of H. L. Young, Purdue University Library.

(28) The procedure utilized in these three runs was developed as a result of our experience in the first two runs (Table II) and represents an improvement over that used in the earlier analyses. Since identical results were realized by both procedures, only the later, improved analytical procedure is here described.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

Kinetic Study of the Aluminum Chloride–Catalyzed Benzoylation of Benzene and Toluene in Nitrobenzene Solution. Partial Rate Factors for the Benzoylation Reaction[1-3]

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The aluminum chloride–catalyzed reaction of benzoyl chloride with benzene in nitrobenzene solution exhibits complex kinetics. For any given concentration of the three reactants, the reaction appears to follow a third order rate expression: rate = $k_3[C_6H_6][C_6H_5COCl][AlCl_3]$. However, with increasing aluminum chloride concentrations, the rate constants decrease in magnitude. The data for the corresponding reaction with toluene appear to follow a seven-halves order rate expression. Comparison of the half-lives of the two reactions leads to a toluene/benzene rate ratio of 149. Comparison of the seven-halves order rate constants for benzene and toluene (with all reactants at equal concentrations) leads to the k_T/k_B value of 153. These values are in excellent agreement with the value of k_T/k_B of 149 predicted from the observed isomer distribution in the benzoylation of toluene (*ortho*, 7.2%; *meta*, 1.1%; *para*, 91.7%). Partial rate factors are calculated for the benzoylation reaction.

The isomer distribution in the aluminum chloride–catalyzed reaction of benzoyl chloride with toluene in nitrobenzene solution at 25° was established to be: *ortho*, 7.2; *meta*, 1.1; *para*, 91.7%.[5] These results indicate that benzoylation is a highly selective reaction.[6] In order to test whether this reaction obeys the quantitative treatment which has been proposed for aromatic substitution,[7,8] it was necessary to have the relative rate of benzoylation of toluene to benzene (k_T/k_B) under conditions identical with those used for establishing the isomer distribution.[9]

Attempts were made to establish the relative reactivities by competition experiments. However, it soon became apparent that the difference in reactivities of benzene and toluene was too great for such methods. Accordingly, we undertook a kinetic study of the benzoylation of benzene and toluene in the hope that the rate ratio might be accurately determined by a direct comparison of the two rate constants.

Kinetic studies have been made of the benzoylation reaction, using excess aromatic hydrocarbon as the reaction medium.[10-13] More recently, a kinetic study has been made of the benzoylation of benzene and toluene in bromobenzene solution.[9] However, our isomer distribution study had utilized nitrobenzene as a reaction medium,[5] so that a kinetic study of the reaction was undertaken with this material as solvent.

RESULTS

The reaction components are highly sensitive to moisture and consistent results could be realized only after considerable experimentation and the development of special apparatus and techniques for handling the reagents and solutions under strictly anhydrous conditions.[14] Largely because of the special sensitivity of the reaction to trace quantities of water or other basic impurities, it proved desirable to operate at somewhat higher concentrations (0.2–0.4*M*) than are customary in kinetic work. Although we encountered difficulties with the kinetics, as far as we could ascertain these difficulties were not attributable to the high concentrations used or to the experimental procedure.

Standard solutions of aluminum chloride in nitrobenzene were prepared and stored in special flasks which permitted the measurement of aliquots without exposure to moisture. A known amount of benzoyl chloride was added to these aliquots, and they were diluted to the desired concentration with nitrobenzene. The reaction was initiated by addition of the aromatic. Aliquots were removed at suitable intervals and the reaction was followed by the change in concentration of benzoyl chloride. By this procedure the rate constants were reproducible to ±3–5%.

(1) Directive Effects in Aromatic Substitution. XVII.

(2) Supported in part by the Petroleum Research Fund of the AMERICAN CHEMICAL SOCIETY.

(3) Based upon a thesis submitted by Herbert L. Young in 1956 in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(4) Standard Oil Co. (Indiana) Fellow at Purdue University, 1953–1955.

(5) H. C. Brown and H. L. Young, *J. Org. Chem.*, **22**, 719 (1957).

(6) H. C. Brown and K. L. Nelson, *J. Am. Chem. Soc.*, **75**, 6292 (1953).

(7) H. C. Brown and C. W. McGary, *J. Am. Chem. Soc.*, **77**, 2300 (1955).

(8) H. C. Brown and C. R. Smoot, *J. Am. Chem. Soc.*, **78**, 6255 (1956).

(9) A value of k_T/k_B of 53 has recently been reported for benzoylation at 40° in bromobenzene solution. F. Smeets and J. Verhulst, *Bull. soc. chim. Belg.*, **63**, 439 (1954).

(10) B. D. Steele, *J. Chem. Soc.*, **83**, 1470 (1903).

(11) L. F. Martin, P. Pizzolato, and L. S. McWaters, *J. Am. Chem. Soc.*, **57**, 2584 (1935).

(12) S. C. J. Olivier, *Rec. trav. chim.*, **37**, 205 (1918).

(13) H. Ulich and G. Heyne, *Z. Elektrochem.*, **41**, 509 (1935); H. Ulich and P. V. Fragstein, *Ber.*, **72**, 620 (1939).

(14) We are indebted to Dr. Frederick R. Jensen who is largely responsible for developing these methods and procedures.

At any given concentration of aluminum chloride, the reaction with benzene appears to follow a simple third order rate expression (1) out to 70–80% reaction:

$$\text{rate} = k_3[C_6H_6][C_6H_5COCl][AlCl_3] \qquad (1)$$

While maintaining the benzoyl chloride and aluminum chloride concentrations essentially constant at 0.4*M*, the benzene concentration was varied from 0.2*M* to 0.8*M* without variation in the value of k_3 (Table I). Similarly, with the benzene and aluminum chloride concentrations fixed at 0.4*M*, a change in the benzoyl chloride concentration from 0.2 to 0.6*M* results in no important change in k_3. (The observed decrease from 3.8 to 3.4 may be significant, or it may be due to a minor solvent effect arising from the high concentrations of benzoyl chloride.)

With the acid chloride and benzene concentrations maintained constant, the aluminum chloride concentration was varied. An *increase* in the aluminum chloride concentration led to a *decrease* in the value of k_3 (Fig. 1). The effect is quite large. Thus,

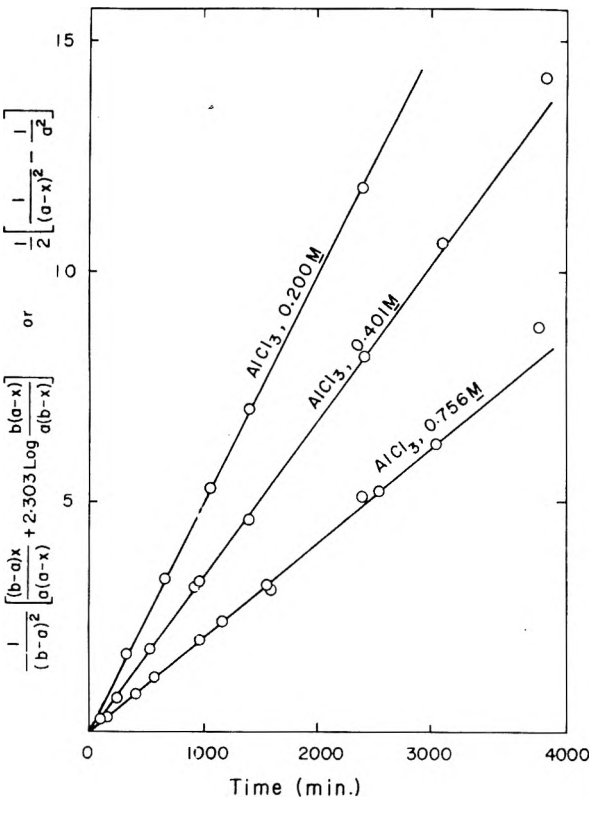

FIG. 1. THIRD ORDER RATE CONSTANTS FOR THE BENZOYLATION OF BENZENE (25°) WITH (C_6H_5COCl) = (C_6H_6) = 0.4 MOLE/LITER AND VARIABLE ALUMINUM CHLORIDE CONCENTRATION

with the acid chloride and benzene concentrations maintained at 0.4*M*, k_3 varies with [$AlCl_3$] as indicated: 0.2*M*, 5.0; 0.4*M*, 3.4; 0.8*M*, 2.1.

A reaction mixture was permitted to go essentially to completion and the product was isolated. A 92% yield of spectroscopically pure benzophenone was isolated. Consequently, the reaction with benzene does not appear to involve any important side reaction.

The results are summarized in Table I.

TABLE I

RATE CONSTANTS FOR THE ALUMINUM CHLORIDE–CATALYZED REACTION OF BENZOYL CHLORIDE WITH BENZENE IN NITROBENZENE SOLUTION AT 25°

Benzene	Reactants, *M* Benzoyl Chloride	$AlCl_3$	10^3k_3[a] liter^2 Mole^{-2} Min.$^{-1}$	Extent of Reaction, %[b]
0.199	0.398	0.397	3.26	
0.409	0.402	0.401	3.40[c]	58
0.398	0.400	0.401	3.38[d]	64
0.795	0.403	0.402	3.33	75
0.406	0.203	0.402	3.83	78
0.392	0.204	0.397	3.77	72
0.394	0.594	0.397	3.56	69
0.376	0.567	0.376	3.21	64
0.397	0.399	0.200	5.02	68
0.395	0.401	0.198	5.22	81
0.392	0.395	0.198	4.74	72
0.387	0.388	0.779	2.14	65
0.400	0.401	0.800	2.10	67
0.397	0.397	0.756	2.07	60
1.162	0.395	0.777	2.06	80
0.608	0.208	0.403	3.91	81
0.598	0.600	0.598	2.48[e]	65

[a] In cases where two or more concentrations are almost equal, mean concentrations were used in the calculations. [b] The extent of the reaction for which the third order plot was linear. See Fig. 1. The value in % is based upon the component present in limiting amount. [c] $k_{3.5}$ 6.25. [d] $k_{3.5}$ 6.05. [e] $k_{3.5}$ 3.90.

A new complication made its appearance in the corresponding kinetic study with toluene. Here the third order treatment, which had been satisfactory for benzene (Fig. 1), failed to give a linear relationship (Fig. 2). The curvature, although real, was not great and the data were approximately linear in the region between 30–40% to 70–80%. We therefore adopted this treatment to obtain an approximate value for the rate constant (k_3). The value of the rate constant obtained in this way was reasonably reproducible (±5%) and we utilized it to explore the effect of changes in the initial concentrations of the three components.

The results were similar to those described for benzene. The rate constant was essentially independent of the initial concentration of the aromatic, decreased moderately with an increase in concentration of benzoyl chloride, and decreased markedly with an increase in the concentration of aluminum chloride.

Typical results are summarized in Table II.

It was then noted that those experiments in which the three reactants were present in essentially equimolar concentrations (0.2*M* or 0.4*M*) gave good linear plots up to 70–80% reaction when the data were treated as a reaction of order seven-

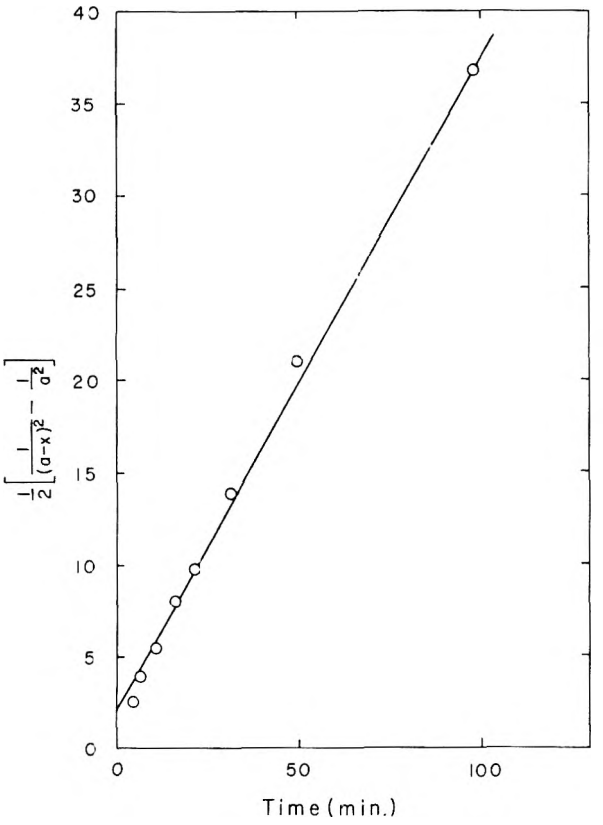

FIG. 2. THIRD ORDER RATE CONSTANTS FOR THE BENZOYLATION OF TOLUENE (25°) WITH (C_6H_5COCl) = ($C_6H_5CH_3$) = 0.4 MOLE/LITER

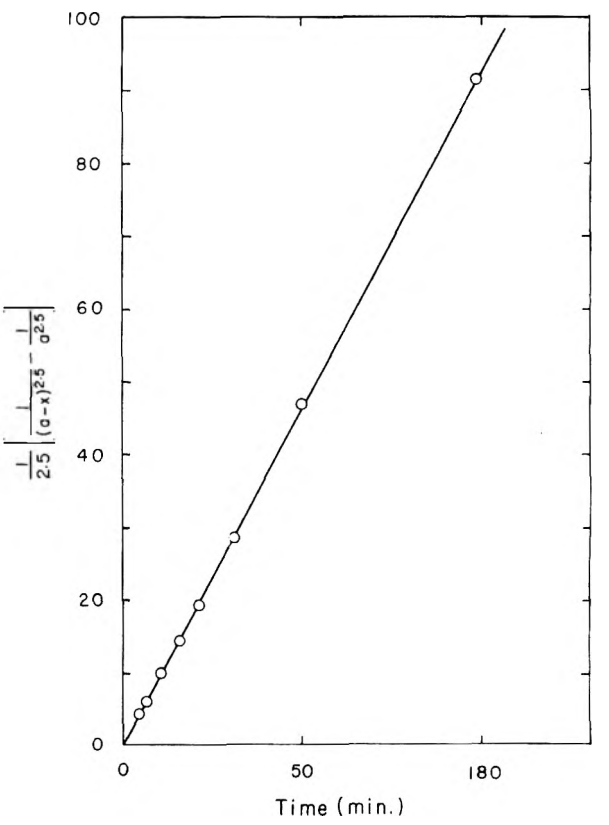

FIG. 3. SEVEN-HALVES ORDER RATE CONSTANT FOR THE BENZOYLATION OF TOLUENE (25°) WITH (C_6H_5COCl) = ($AlCl_3$) = ($C_6H_5CH_3$) = 0.4 MOLE/LITER

TABLE II

RATE CONSTANTS FOR THE ALUMINUM CHLORIDE–CATALYZED REACTION OF BENZOYL CHLORIDE WITH TOLUENE IN NITROBENZENE SOLUTION AT 25°

Reactants, *M*			k_3[a]	$k_{3.5}$
Toluene	Benzoyl Chloride	$AlCl_3$	Liter^2 Mole^{-2} Min.$^{-1}$	Liter$^{2.5}$ Mole$^{-2.5}$ Min.$^{-1}$
0.404	0.203	0.398	0.495	
0.404	0.199	0.398	0.488	
0.610	0.204	0.399	0.470	
0.603	0.206	0.401	0.474	
0.400	0.402	0.401	0.356	0.89
0.400	0.401	0.401	0.385	1.01
0.400	0.401	0.400	0.353	0.93
0.397	0.400	0.797	0.285	
0.398	0.400	0.801	0.298	
1.213	0.406	0.810	0.288	
1.221	0.412	0.807	0.339	
0.200	0.200	0.198	0.525	1.86
0.205	0.201	0.201	0.610	2.09

[a] In cases where two or more concentrations are almost equal, mean concentrations were used.

halves. Thus, in Fig. 3, a significant upward deviation is evident only after the reaction is 85% complete.

This encouraged us to examine a seven-halves plot for benzene. Such a plot exhibited satisfactory linearity up to 40–50% reaction, but deviated upward beyond this point (Fig. 4). Thus in the case

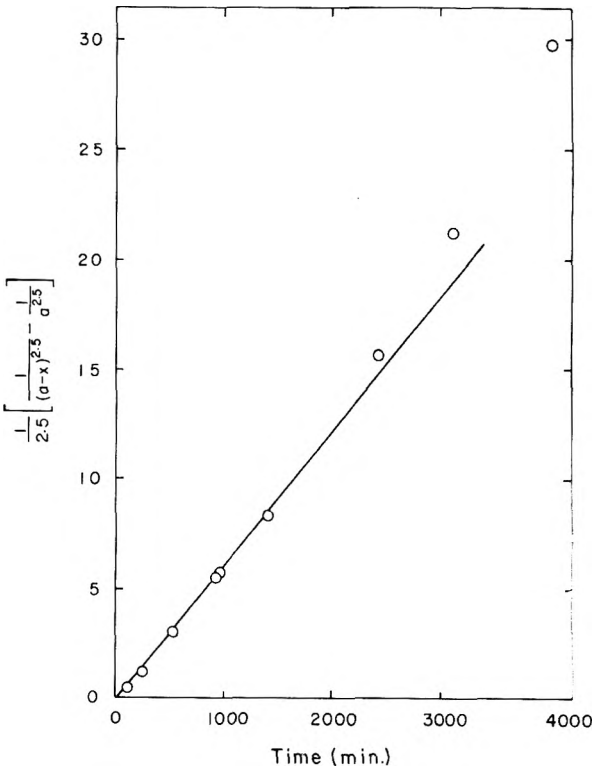

FIG. 4. SEVEN-HALVES ORDER RATE CONSTANT FOR THE BENZOYLATION OF BENZENE (25°) WITH (C_6H_5COCl) = ($AlCl_3$) = (C_6H_6) = 0.4 MOLE/LITER

of benzene such a treatment is less satisfactory than the third order analysis previously utilized. The values of $k_{3\cdot5}$ (Tables I and II) appear to vary inversely with the first power of the initial concentration of aluminum chloride. Unfortunately, the treatment of seven-halves order kinetics for cases other than equal concentration of reactants is too cumbersome to be practical. Consequently, we were able to explore the change in rate constant only for the runs in which all reactants had been maintained essentially constant.

Efforts were made to determine the possible existence of any simple rate law by calculating the order of the reaction using means other than application of the integrated forms of various rate expressions. Thus, if all reactants have equal concentrations, any simple rate expression reduces to the form

$$-\frac{dc}{dt} = kc^n$$

and

$$\log\left(-\frac{dc}{dt}\right) = \log k + n \log c$$

The rates of reaction $\left(-\frac{dc}{dt}\right)$ were determined by constructing tangents with the aid of a small mirror at several points on the curve obtained by plotting the concentration of benzoyl chloride *vs.* time. The logarithm of the rate $\left[\log\left(-\frac{dc}{dt}\right)\right]$ was plotted *vs.* the logarithm of the concentration ($\log c$) and the slope (n) determined. With all reactants at a concentration of 0.4 mole/liter, the over-all order (n) was 2.9 for benzene and 3.4 for toluene. This agrees with previous results that individual benzene experiments follow third order kinetics, while those of toluene are closer to seven-halves order.

DISCUSSION

Kinetics. Although a general rate expression was not obtained, several conclusions concerning the kinetics can be drawn. Thus, individual benzene runs are third order, while those of toluene are closer to seven-halves order. The reaction appears to be cleanly first order with respect to the aromatic component, indicating that the latter is involved in a rate-determining stage. The order with respect to the benzoyl chloride is only approximately unity, since the rate constants exhibit minor changes with change in the initial concentration of this component.

The order with respect to aluminum chloride is ill-defined. Individual experiments with benzene appear to be first order, and those with toluene three-halves order in this component. Moreover, the rate constants decrease markedly with an increase in the initial concentration of the metal halide. The over-all data clearly establish that the rate is not a simple function of some power, integral or not, of the aluminum chloride concentration.

The question necessarily arises as to whether the complicated kinetics are a consequence of the acylation reaction itself, or are to be attributed to some peculiarity of the aluminum chloride-nitrobenzene system.

Rothstein and Saville previously examined the behavior of aluminum chloride in nitrobenzene solution on the reaction of pivaloyl chloride with a number of aromatic components.[15] The kinetics were complex. However, the reaction itself is not simple since it involves both acylation and alkylation (with loss of carbon monoxide). Consequently, no definite conclusion can be drawn from the complexity of the kinetics.

Recently we examined the kinetics of the aluminum chloride–catalyzed reactions of arylsulfonyl chlorides with aromatics.[16] Similar complex kinetics were observed. In a recent study of the aluminum chloride–catalyzed reaction of cyclohexyl chloride with benzene, Lebedev noted that the order with respect to aluminum chloride varied from 0.35 for 85% nitrobenzene–12.5% benzene to 1.5 for 22.5% nitrobenzene–75% benzene.[17] He concludes that the order approximates 0.5 for pure nitrobenzene and is near 2 for pure benzene, with rapidly changing intermediate values for mixtures of the two solvents.

On the other hand, there is evidence that the acylation reaction itself can be kinetically simple. Thus, Smeets and Verhulst report clean second order kinetics for the reaction of the benzoyl chloride–aluminum chloride complex with aromatics in bromobenzene solution.[9] Likewise in benzoyl chloride as solvent we have found the acylation reaction to be cleanly first order in aluminum chloride and first order in aromatic.[16]

Therefore, it appears that the complex kinetics are not the result of any peculiarity of the acylation reaction, but must be attributed instead to the peculiarities of the aluminum chloride-nitrobenzene system.[18] It is probable that the unraveling of the kinetics must await a better understanding of the molecular and ionic species present in a solution of aluminum chloride in nitrobenzene.

We explored a number of possible explanations for the observed kinetics. Since we were unable to

(15) E. Rothstein and R. W. Saville, *J. Chem. Soc.*, 1954, 1959, 1961 (1949).

(16) Frederick R. Jensen, Ph.D. thesis, Purdue University Library.

(17) N. N. Lebedev, *J. Gen. Chem.* (*U.S.S.R.*), **24**, 664 (1954).

(18) E. P. Kohler, *J. Am. Chem. Soc.*, **24**, 385 (1900). R. E. Van Dyke and H. E. Crawford, *J. Am. Chem. Soc.*, **73**, 2018 (1951). V. A. Plotnikov and R. G. Vaisberg, *Rep. Inst. Chem. Acad. Sci. Ukrain. S.S.R.*, **3**, 337 (1936); *Chem. Abstr.*, **31**, 5689 (1937). V. A. Plotnikov and E. Y. Gorenbein, *Rep. Inst. Chem. Acad. Sci. Ukrain. S.S.R.*, **3**, 471 (1936); *Chem. Abstr.*, **31**, 7764 (1937).

TABLE III

HALF-LIVES AND RELATIVE RATES

Reactants				Reactants				
Benzene	Benzoyl Chloride	$AlCl_3$	$t_{0.5}$ (Min.)	Toluene	Benzoyl Chloride	$AlCl_3$	$t_{0.5}$ (Min.)	k_T/k_B
0.413	0.210	0.399	1600	0.409	0.208	0.400	10.5	
0.406	0.203	0.402	1650	0.404	0.203	0.398	10.5	
0.392	0.204	0.397	1750	0.404	0.199	0.398	10.4	
0.399	0.202	0.400	1580					
		Mean	1640 ± 55			Mean	10.5 ± 0.03	156
0.409	0.402	0.401	2700	0.400	0.401	0.402	21.0	
0.398	0.400	0.401	2700	0.401	0.400	0.401	19.1	
				0.400	0.401	0.400	20.4	
		Mean	2735 ± 35			Mean	20.2 ± 0.7	136
0.397	0.399	0.200	1170	0.399	0.400	0.200	7.9	
0.395	0.401	0.198	1140	0.397	0.398	0.199	8.1	
0.392	0.395	0.198	1180					
		Mean	1160 ± 17			Mean	8.0 ± 0.1	145
0.387	0.388	0.779	1710	0.397	0.400	0.787	11.0	
0.400	0.401	0.800	1910	0.398	0.400	0.801	11.0	
0.397	0.397	0.756	1910					
		Mean	1840 ± 90			Mean	11.0 ± 0.0	167
0.795	0.403	0.402	1130	0.791	0.397	0.397	8.1	140
							Mean	149 ± 10

arrive at a satisfactory interpretation, we shall not attempt to discuss these here.[19]

Relative rate. The question remains whether the data can be used to answer the primary objective of this investigation, the relative rate of benzoylation of toluene and benzene.

The halogenation of aromatics exhibits certain complexities in the kinetics. In these cases the relative reactivities have been established with considerable reproducibility and consistency by comparing the 10% and 20% reaction times.[20,21] We therefore examined this approach. Since the speed of the toluene reaction is so great, we compared the half-lives ($t_{0.5}$) instead of the $t_{0.1}$ and $t_{0.2}$ values used in the halogenation studies. In all cases the rates were compared under closely comparable concentrations of reactants.

The results are summarized in Table III.

The relative rate is 149 ± 10 and appears to be essentially independent of the concentrations of the reagents, within the relatively large experimental uncertainty.

As was pointed out, the reaction of toluene exhibits a good fit with the seven-halves order treatment, whereas the corresponding treatment of benzene exhibits satisfactory linearity over the first 50% of reaction. Accordingly, we compared the two values of the rate constants calculated in this way for all concentrations essentially 0.4*M* (Tables I and II). The relative rate k_T/k_B calculated from the mean value of three toluene runs (0.943 ± 0.045 liter$^{2.5}$ mole$^{-2.5}$ min.$^{-1}$) and the mean value of two benzene runs (0.00615 ± 0.00010 liter$^{2.5}$ mole$^{-2.5}$ min.$^{-1}$) is 153.

The determination of relative rates by such a comparison of rate constants involves two assumptions: (a) the rate determining step consists, in the case under discussion, of the reaction of the aromatic component with the substituting species, and (b) the rate expressions for the reactions with benzene and toluene are the same. Since the kinetics of the benzoylation reaction in nitrobenzene solution are not understood, neither of these conditions can be explicitly assumed to apply in this case.

Arguments can be advanced to support the position that both assumptions are approximately fulfilled in this reaction. Thus, the essentially clean first order dependence on the concentration of both benzene and toluene and the large difference in observed rate points to the aromatic being involved in a rate-determining reaction of the hydrocarbon with the substituting species, whatever that may be.

Second, the ratio of k_T/k_B as measured by the half-lives exhibits a remarkable constancy over large changes in the concentrations of the components. This also argues that the actual substitution step is the major controlling factor in the rates.

Finally, the agreement realized between the k_T/k_B value from the half-lives (149) and the k_T/k_B value from the ratio of the seven-halves rate constants (153) also supports the same conclusions. It would appear that the complex kinetics arise from those reactions which produce the molecular or ionic intermediate which reacts with the aromatic and that this complication is effectively eliminated by comparing the half-lives or seven-halves order rate constants under essentially identical conditions.

(19) For a fuller discussion of the kinetic investigation together with additional kinetic data obtained in our efforts to understand the reaction, the original theses should be consulted (refs. 3 and 16).

(20) P. W. Robertson, P. B. D. de la Mare and W. T. G. Johnston, *J. Chem. Soc.*, 276 (1943); P. B. D. de la Mare and P. W. Robertson, *J. Chem. Soc.*, 279 (1943).

(21) H. C. Brown and L. M. Stock, *J. Am. Chem. Soc.*, 79, 1421 (1957).

In the absence of contrary evidence, the average value, $k_T/k_B = 151$, may be adopted for the relative rate of benzoylation of the two hydrocarbons.

Partial rate factors. Utilizing the k_T/k_B rate ratio of 151 and the observed isomer distribution[5] of 7.2% *ortho*, 1.1% *meta*, and 91.7% *para*, the partial rate factors may be calculated. These are listed in Table IV.

TABLE IV
OBSERVED AND CALCULATED VALUES OF THE PARTIAL RATE FACTORS FOR THE BENZOYLATION REACTION IN NITROBENZENE AT 25°

	Partial Rate Factors			Relative Rate,
	o_f	m_f	p_f	k_T/k_B
Obsd.[a]	32.6	5.0	831	151
Calcd.[b]	32.0	4.9	817	149

[a] This study. [b] Ref. 5.

Recently a procedure was poposed for the calculation of the partial rate factors for toluene substitution and the relative rates of reaction solely from the observed isomer distribution.[8] The values calculated in this way[5] are also listed in Table IV. The agreement is excellent, well within the probable uncertainty in the experimental k_T/k_B value. The correlation of the benzoylation reaction with other substitution reactions of toluene is indicated by Fig. 5. The excellent agreement realized lends support to the conclusion that the reaction of the aromatic with the substituting species must be rate-controlling in the benzoylation reaction.

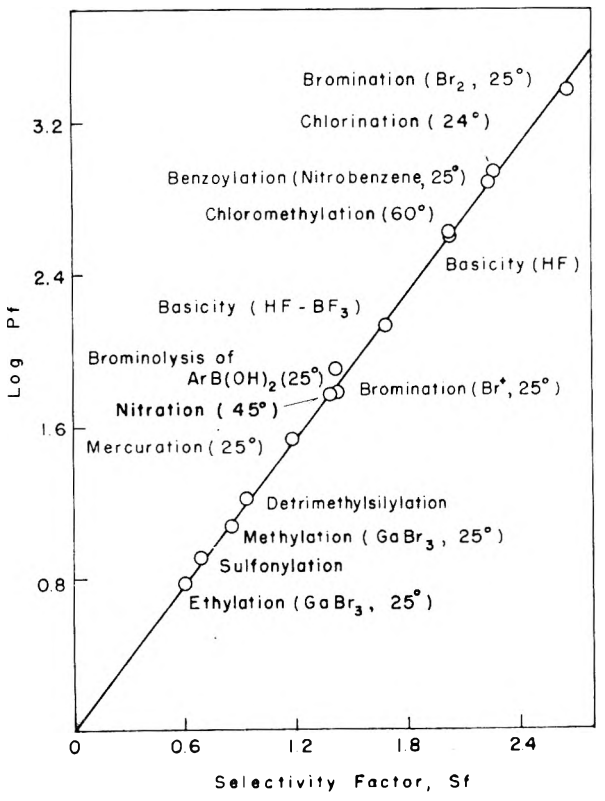

FIG. 5. BENZOYLATION OF TOLUENE IN THE SELECTIVITY RELATIONSHIP

It is concluded that benzoylation, specifically, and presumably acylation, generally, obeys the Selectivity Relationship.

EXPERIMENTAL

Materials. The purification and properties of the various compounds used in this study are described in an earlier paper.[6]

The benzoyl chloride and nitrobenzene were distilled directly into special storage and dispensing flask equipped with a buret side arm. The solution of aluminum chloride in nitrobenzene was also prepared and stored in and dispensed from a special flask of this kind. All flasks were maintained under pressure of dry nitrogen (~1.3 atmos.).

Kinetic Procedure. The reaction flasks consisted of calibrated Pyrex graduated cylinders equipped with a side arm for dry nitrogen. The reagents were introduced into the reaction flask from the special dispensing flasks in a stream of dry nitrogen. With the reaction mixture (aluminum chloride and benzoyl chloride in nitrobenzene) at bath temperature (25.0 ± 0.03°), the reaction was initiated by the introduction of the aromatic by means of a syringe. Samples were removed at appropriate time intervals and the course of the reaction was followed by determining the concentration of unreacted benzoyl chloride.

Two analytical procedures were employed. In the first of these, 5-ml. aliquots of the reaction mixture were run into

TABLE V
TYPICAL KINETIC DATA FOR THE BENZOYLATION OF BENZENE AHD TOLUENE IN NITROBENZENE SOLUTION AT 25°

Reagents, *M*				Time,	
Benzene	Toluene	Benzoyl chloride	$AlCl_3$	Min.	x^a
0.397		0.399	0.200	320	0.043
				664	0.070
				1060	0.093
				1395	0.108
				2400	0.136
				2855	0.150
				3845	0.166
0.398		0.400	0.401	310	0.056
				750	0.103
				1175	0.134
				1525	0.151
				2350	0.187
				2830	0.205
				4165	0.225
				6065	0.254
				8220	0.277
0.400		0.401	0.800	275	0.058
				600	0.110
				960	0.143
				1265	0.161
				2320	0.222
				3751	0.269
	0.400	0.401	0.402	5.8	0.118
				12.1	0.167
				17.5	0.190
				27.4	0.218
				40.2	0.242
				70.2	0.272
				127.8	0.300

[a] Benzoyl chloride reacted, moles per liter.

20 ml. of 2*M* sodium hydroxide solution and the mixtures heated under reflux for 1–2 hr. The nitrobenzene phase was separated, washed with 10 ml. of water, which was joined with the aqueous phase. This was then acidified with 10 ml. of 6*N* hydrochloric acid and extracted with 25 ml. portions of ether. Each ether portion was washed with 10 ml. of water, which was added to the aqueous phase for the next extraction. The combined ether extracts were evaporated under reduced pressure at room temperature and the residue taken up in 50 ml. of 95% ethanol. This was then titrated with standard base. Blank determinations revealed that this procedure accounted for 98–99+% of the benzoyl chloride present in typical reaction mixtures.

A more convenient analytical procedure was developed subsequently.[16] This procedure involved the neutralization of the aluminum chloride and hydrogen chloride in the reaction mixture, followed by a direct titration of the benzoic acid and hydrochloric acid produced by the hydrolysis of the benzoyl chloride present. A detailed description of this procedure will be published shortly.[22]

Both procedures gave identical results.

Typical kinetic studies are reported in Table V.

LAFAYETTE, IND.

(22) H. C. Brown, F. R. Jensen, and B. A. Bolto, paper in preparation.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Formation of Naphthalenes from Indenes. III.[1] Substituted Methanes as Carbene Precursors

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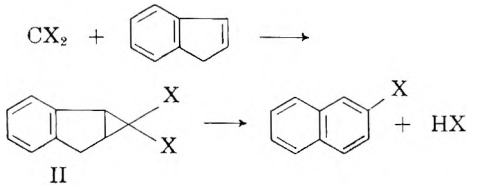
Seven substituted methanes have been examined as possible carbene precursors in reactions with potassium *t*-butoxide and indene. Dichlorobromomethane (III) gives principally the adduct of dichlorocarbene, and the apparent tendency for bromide ion to be eliminated from the anion of III is at least six times greater than for chloride ion. The thermally unstable adduct obtained from reactions employing dibromochloromethane (IV) was converted in high over-all yield to an approximately equimolar mixture of 2-chloro and 2-bromonaphthalene. Thus, there appears to be far less apparent selectivity of the halogen eliminated from the cyclopropane intermediates, than from the anions of the haloforms. Data obtained from reactions with dichlorofluoromethane (V) furnish direct evidence for the existence of chlorofluorocarbene, and indirect evidence to support the conclusion that the cyclopropane derived from this carbene and indene is more stable than other analogs studied. If carbene intermediates are involved in reactions of the substituted methanes VI–IX, they do not add appreciably to indene.

We have previously described a synthesis of 2-halonaphthalene[1,4] which involves the reaction of indene, or a substituted indene, with chloroform or bromoform and base.

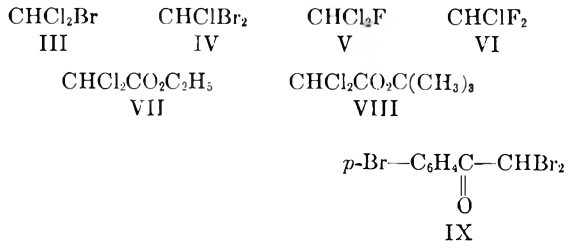
$$CHX_3 + B^- \longrightarrow CX_2 + X^- + HB$$

I



II

The principal product of this reaction is a dihalocyclopropyl compound (II), which loses hydrogen halide quantitatively, by a unimolecular process in polar solvents, to give 2-halonaphthalene. It is apparent[1,4] that dihalocarbenes (I) are intermediates in these reactions, and the existence of such intermediates has been more conclusively established by the work of Hine,[5] Doering,[6] Skell,[7] and their coworkers. The purpose of this study was to evaluate the substituted methanes III–IX as carbene precursors in the reaction of indene, substituted methane, and base.



(1) Preceding paper, W. E. Parham, H. E. Reiff, and P. Swartzentruber, *J. Am. Chem. Soc.*, **78**, 1437 (1956).

(2) This work was supported in part by a grant (NSF-G2163) from the National Science Foundation.

(3) Parke, Davis and Co. fellow (1955–56), E. I. du Pont de Nemours fellow (summer 1955).

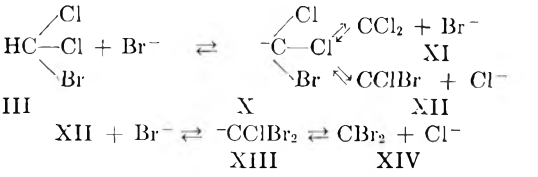
(4) W. E. Parham and H. E. Reiff, *J. Am. Chem. Soc.*, **77**, 1177 (1955).

(5) (a) J. Hine, *J. Am. Chem. Soc.*, **72**, 2438 (1950); (b) J. Hine and A. M. Dowell, Jr., *J. Am. Chem. Soc.*, **76**, 2688 (1954); (c) J. Hine, P. C. Peck, Jr., and B. D. Oakes, *J. Am. Chem. Soc.*, **76**, 6162 (1954); (d) J. Hine, A. M. Dowell, Jr., and J. E. Singley, Jr., *J. Am. Chem. Soc.*, **78**, 479 (1956); (e) J. Hine and N. W. Burske, *J. Am. Chem. Soc.*, **78**, 3337 (1956).

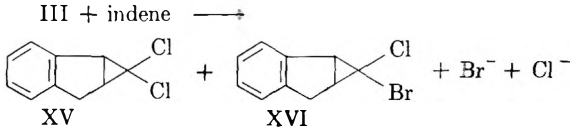
(6) (a) W. von E. Doering and A. Hoffman, *J. Am. Chem. Soc.*, **76**, 6162 (1954); (b) W. von E. Doering and P. LaFlamme, *J. Am. Chem. Soc.*, **78**, 5448 (1956).

(7) (a) P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, **78**, 3409 (1956); (b) P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, **78**, 5430 (1956); (c) P. S. Skell and R. C. Woodworth, *J. Am. Chem. Soc.*, **78**, 4496 (1956).

In the formation of a carbene from a haloform an S_N1 ionization occurs.[5b] When two different halogens are present, as in the haloform III, three different carbenes (XI, XII, XIV) are possible, provided equilibrium is attained.[5b] In the nonpolar solvent indene, in which potassium halide has limited solubility, it was considered unlikely that the equilibria involving XIII and XIV would be established; consequently, it was anticipated that only the two carbenes XI and XII would be formed and that the ratio of bromide ion to chloride ion formed in the first step (III → II) would serve to establish their relative concentrations.

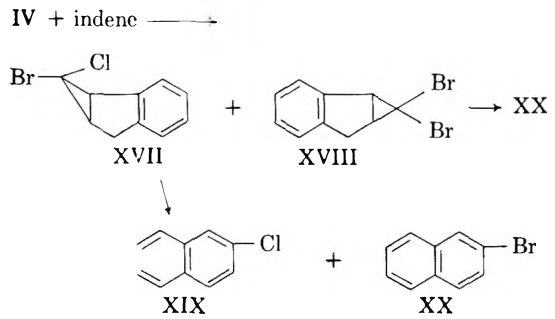


The reaction product of dichlorobromomethane (III), indene, and potassium *t*-butoxide was processed in a manner[8] which allowed separation of the the inorganic salts that were formed, and isolation of the intermediate cyclopropyl compounds (XV and XVI).



It was apparent, by examining the mixture of XV and XVI, that the reaction had followed the expected course[9,10] leading principally to XV. Essentially pure XV (60% of the crude product) was readily obtained merely by washing the crude product (56% yield) with cold petroleum ether. More quantitative data were obtained by determining the ratio of bromide ion to chloride ion formed, and this ratio proved to be about 3 to 1. Thus, the apparent tendency for bromide ion to be eliminated from the anion of III is at least six times greater than for chloride ion.

The results obtained with dichlorobromomethane suggested that the reaction of dibromochloromethane, indene, and base should lead preferentially to the formation of XVII (*exo-endo* isomers) rather than XVIII. Thus, a method was available for obtaining additional information concerning the elimination of hydrogen halide (conversion to naphthalenes) from the intermediate cyclopropyl derivatives. The crude cyclopropyl derivative, obtained



from this reaction, proved to be thermally unstable, and attempts to isolate pure products have so far been unsuccessful. However, when the crude product was steam-distilled a high yield of a mixture of 2-bromo and 2-chloronaphthalene (70%, contaminated only by a small amount of indene) was obtained. The composition of the mixture was estimated, by elementary analysis both before and after further purification, to contain 50 ± 2% of each naphthalene. Although the method of sampling was not as good as the analytical method, there was no reason to assume that the composition of the mixture deviated markedly from the equimolar mixture. If the same relative order of halide elimination obtained for IV, as was observed for III, then the amount of XVII in the crude product should have exceeded that of XVIII by a factor of about 12 to 1. Thus, it would appear that the factors generally associated with hydrogen halide[9,10] elimination do not obtain for eliminations in this cyclopropyl series. We hope ultimately to decide whether the course of elimination is controlled stereochemically (*i.e.* from the two possible isomers of XVII, with chlorine being either *exo* or *endo* to the benzene ring), or whether the carbon-carbon bond is broken in the rate determining step.[11]

Hine and Burske[12] have obtained kinetic evidence for the existence of chlorofluorocarbene. Our initial results, obtained with difluorochloromethane, indene, and base were rather discouraging, since only recovered indene, tars, and polymeric material were obtained. There were small amounts of volatile material obtained; however, the small yield, and our inability to separate them from indene, precluded their identification as possible products derived from difluorocarbene (F_2C).

We then directed our attention to dichlorofluoromethane (V), and the initial reactions were carried out with cyclohexene, instead of indene, to facilitate purification of the anticipated fluorochlorocyclopropane products. We have been unsuccessful in

(8) We have previously shown (ref. 4) that halonaphthalene is not produced when the product is processed in nonpolar solvents at temperatures below 60°.

(9) (a) J. Hine and D. E. Lee, *J. Am. Chem. Soc.*, **74**, 3182 (1952); (b) J. Hine and D. E. Lee, *J. Am Chem. Soc.*, **73**, 22 (1951).

(10) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., (1953) p. 339.

(11) An alternate possibility involves the rate-determining rupture of the carbon-carbon bond of the cyclopropane, with more random elimination of halogen.

(12) J. Hine and N. W. Burske, *J. Am. Chem. Soc.*, **78**, 3337 (1956).

elucidating the exact course of this reaction. The initial product was thermally unstable (eliminated hydrogen chloride); however, when the excess cyclohexene was removed slowly a thermally stable product was obtained in 24% yield. This product (b.p. 185–186°/736) contained a small amount of carbonyl impurity (infrared absorption at 1720 cm.$^{-1}$) which was readily removed, with little loss, by chromatography. The resulting product reacted slowly with bromine in carbon tetrachloride, and with potassium permanganate; the product had the empirical formula $C_7H_{10}ClF$, and showed the following absorption in the infrared region: C-F (1085 cm.$^{-1}$),[13a] cyclopropane ring (1020 cm.$^{-1}$),[13b] cyclohexene ring (1447,[14] 1042 and 975 cm.$^{-1}$),[13b] and absence of unsaturation (lack of absorption in the 1600–1700 cm.$^{-1}$ region).[13c] We feel that this product is XXI, which resulted by the direct addition of fluorochlorocarbene to cyclohexene; however, the thermal instability of the crude reaction product, together with the rather poor elementary analysis obtained, precluded positive identification with the available data.

More conclusive evidence for the addition of chlorofluorocarbene to an olefin was obtained by a study of the reaction of dichlorofluoromethane, indene and potassium *t*-butoxide. Analysis of the

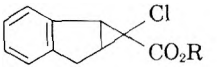
$$B^- + Cl_2CHF \longrightarrow ClCF + Cl^- + BH$$

$$ClCF + \text{indene} \longrightarrow \underset{\text{XXII}}{\text{Cl, F}} \longrightarrow \underset{\text{XXIII}}{\text{F}} + HCl$$

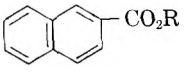
inorganic salt obtained from this reaction gave 91% of the theoretical value, calculated for carbene formation as shown in the above equation. A qualitative test for fluoride ion was weakly positive. The organic product was steam-distilled, and the residual aqueous solution was analyzed for halogen. Fluoride ion was absent, and the value obtained for chloride was 13.2% of theory. This low value for chloride ion was in sharp contrast to the results previously obtained when chloroform or bromoform were employed. In these latter cases, steam-distillation caused essentially quantitative loss of halogen acid to yield naphthalenes.[4] It was not, of course, assumed that all of the chloride ion produced in the initial reaction arose from the formation of fluorochlorocarbene, or that all of the fluorochlorocarbene produced reacted with indene; however, these results strongly suggested that the cyclopropane XXII was considerably more stable than analogous cyclopropanes containing chlorine or bromine. This conclusion is in accord with Hine's[9a] investigation of the effect of *alpha* fluorine atoms on S_N1 reactivity of other halogens. Further evidence that the steam-distillation had not completed the conversion of XXII to XXIII was obtained by examining the reaction product. This product (24% yield as XXIII) was an oil with strong odor of fluoronaphthalene; however, the material liberated hydrogen chloride upon attempted distillation. A thermally stable product was not obtained until the material was heated over a prolonged period in ethanol.[4] The yield of isolated pure 2-fluoronaphthalene was 7–9%.

The reaction of α,α-dibromoacetophenone (IX) with potassium *t*-butoxide in the presence of an olefin could yield a variety of products. If carbene intermediates are involved, then high dilution with olefin should favor the formation of the corresponding olefin-carbene adduct. The reaction of IX, potassium *t*-butoxide, and excess indene was examined; however, only recovered indene, tars and polymeric material were obtained. When a similar reaction was carried out in excess cyclohexene, some alcohol-soluble material was obtained. This product gave, by reaction with 2,4-dinitrophenylhydrazine, a substance considered to be the osazone of *p*-bromophenylglyoxal.[15] Though the above product was not positively identified, it was obviously not an adduct of *p*-bromobenzoyl bromocarbene and cyclohexene.

Finally, the reactions of ethyl dichloroacetate (VII) and of *t*-butyl dichloroacetate (VIII) with potassium *t*-butoxide and indene were examined. The reaction products were examined carefully for esters or acids of structures XXIV or XXV; however, only trace amounts of acidic products were obtained. In the reaction employing *t*-butyl dichloroacetate a small amount of acidic material was obtained in a rather pure state. The structure of this acid (m.p. 199–202° dec.) was not established; however, the product was not XXIV or XXVI. Hence, it can be concluded that if ethyl dichloroacetate and *t*-butyl dichloroacetate are converted into carbenes under these experimental conditions, these carbenes do not add appreciably to indene. On the other hand, studies now in progress involving these esters and other olefins indicate that carbenes are produced, but that these particular carbenes will add only to olefins more reactive than indene.



XXIV



XXV

(13) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., 1954. (a) p. 270; (b) p. 28; (c) p. 31; (d) p. 37.

(14) A. Weissberger, *Technique of Organic Chemistry*, Vol. IX, Interscience Publishers, Inc., New York, N. Y., (1956), p. 564.

(15) E. Bayers and C. R. Hauser, *J. Am. Chem. Soc.*, **65**, 1095 (1943) have shown that the reaction of α,α-dibromoacetophenone with aqueous alkali gives phenylglyoxal.

EXPERIMENTAL

Reaction of dichlorobromomethane (III), *indene and potassium t-butoxide.* Freshly distilled dichlorobromomethane (0.172 mole, 28.2 g.) was added over a 20-min. period to a cold (0–10°) mixture of potassium *t*-butoxide (0.174 mole)[4,6a] and purified indene (1.72 mole, 200 g.). The resulting mixture was stirred for 75 min. (at 0–5°), and then allowed to stand (at 25°) for 12 hr. Petroleum ether B (200 ml.) was added to the reaction mixture, and the solids were removed by filtration. The flask and the solids (designated solid A) were washed with petroleum ether and the combined ether solution was concentrated to remove petroleum ether (aspirator) and excess indene (pressure 2–3 mm., pot temperature[4] less than 60°). The residue was chromatographed on Merck alumina (200 g.) using petroleum ether B as both developer and eluant. The yellow eluant (3–4 liters) was concentrated under reduced pressure (pot temperature less than 60°), and the resulting solid (19.1 g., 56% yield), which still contained some indene, was slurried with cold petroleum ether B (50 ml.) and filtered. The white solid (11.45 g., 33.5%) thus obtained, melted at 73–76° and was essentially pure 1,1-dichloro-1a,6a-dihydrocycloprop[*a*]indene (II, X = Cl) (reported m.p. 74.5–76°).[4] A sample of this material was recrystallized from 95% ethanol for analysis. The infrared spectrum of this product was identical with that of authentic material.[4]

Anal. Calcd. for $C_{10}H_8Cl_2$: C, 60.33; H, 4.05. Found: C, 60.07; H, 4.27.

The mixed solids (A) were analyzed for total halogen by precipitation as silver halide. The bromide ion was determined by modification[16] of the procedure reported by D'Ans and Höfer,[17] and the chloride ion was obtained by difference. The total halide ion obtained corresponded to 96.5 ± 1% of one mole, and the molar ratio of bromide to chloride ion was 2.81 ± 0.24. (The best data for this ratio is 3.04.)

Reaction of chlorodibromomethane (IV), *indene and potassium t-butoxide.* The reaction of chlorodibromomethane (35.8 g., 0.172 mole), potassium *t*-butoxide (0.174 mole), and indene (1.72 mole, 200 g.) was carried out as described above for the reaction with dichlorobromomethane; however, the reaction mixture was stirred at 0–10° for 5 hr. The reaction mixture was diluted with water (100 ml.), and then distilled with steam. The distillate was saturated with sodium chloride, and the organic phase was separated by extraction with petroleum ether F. The ether extract was dried (magnesium sulfate) and concentrated under reduced pressure (maximum pot temperature 60°). The residue (37.9 g.) was chromatographed on Merck alumina (200 g.) employing petroleum ether B as both developed and eluant. Evaporation of the eluant afforded 27.2 g. of waxy crystalline material, which was shown to be a mixture of 2-chloronaphthalene, 2-bromonaphthalene, and a small amount of residual indene. This material corresponded to an 84% yield of mixed naphthalenes. The solid was transferred (with some mechanical loss) to a desiccator, and was dried over paraffin. The product weighed 22.5 g. (70% yield) and melted at 41–48°. A sample (1 g.) of this material was sublimed at room temperature with little loss (0.05 g.). The white solid, thus obtained, melted at 51–55° (solid A), and probably contained a small amount of indene. The remaining product was separated into two fractions by crystallization from ethanol: solid B (6.67 g., m.p. 58–59°), total residue (14.1 g., m.p. 47–53°).

Anal. Calcd. for 50% 2-chloronaphthalene–50% 2-bromonaphthalene: C, 64.98; H, 3.81. Found: Solid A, C, 65.14; H, 4.19; Solid B, C, 65.14; H, 4.03.

The infrared spectrum of solid A showed only absorption found in the spectrum of 2-chloro- and 2-bromonaphthalene. Calculations of change in percent composition for C, H, Cl, and Br over the range 2-chloronaphthalene (38–62%)–2-bromonaphthalene (62–38%) revealed maximum change in % C (0.16% per 1% change of component) and minimum change in % H (0.007% per 1% change). Thus, the values obtained indicate that 2-chloro- and 2-bromonaphthalene were formed essentially in equal amounts (±2%).

Reaction of fluorodichloromethane (V), *indene, and potassium t-butoxide.* The reaction of fluorodichloromethane (*ca.* 16 g., 0.16 mole, b.p. 9°), indene (100 g., 0.86 mole), and potassium *t*-butoxide (0.087 mole) was carried out as described above for the reaction with dichloromethane, but with the following modifications: A total reflux condenser (dry-ice and acetone) was employed, the haloform was added over a 2-hr. period, a temperature of −10° was maintained, and the time of reaction at reduced temperature was 2 hr. Petroleum ether B (100 ml.) was added, and the reaction mixture was filtered. Analysis of the solid for chloride ion by the Mohr method[18] indicated that 91% (0.79 mole/0.086 mole × 100) of the theoretical amount of chloride ion was produced. The organic filtrate was steam-distilled, and the distillate was saturated with sodium chloride. Analysis of the residual aqueous phase revealed that only 13.2% of an additional mole of chloride ion had been formed during steam distillation, and that no fluoride ion was produced. The organic phase was separated with ether, and the resulting solution was dried (magnesium sulfate) and concentrated (10-inch glass helices column, maximum pot temperature 60°, 1 mm. pressure). The residue was slurried with petroleum ether B and chromatographed on Merck alumina (50 g.), using petroleum ether B as developer and eluant. The combined eluant (*ca.* 1 l.) was concentrated under reduced pressure, and the yellow oil (3.03 g., 24% as 2-fluoronaphthalene), thus obtained, had the characteristic odor of halonaphthalene. Preliminary experiments indicated that this material still contained dihalocyclopropane, since attempted distillation at 1 mm. resulted in decomposition accompanied by the elimination of hydrogen chloride. The oil was dissolved in ethanol (20 ml.), containing potassium hydroxide (3 g.), and the resulting solution was heated at the reflux temperature for 45 min. Water was added to the cooled ethanol solution and the oil that separated was extracted with ether. The ether extract was dried (magnesium sulfate), and concentrated, and the residue was distilled. The product solidified in the column head, condenser, and in the receivers. There was obtained 0.96 g. (7.6% yield) of 2-fluoronaphthalene which melted at 58–59° (reported m.p. 61°).

Anal. Calcd. for $C_{10}H_7F$: C, 82.17; H, 4.83. Found: C, 82.36; H, 4.99.

A mixture melting point of this product with authentic 2-fluoronaphthalene showed no depression. The infrared spectrum of the product and that of authentic 2-fluoronaphthalene were essentially identical.

The above experiment was repeated; however, the product obtained from the steam distillate, subsequent to removal of indene, was treated with hot ethanol prior to chromatography in an attempt to complete the conversion of the cyclopropyl intermediate to fluoronaphthalene. This conversion was apparently not complete, however, since it was necessary to repeat the alcohol treatment before a thermally stable product resulted. The yield of pure 2-fluoronaphthalene in this experiment was 9.4%.

Reaction of fluorodichloromethane, cyclohexene and potassium t-butoxide. The reaction of fluorodichloromethane (7.60 g., 0.074 mole), potassium *t*-butoxide (0.097 mole), and cyclohexene (40 g., 0.486 mole) was carried out as described above for indene with the following modifications: The addition time was 1 hr., the reaction temperature was −15° to −20°, and the reaction time at reduced temperature (−10°) was 3 hr. Water (100 ml.) was added to the

(16) H. C. Yutzy, Ph.D. thesis, University of Minnesota (1936), p. 78.

(17) J. D'Ans and P. Höfer, *Angew Chem.*, **47**, 73 (1934).

(18) I. M. Kolthoff and E. B. Sandell, *Textbook of Quantitative Inorganic Analysis*, The Macmillan Co., New York, N. Y. (1947).

reaction mixture, and the solids were dissolved by vigorous stirring. The organic solution was separated and the aqueous phase was extracted with ether. The combined organic solution was dried (magnesium sulfate), and ether and excess cyclohexene were removed by distillation at atmospheric pressure (4-inch Vigreux column). Near the end of the distillation the residue darkened and acidic vapors were evident. The residue was then distilled at reduced pressure and 2.72 g. (24.5% yield as XXI) of oil was obtained; b.p. 56–60°/20 mm., n_D^{25} 1.4567–1.4578. The material was washed with dilute sodium bicarbonate, and then redistilled to give 2.07 g. of product; b.p. 74°/40 mm., n_D^{25} 1.4554–1.4572. The infrared spectrum of this material showed absorption at 1720 cm.$^{-1}$, which suggested the presence of small amounts of carbonyl impurity. The carbonyl impurity was easily removed, with little loss of weight, by passing a solution of the product in petroleum ether over Merck alumina (100 g. of alumina for 8 g. of product in 160 ml. of ether). The product was then distilled; b.p. 158–159°/739 mm., n_D^{25} 1.4571–1.4577.

Anal. Calcd. for $C_7H_{10}ClF$: C, 56.57; H, 6.78; Cl, 23.86; F, 12.78; mol. wt., 148.6. Found: C, 57.10; H, 6.97; Cl, 22.87; F, 11.87; mol. wt. (ebullioscopic in benzene) 139.

The product reacted slowly with permanganate (2%) solution and with bromine (5% in carbon tetrachloride); the infrared spectrum showed absorption characteristic of C-F (1085 cm.$^{-1}$),[13a] cyclopropane[13b] (1020 cm.$^{-1}$), cyclohexane (1447 cm.$^{-1}$,[14] 1042 and 975 cm.$^{-1}$),[13b] and the absence of unsaturation (no absorption in the 1600–1700 cm.$^{-1}$ region).[13c]

The above reaction was repeated several times in an attempt to avoid the decomposition which occurred when the excess cyclohexane was removed. More rapid distillation of the excess cyclohexene, under reduced pressure, gave residues that foamed badly upon distillation (at 760 mm. or 20 mm.). The use of a photo-flood lamp as the sole heat source for distillation of these residues gave a clear distillate (n_D^{25} 1.4265) which liberated hydrogen chloride slowly at room temperature, and rapidly (with decomposition) at 120–125°.

Reaction of difluorochloromethane, indene, and potassium t-butoxide. (a) The reaction of difluorochloromethane (*ca.* 40 g., 0.46 mole, b.p. −41°), potassium *t*-butoxide (0.088 mole), indene (100 g., 0.86 mole), in olefin-free *n*-hexane (50 ml.) was carried out essentially as described above for the reaction of dichloromethane with indene. Water (100 ml.), containing sodium carbonate hydrate (12 g., 0.1 mole), was added, and the resulting mixture was steam-distilled. The residual aqueous solution gave a negative test for fluoride. The organic distillate was separated (petroleum ether F), dried (magnesium sulfate), and concentrated at 20 mm. to remove solvent and at 1 mm. (maximum pot temperature 60°) to remove indene. There was obtained a 92.8% recovery of indene and 2.35 g. of dark polymeric residue.

(b) The above reaction was repeated in an oxygen-free autoclave. The initial temperature was −10° and the contents were allowed to stand, with occasional stirring, for 84 hr. at 25°. The reaction mixture, and similar ones obtained by variations of reaction conditions, were processed by a variety of procedures similar to those previously described for related reactions; however, no isolable products were obtained. Analysis of inorganic material revealed 65.5% of the theoretical amount calculated for one mole of chloride ion; however, qualitative tests revealed that fluoride ion was also positive. The recovery of indene usually amounted to 70–80%; however, the latter fractions of indene contained some material of higher refractive index. Attempts to separate this component by careful fractionation (Podbielniak concentric tube column) were unsuccessful. Decomposition and polymerization of indene accompanied these distillations; some fractions of the indene distillate slowly polymerized (absorption at 1715 cm.$^{-1}$ in the infrared was observed). Other products were generally polymeric and tarry in nature.

Reaction of IX *with cyclohexene and potassium t-butoxide.* The procedure used was similar to that described for reactions employing haloform; the quantities of reactants were cyclohexene (1.49 mole), IX (0.087 mole), and base (0.087 mole). The crude oil, obtained after removal of solvent, was treated with hot ethanol, and the ethanol extract was concentrated. The amorphous solid (4.45 g.), thus obtained, was treated with 2,4-dinitrophenylhydrazine, and the product (5.0 g., m.p. ~300° dec., insoluble in most organic solvents) and recrystallized from dimethylformamide. Recovery from the recrystallization was poor, and decomposition was evident (solution turned black). The red solid that was obtained melted at 317–318° dec.

Anal. Calcd. for $C_{20}H_{13}N_8BrO_8$: C, 41.90; H, 2.28; N, 19.25. Found: C, 42.34; H, 3.03; N, 19–25%.

t-Butyl dichloroacetate. This ester was prepared from technical grade dichloroacetic acid (0.48 mole) by the procedure described in *Organic Syntheses*[19] for the preparation of *t*-butyl malonate. The yield of product (n_D^{25} 1.4316) was 42%.

Anal. Calcd. for $C_6H_{10}Cl_2O_2$: C, 38.94; H, 5.45; M.R., 41.3. Found: C, 39.19; H, 5.61; M.R., 41.1.

Reaction of ethyl dichloroacetate and reaction of t-butyl dichloroacetate with indene and potassium-t-butoxide. These reactions were carried out according to the same general directions previously described for reactions involving haloforms. The same quantities and ratio of reactants were observed. Fractions that could contain esters were hydrolyzed, both with alkali and with acid; however, only trace amounts of acidic materials were obtained. The crude acid (0.5 g.), obtained in the reaction employing the *t*-butyl ester, was purified by chromatography (alumina–petroleum ether B). The acid (0.25 g., m.p. 185–190°), thus obtained, melted at 199–202° after purification by recrystallization (petroleum ether C) and sublimation (120° at 0.02 mm.).

Anal. Found: C, 78.67; H, 5.62; Cl, 0; neut. equiv. 184. The identity of this acid, which appears to have the formula $C_{12}H_{10}O_2$, was not established.

MINNEAPOLIS, MINN.

(19) A. L. McCloskey, G. S. Fonken, R. W. Kliuber, and W. S. Johnson, *Org. Syntheses*, **34**, 28 (1954).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ARKANSAS]

An Oxygen-18 Tracer Study of the Stobbe Condensation[1]

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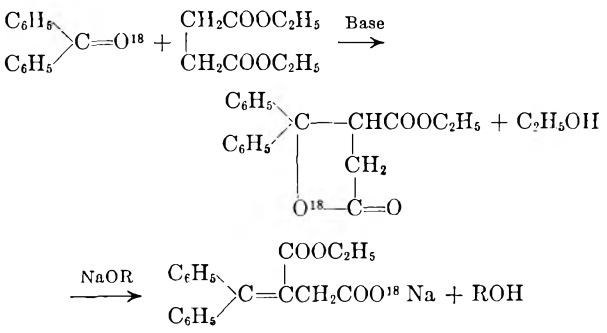
A tracer study of the Stobbe condensation of diethyl succinate and benzophenone-O^{18} has been carried out. The product, β-carbethoxy-γ,γ-diphenylvinylacetic acid, has been shown to contain all of the oxygen-18 enrichment of the starting ketone. Upon degradation, all of the enrichment was found to be located in the free carboxyl group of the half-ester. These facts offer confirmatory evidence for the currently favored mechanism for the reaction. Considerable incidental information is presented concerning oxygen exchange between carboxylic acids and aqueous media.

The Stobbe condensation,[3] which consists of the base-catalyzed reaction of an aldehyde or ketone with an ester of succinic acid to give a half-ester of a substituted alkylidenesuccinic acid, has been reviewed by Johnson and Daub[4] in *Organic Reactions*. The salient features of the stoichiometry and scope of the reaction have been well established, and the reaction sequence presented by Johnson, McCloskey, and Dunnigan[5] seems to be consistent with all the known facts.

An essential feature of this mechanism is the formation of a paraconic acid ester intermediate in which the oxygen atom of the carbonyl compound becomes attached to the carbonyl carbon of one of the original ester groups. Subsequent cleavage of the lactone ring results in complete transfer of this same oxygen atom to the carboxylate anion of the resulting half-ester. This sequence is illustrated below for the reaction between benzophenone-O^{18} and diethyl succinate, the compounds used in this work.



Although no obvious reaction sequence by which it might be accomplished is apparent, it is conceivable that the oxygen-containing group which is eliminated could contain the oxygen of the carbonyl compound. The intramolecular transfer of oxygen from one carbon atom to another appeared sufficiently unusual to make it worthwhile to check this point by a tracer experiment.

DISCUSSION

The condensation of oxygen-18 labeled benzophenone and diethyl succinate was chosen as a suitable reaction for this study. The reported yields of product are high by both the potassium *t*-butoxide method[4] and the sodium hydride method.[6] The starting ketone, the product of the condensation and all degradation products are easily purified solids with characteristic melting points. Two of the four degradation procedures attempted had already been applied to the product of this reaction, β-carbethoxy-γ,γ-diphenylvinylacetic acid. The oxygen-18 labeled benzophenone was readily accessible by the method of Doering and Dorfmann.[7]

When the product of the reaction, β-carbethoxy-γ,γ-diphenylvinylacetic acid, was analyzed for oxygen-18, it was found to contain the total enrichment (1.10 atom per cent excess) of the starting ketone (1.09 atom per cent excess). This fact, in itself, shows that the ketone oxygen atom has been transferred to the product half-ester.

However, in order to establish unequivocally that the labeled atom had been transferred to the carboxylate anion, it was necessary to degrade the β-carbethoxy-γ,γ-diphenylvinylacetic acid. The several degradative procedures on which some experimental work was done were (a) an acid-catalyzed decarbethoxylation of the β-carbethoxy-γ,γ-diphenylvinylacetic acid or an acid-catalyzed decarboxylation of the γ,γ-diphenylitaconic acid arising from its hydrolysis;[8] (b) a thermal decarboxylation of the β-carbethoxy-γ,γ-diphenylvinylacetic acid; (c) a degradation of β-carbethoxy-γ,γ-diphenylvinylacetic acid according to the reaction scheme of Stobbe;[9] (d) an application of the

(1) This work is abstracted from the M.S. thesis of David A. Jeffery, University of Arkansas, 1957, and was supported by the Atomic Energy Commission.

(2) Coulter W. Jones Scholar, 1956.

(3) H. Stobbe, *Ber.*, **26**, 2312 (1893).

(4) W. S. Johnson and G. H. Daub, *Org. Reactions*, **6**, 1 (1951).

(5) W. S. Johnson, A. L. McCloskey, and D. A. Dunnigan, *J. Am. Chem. Soc.*, **72**, 514 (1950).

(6) G. H. Daub and W. S. Johnson, *J. Am. Chem. Soc.*, **70**, 418 (1948); **72**, 501 (1950).

(7) W. von E. Doering and E. Dorfman, *J. Am. Chem. Soc.*, **75**, 5595 (1953).

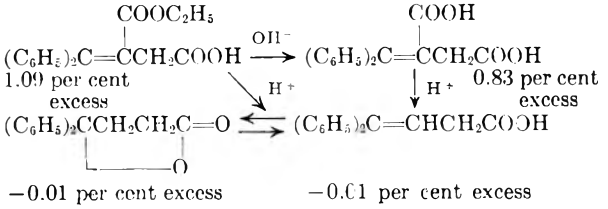
(8) W. S. Johnson, J. W. Petersen, and W. P. Schneider, *J. Am. Chem. Soc.*, **69**, 74 (1947).

(9) H. Stobbe, *Ann.*, **308**, 104 (1899).

Hunsdiecker degradation[10] of the silver salt of β-carbethoxy-γ,γ-diphenylvinylacetic acid.

During the application of these methods considerable incidental information concerning the oxygen exchange reaction of the carboxylic acids involved was also obtained. The very fact that the product half-ester contained all of the enrichment of the starting ketone demonstrates the lack of exchange between β-carbethoxy-γ,γ-diphenylvinylacetic acid and the aqueous acetic and hydrochloric acids and 1*N* aqueous ammonium hydroxide used in its work-up procedure.

When the method of Johnson, Peterson, and Schneider[8] for the acid-catalyzed decarbethoxylation of β-carbethoxy-γ,γ-diphenylvinylacetic acid or the acid-catalyzed decarboxylation of its hydrolysis product, γ,γ-diphenylitaconic acid, was tried on oxygen-18 labeled compounds, it was found that the equilibrium mixture of γ,γ-diphenylvinylacetic acid and γ,γ-diphenylbutyrolactone produced contained no excess oxygen-18. This result, which was not unexpected, indicates that exchange of the carboxyl group oxygen with the aqueous reaction medium was essentially complete under these conditions.

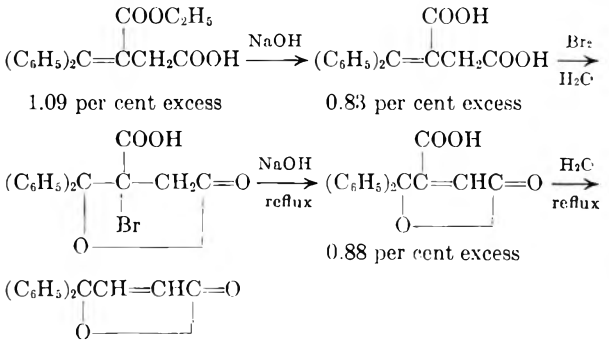


This exchange probably takes place by the mechanism proposed by Bender, Stone, and Dewey[11] for the acid-catalyzed oxygen exchange of substituted benzoic acids with water. The mechanism involves addition of a molecule of water to the carboxylic acid to give an ortho acid, which can break down to give the exchange products.

It is noteworthy that the basic hydrolysis of β-carbethoxy-γ,γ-diphenylvinylacetic acid to γ,γ-diphenylitaconic acid shown above resulted in partial loss of oxygen-18 enrichment (1.10 atom per cent excess in the half-ester and only 0.83 atom per cent excess in the dibasic acid). This fact is not in line with the conclusions reported in Dole's review article[12] to the effect that carboxyl groups undergo exchange only in the presence of strong acids, while the oxygen of peptide bonds, amides, and ureas does not undergo exchange in either acidic or alkaline medium. It is not inconceivable that the exchange may occur during the working-up of the γ,γ-diphenylitaconic acid, but this would imply an extremely fast rate of exchange at low temperature, which appears unlikely, especially in view of the fact that there was no exchange in the acidic work-up of the original half-ester. The approximate agreement of the oxygen-18 analysis values for γ,γ-diphenylitaconic acid (0.83 atom per cent excess) and γ,γ-diphenylaconic acid (0.88 atom per cent excess) also suggests that exchange must have occurred during hydrolysis since no apparent exchange was observed in this conversion.

Thermal decarboxylation of β-carbethoxy-γ,γ-diphenylvinylacetic acid containing 1.10 atom per cent excess oxygen-18 in refluxing quinoline using copper chromite as a catalyst gave carbon dioxide with 0.69 atom per cent excess oxygen-18. Presumably the chief source of carbon dioxide would be the free carboxyl group of the half-ester, indicating that at least part of the enrichment was located there. However, since exchange of some kind or dilution with unenriched carbon dioxide had obviously taken place, and since all efforts to isolate crystalline products from the residue failed, this experiment must be regarded as inconclusive.

The experimental work done by Stobbe[9] on the compound β-carbethoxy-γ,γ-diphenylvinylacetic acid suggested a means of degrading this compound and establishing the position of the labeling. This series of reactions is outlined below and involved hydrolysis of the half-ester to the diacid, γ,γ-diphenylitaconic acid, followed by bromination of the diacid to give γ,γ-diphenyl-β-bromoparaconic acid which was subsequently dehydrohalogenated to yield γ,γ-diphenylaconic acid. Subsequent dissolution of the γ,γ-diphenylaconic acid in a large excess of water, and refluxing, led to decarboxylation to give γ,γ-diphenylcrotonlactone. The γ,γ-diphenylcrotonlactone should contain the total enrichment of the β-carbethoxy-γ,γ-diphenylvinylacetic acid if there were no exchange of the oxygen of the carboxyl group with the reaction medium during the course of such a series of reactions.



When this reaction sequence was carried out on the labeled compounds, the oxygen-18 results indicated above were obtained. It should be noted that exchange with the aqueous medium did not occur during the conversion of γ,γ-diphenylitaconic acid to γ,γ-diphenylaconic acid, but that partial exchange did occur during the decarboxylation of the latter compound to γ,γ-diphenylcroton-

(10) J. Kleinberg, *Chem. Revs.*, **40**, 381 (1947).

(11) M. L. Bender, R. R. Stone, and R. S. Dewey, *J. Am. Chem. Soc.*, **78**, 319 (1956).

(12) M. Dole, *Chem. Revs.*, **51**, 263 (1952).

lactone. This last observation is in accord with the evidence put forth by Long and Friedman[13] through an oxygen-18 study of the hydrolysis of γ-butyrolactone. This lactone upon acidic hydrolysis is known to form an equilibrium mixture of lactone and γ-hydroxybutyric acid. When this reaction was carried out in oxygen-18 enriched water it was found that exchange of the oxygen of the carboxylic acid group of the γ-hydroxybutyric acid with water took place in both acidic and alkaline media. The fact that *any* enrichment remained in the γ,γ-diphenylcrotonlactone indicates clearly that *at least part* of the original enrichment was in the free carboxyl group of the β-carbethoxy-γ,γ-diphenylvinylacetic acid.

A final conclusive proof that all of the original enrichment of the benzophenone was in the free carboxyl group of the half-ester is found in the results of the Hunsdiecker degradation. When the silver salt of β-carbethoxy-γ,γ-diphenylvinylacetic acid (1.10 atom per cent excess oxygen-18) was treated with bromine, the carbon dioxide evolved contained all of the enrichment (1.18 atom per cent excess).

$$(C_6H_5)_2C{=}C(COOC_2H_5)CH_2COOH \xrightarrow{AgNO_3} (C_6H_5)_2C{=}C(COOC_2H_5)CH_2COOAg \xrightarrow[CCl_4]{Br_2}$$

1.10 per cent excess

$$(C_6H_5)_2C{=}C(COOC_2H_5)CH_2Br + CO_2$$

1.18 per cent excess

The results of this study are in full agreement with the mechanism involving a paraconic acid ester intermediate as proposed by Johnson, McCloskey, and Dunnigan.[5] These results, however, do not rule out the possibility of a mechanism such as condensation of the ketone with diethyl succinate to yield the diester which in turn may be partially hydrolyzed. This last possibility appears to be highly unlikely in view of the evidence presented by Johnson and Daub,[4] and we feel that the essential features of the Johnson, McCloskey, and Dunnigan[5] mechanism have been unequivocally established.

EXPERIMENTAL

Preparation of oxygen-18 labeled β-carbethoxy-γ,γ-diphenylvinylacetic acid. Benzophenone-O^{18}, m.p. 47–48°, containing 1.10 atom per cent excess oxygen-18 was prepared according to the procedure of Doering and Dorfman[7] and treated with diethyl succinate and sodium hydride[14] according to the method of Daub and Johnson.[6] The crude β-carbethoxy-γ,γ-diphenylvinylacetic acid, m.p. 124.5–125°, was obtained in 97.5 per cent yield. Recrystallization from benzene-petroleum ether gave a product of m.p. 123.5–124°, reported[4] m.p. 123–124.5°, which contained 1.09 atom per cent excess oxygen-18.

Preparation of oxygen-18 labeled γ,γ-diphenylitaconic acid. Oxygen-18 labeled β-carbethoxy-γ,γ-diphenylvinylacetic acid containing 1.09 atom per cent excess oxygen-18 was refluxed in 2*N* sodium hydroxide for 3 hr. After cooling, acidification with 6*N* hydrochloric acid, and recrystallization from dilute ethanol, γ,γ-diphenylitaconic acid was obtained in 89.9 per cent yield. The acid melted at 169–170°, reported[9] m.p. 170–171°, and contained 0.83 atom per cent excess oxygen-18.

Acid-catalyzed decarbethoxylation of β-carbethoxy-γ,γ-diphenylvinylacetic acid. β-Carbethoxy-γ,γ-diphenylvinylacetic acid containing 1.09 atom per cent excess oxygen-18 was treated with a mixture of acetic and hydrobromic acids according to the procedure of Johnson, Petersen, and Schneider.[8] γ,γ-Diphenylvinylacetic acid was isolated in 64 per cent yield, and upon recrystallization from dilute ethanol melted at 116–117°, reported[8], m.p. 117–118.5°. γ,γ-Diphenylbutyrolactone, m.p. 91.5–92°, reported[8] m.p. 90–91° was also isolated in 30 per cent yield. The γ,γ-diphenylvinylacetic acid contained −0.01 atom per cent excess oxygen-18. The lactone was not analyzed for oxygen-18.

Acid-catalyzed decarboxylation of γ,γ-diphenylitaconic acid. γ,γ-Diphenylitaconic acid containing 0.83 atom per cent excess oxygen-18 was decarboxylated following the procedure of Johnson, Petersen, and Schneider[8] used above. γ,γ-Diphenylvinylacetic acid, m.p. 117–118°, and γ,γ-diphenylbutyrolactone, m.p. 91–92°, were isolated in 63 and 35 per cent yields, respectively. The γ,γ-diphenylbutyrolactone contained −0.01 atom per cent excess oxygen-18. The acid was not analyzed for oxygen-18.

Attempted thermal decarboxylation of β-carbethoxy-γ,γ-diphenylvinylacetic acid. One-half gram of oxygen-18 labeled β-carbethoxy-γ,γ-diphenylvinylacetic acid was dissolved in 3 ml. of quinoline in a 25 ml. two-necked flask fitted with a dropping funnel and reflux condenser. A trace of copper chromite catalyst was added and the temperature was maintained at the reflux temperature of quinoline for a period of 2.5 hr. Nitrogen, previously dried by passage through Fieser's solution, sulfuric acid, a magnesium perchlorate tube, and an Ascarite tube, was used as a sweep gas. The carbon dioxide evolved was collected in a sample tube maintained at liquid nitrogen temperature. Excess nitrogen was pumped off prior to oxygen-18 analysis of the carbon dioxide. The reaction mixture was taken up in ether and washed 5 times with dilute hydrochloric acid to remove quinoline. The ether extract was dried over magnesium sulfate and upon filtration and subsequent evaporation of the ether yielded an intractable dark red oil. The evolved carbon dioxide contained 0.69 atom per cent excess oxygen-18.

Preparation of oxygen-18 labeled γ,γ-diphenyl-β-bromoparaconic acid. Twenty-five grams of the oxygen-18 labeled γ,γ-diphenylitaconic acid prepared above was suspended in 50 ml. of water. To this mixture, 14 g. of bromine was added dropwise. The mixture was stirred for a period of 3 hr. during which time the resinous mass initially formed on addition of bromine was broken up into fine crystalline particles. The mixture was filtered and the residue on the filter was washed thoroughly with water and dried. Thirty-one grams of a crude mixture was obtained which was fractionally crystallized from benzene to yield 10.5 g. of a bromine containing compound melting at 150–170° with decomposition; reported for γ,γ-diphenyl-β-bromoparaconic acid[9], m.p. 170–171°. The filtrate was concentrated to give a brownish colored crystalline mass which was not further purified. Repeated attempts to further purify the bromine containing compound by crystallization failed to give a sharp melting point and as a result this material was not analyzed for oxygen-18.

Preparation of γ,γ-diphenylaconic acid. Three grams of the crude γ,γ-diphenyl-β-bromoparaconic acid prepared above was dissolved in 100 ml. of 3% sodium hydroxide solution

(13) F. A. Long and L. Friedman, *J. Am. Chem. Soc.*, **72**, 3692 (1950).

(14) In preliminary experiments both the potassium *t*-butoxide and the sodium hydride methods were investigated. The labeled experiments utilized only the sodium hydride method.

and refluxed for 2 hr. The cooled solution was diluted to 10 times its original volume and acidified with 6*N* hydrochloric acid. The resulting precipitate was filtered and dried, yielding 2.17 g. (94.8 per cent) of γ,γ-diphenylaconic acid. A portion of this was recrystallized from benzene for oxygen-18 analysis. The purified acid melted at 136–137°, reported[9] 138–139°, and contained 0.88 atom per cent excess oxygen-18.

Preparation of γ,γ-diphenylcrotonlactone. Two grams of γ,γ-diphenylaconic acid was dissolved in 500 ml. of water and refluxed for 1 week. The solution was concentrated and extracted with ether. The ethereal solution was extracted with a 5 per cent solution of sodium carbonate to remove acidic material. The ethereal solution was concentrated and 0.15 g. of γ,γ-diphenylcrotonlactone was obtained which was further purified by recrystallization from ether to give a product of m.p. 130–131°, reported[9] m.p. 130–131°. The compound contained 0.31 atom per cent excess oxygen-18.

Silver salt degradation of β-carbethoxy-γ,γ-diphenylvinylacetic acid. The silver salt of β-carbethoxy-γ,γ-diphenylvinylacetic acid was treated with bromine in refluxing carbon tetrachloride in the usual Hunsdiecker degradation procedure.[10] The carbon dioxide evolved during the reaction was swept out of the system by helium and trapped in a sample tube at liquid nitrogen temperature after first passing through a dry ice trap to condense bromine vapor. The crude product obtained from the carbon tetrachloride solution was further purified by recrystallization from an ether-petroleum ether mixture, to give ethyl α-benzhydrilidene-β-bromopropionate. The purified product melted at 96–97°.

Anal. Calcd. for $C_{18}H_{17}BrO_2$: C, 62.62; H, 4.96; Br, 23.15. Found: C, 62.56; H, 4.92; Br, 22.98. The carbon dioxide contained 1.18 atom per cent excess oxygen-18. The bromide was not analyzed for oxygen-18.

Analysis of organic compounds for oxygen-18. The procedure employed in this laboratory was one recently reported by Doering and Dorfman.[7] This method involved the pyrolysis of oxygen-containing organic compounds over carbon at 1120° to carbon monoxide followed by oxidation of the carbon monoxide by iodine pentoxide to carbon dioxide. The apparatus was essentially that described by Dinerstein and Klipp.[15] Helium was used as a sweep gas and was passed through Fieser's solution and concentrated sulfuric acid prior to passage through the reduction tube. The effluent gases were passed through a U-tube cooled in dry ice-isopropyl alcohol to condense iodine vapor; the carbon dioxide was finally collected in a sample trap immersed in liquid nitrogen.

The apparatus had an apparent memory effect for the sample which had immediately preceeded. At most, two consecutive analyses were required to remove this effect and give reproducible results with a given compound. The precision of this method for determining oxygen-18 concentration in organic compounds is excellent as can be seen from the reproducibility of the results shown in Table I. No suitable explanation is at hand for the fairly large difference between the oxygen-18 value for β-carbethoxy-γ,γ-diphenylvinylacetic acid and the carbon dioxide obtained from its degradation.

The isotopic $CO^{16}O^{18}/CO^{16}O^{16}$ ratios were determined in a Consolidated Model 21-401 mass spectrometer. The heights of the 46 and 44 mass/charge peaks were assumed to be proportional to the $CO^{16}O^{18}$ and $CO^{16}O^{16}$ concentrations, respectively. The $CO^{16}O^{18}$ value used here neglects any contribution from the $C^{13}O^{16}O^{17}$ peak, which is considered to be negligible. For each sample the mass spectrum was scanned at least five times, and the values reported are averages of the ratios obtained.

(15) R. A. Dinerstein and R. W. Klipp, *Anal. Chem.*, 21, 545 (1949).

Calculations and results.[16] In calculating the results of these experiments, the main problem involved is proper treatment of the dilution of the oxygen-18 enrichment which takes place during pyrolysis of the organic compound and the subsequent oxidation of the carbon monoxide to carbon dioxide. In the benzophenone, all of the oxygen-18 is concentrated in the one oxygen position. For comparison purposes, these calculations attribute all of the *excess* oxygen-18 (over that normally present) in all of the other compounds to a single position also. This procedure makes no assumption concerning the actual position in the molecule which contains excess oxygen-18, or even concerning the number of positions which contain excess oxygen-18. It does assume that the oxygen introduced into the organic compounds from other sources than benzophenone (including that introduced from the iodine pentoxide in the oxidation of carbon monoxide to carbon dioxide) is of normal isotopic composition.

TABLE I

RESULTS OF MASS SPECTROMETER ANALYSES

Compound	$(n+1)$	$c_1 \times 10^3$	$c_2 \times 10^3$	Excess atom Per Cent $y \times 100$
Benzophenone	2	14.39	3.66	1.07
		15.52	3.91	1.12
		14.96	3.82	1.11
		14.60	3.83	1.08
			Average	1.10
β-Carbethoxy-γ,γ-diphenylvinylacetic acid	8	6.38	3.66	1.08
		6.66	3.86	1.11
		6.58	3.83	1.09
			Average	1.09
γ,γ-Diphenylitaconic acid	8	5.95	3.91	0.81
		6.06	3.91	0.85
			Average	0.83
γ,γ-Diphenylvinylacetic acid	4	3.82	3.85	−0.01
γ,γ-Diphenylbutyrolactone	4	3.84	3.88	−0.01
CO_2 from thermal decarboxylation of β-carbethoxy-γ,γ-diphenylvinylacetic acid	2	10.83	3.89	0.69
γ,γ-Diphenylaconic acid	4	6.18	3.95	0.89
		6.15	3.95	0.88
		6.16	3.95	0.88
			Average	0.88
γ,γ-Diphenylcrotonlactone	4	5.55	3.94	0.32
		5.47	3.94	0.30
		5.53	3.94	0.32
			Average	0.31
CO_2 from silver salt degradation of β-carbethoxy-γ,γ-diphenylvinylacetic acid	2	15.81	3.93	1.18
		15.78	3.93	1.17
			Average	1.18

(16) The authors are indebted to Dr. T. C. Hoering of this laboratory for several helpful discussions of the mass spectrometer analytical techniques and methods of calculation.

It can readily be shown that the excess atom fraction of oxygen-18 of a single position to which all enrichment is attributed, y, can be related to the observed mass spectrometer ratios by the following equation:

$$y = (n + 1)\left[\frac{c_2}{2 + c_2} - \frac{c_1}{2 + c_1}\right]$$

where c_1 = $CO^{16}O^{18}/CO^{16}O^{16}$ ratio in tank carbon dioxide as measured on the mass spectrometer

c_2 = $CO^{16}O^{18}/CO^{16}O^{16}$ ratio in enriched carbon dioxide as measured on the mass spectrometer

and n = the number of atoms of oxygen of normal isotopic composition which are added to the single enriched atom during analysis.

Using this equation and the values of n, c_1, and c_2 determined experimentally, the results given in Table I were calculated.

FAYETTEVILLE, ARK.

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

Coplanarity and Chromatographic Adsorbability of Some Isomeric Naphthylcycloalkenes and Polycyclic Aromatic Hydrocarbons[1,2]

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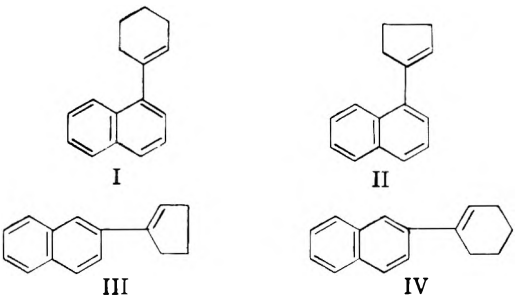
Received January 21, 1957

Binary mixtures (dissolved in isooctane) of (a) isomeric α- and β-substituted naphthalenes bearing phenyl, cyclohexenyl (I and IV), and cyclopentenyl (II and III) groups; (b) II and IV, and; (c) anthracene and phenanthrene, were investigated by down-flow frontal analysis for relative chromatographic adsorbability on silicic acid impregnated with picric acid or 2,4,7-trinitrofluorenone. In cases (a) and (b) the more nearly coplanar β-substituted naphthalene was adsorbed more tenaciously while in (c) little difference in adsorbability was evident. Results were consistent with data for displacement analysis of binary mixtures from alumina. The characteristics of impregnated silicic acid as an adsorbent are described. In particular it is proposed that adsorption of the substrate occurs principally *via* a steady-state process in which the impregnant molecules serve as "active sites" for molecular compound formation on the surface of the ground mass, silicic acid.

A survey of published observations reveals that coplanarity factors may play an important part in chromatographic adsorbabilities of conjugated isomeric biaryls and arylalkenes on alumina. Thus Orchin and Reggel[5] found that 2,2′-binaphthyl (effectively coplanar) was held more tenaciously than the more twisted 1,2′-binaphthyl. For mixtures of the geometric isomers of stilbene, 4,4′-dimethylstilbene, and 4,4′-dimethoxystilbene the coplanar *trans* form was adsorbed more strongly in every case.[6] A mixture of the three possible 1,4-diphenylbutadienes, moreover, showed the order of adsorbability *trans-trans* (coplanar) > *trans-cis* > *cis-cis* (noncoplanar).[7] Also indicative of such an effect are the findings of Orchin and coworkers[5,8] that adsorbabilities of certain conjugated iso-π-electronic (though not isomeric) aromatic hydrocarbons fall in the orders: fluoranthene > mixed 1- and 2-phenylnaphthalenes > 1-phenylnaphthalene; benzofluoranthene > 1,2′-binaphthyl;[9] and perylene > 1,1′-binaphthyl.[10] The authors report herewith semiquantitative studies on the relative adsorbabilities of various other such pairs of hydrocarbons (usually isomeric substituted naphthalenes) on alumina, silicic acid impregnated with picric acid (TNP) or 2,4,7-trinitrofluorenone (TNF),[11] and silicic acid alone.



In studies with alumina, limited approximately equimolar amounts of the isomeric pairs I plus IV

(1) Supported (in part) by the Petroleum Research Fund of the AMERICAN CHEMICAL SOCIETY and (in part) through sponsorship by the Office of Ordnance Research, U. S. Army, contract number DA-04-200-ORD-176.

(2) Part of this material was presented at the Symposium on Polycyclic Hydrocarbons at the Atlantic City Meeting of the AMERICAN CHEMICAL SOCIETY, September, 1956. Part IX in the series on Chemical Reactivities of Arylcycloalkenes. For paper VIII see L. H. Klemm, J. W. Sprague, and E. Y. K. Mak, *J. Org. Chem.*, 22, 161 (1957).

(3) Research assistant, 1955–56.

(4) Research associate, 1956.

(5) M. Orchin and L. Reggel, *J. Am. Chem. Soc.*, 69, 505 (1947).

(6) L. Zechmeister and W. H. McNeely, *J. Am. Chem. Soc.*, 64, 1919 (1942).

(7) Alumina containing 25% of celite was used; J. H. Pinckard, B. Wille, and L. Zechmeister, *J. Am. Chem. Soc.*, 70, 1938 (1948).

(8) M. Orchin and R. A. Friedel, *J. Am. Chem. Soc.*, 68, 573 (1946).

(9) *Cf.* M. Orchin and L. Reggel, *J. Am. Chem. Soc.*, 73, 436 (1951).

(10) In the last of these cases the alumina was diluted with the apparently relatively inactive Super-Cel.

(11) The use of silica gel impregnated with a polynitroaromatic complexing agent for gross separation of hydrocarbon mixtures into aromatic, hydroaromatic and alkenic, and saturated hydrocarbons was reported by M. Goldewicz, *Nature*, 164, 1132 (1949).

and 1-phenylnaphthalene (V) plus 2-phenylnaphthalene (VI) were first adsorbed on the column and then eluted with an appropriate solvent (isooctane in the former case, 2 volume % acetone in isooctane in the latter). Spectral investigation of the effluent showed that in both cases the column was virtually, if not completely, depleted of 1-isomer before the 2-isomer began to appear.

For adsorption on impregnated silicic acid a down-flow frontal analysis method was used wherein standard isooctane influent solution approximately equimolar in each of the two components to be compared was allowed to percolate continuously through the column under gravity. Combinations of substituted naphthalenes used as solutes (α and β, respectively) were the isomeric pairs I and IV, II and III, and V and VI (adsorbed on columns of both TNF- and TNP-impregnated silicic acid) as well as the nonisomeric pair II and IV (adsorbed on the former column only). Through periodic ultraviolet spectrophotometric analysis of the effluent values were obtained for the retention ratio, Q (ratio of moles of β-compound retained on the column to moles of α-compound retained), as a function of cumulated volume of influent. Though not all experiments were pursued to the same relative degree of completeness, the typical resultant curve (Fig. 1) had a sigmoid shape and incorporated the features of (a) an initial horizontal portion (all α and β retained on column) where the retention ratio equals the ratio of concentrations of β to α in the standard influent; (b) a region of continuous and relatively rapid rise due to greater adsorbability of β than of α; and (c) a region wherein the curve levels off rapidly and attains a constant maximum value (corresponding to a steady state in the system). However, inasmuch as the present exploratory research was designed only for qualitative checking of the relationship between coplanarity and adsorbability, we record herewith (Table I) simply the maximum retention ratio (Q_{max}) observed in each case, irrespective of whether a steady state was attained or not.

Examination of Fig. 1 and Table I shows that in every instance the β-substituted naphthalene is adsorbed more strongly than the corresponding α-derivative, in accordance with the inherent smaller angle of twist and the decreased restriction to attainment of coplanarity in the former. This occurs even for the pair II and IV, where the difference in conjugative effect[12] of the cyclopentenyl and cyclohexenyl groups is still insufficient to offset the factor of twist.[13] However, in view of the suggestion[14] that the strength of adsorption should increase with increasing melting point it seems pertinent to inquire if the relationship found here might not fundamentally be associated with relative melting points rather than with relative angles of twist. In this regard there are recorded in Table I melting points of the hydrocarbons themselves as well as of their corresponding TNP and TNF molecular compounds. Included are also data on the phenanthrene-anthracene pair, selected for study because the components are both iso-π-electronic and planar and because their analogous TNP and TNF molecular compounds have essentially identical melting points. Examination of Table I shows that no consistent correlation of melting point and adsorbability prevails. Thus the orders of adsorbability IV > I on TNP-impregnated silicic acid, IV > II on TNF-impregnated silicic acid, and anthracene $\cong$ phenanthrene on plain silicic acid are inconsistent with the respective orders of melting points I.TNP > IV.TNP, IV.TNF $\cong$ II.TNF, and anthracene >> phenanthrene.

For the substrate mixtures I–IV and anthracene-phenanthrene experiments were conducted, under otherwise identical conditions, with adsorbents of both plain and impregnated silicic acids. Comparison of the results showed that (1) the presence of the complexing agent on the column serves to increase the total quantity of hydrocarbon adsorbed and (2) the molar ratio of hydrocarbon adsorbed to complexing agent present on the column is considerably less than 1 in all cases, but is closer to 1 for TNF as an impregnant than for TNP as an impregnant. Observation (2) is consistent with the generalization that TNF displays greater potency as a complexing agent than does TNP.

Pending further investigation, the authors tentatively propose the following as characteristics of these impregnated silicic acid columns: (a) The polynitro complexing agent, A, is adsorbed flatwise and monomolecularly at selected spots on the surface of the silicic acid ground mass. (b) Each such molecule of A constitutes an "active site" (designated as P) upon which only one molecule (in the usual case) of hydrocarbon substrate, B, may be adsorbed. (c) Adsorption of B on A is identifiable with molecular compound formation, of a type essentially like that which occurs in solution rather than like that which occurs in a crystalline solid.

It follows from characteristic (b) that the number of active sites of type P can be varied at will and in a quantitatively calculable fashion by varying the amount of complexing agent used for impregnation. Unfortunately silicic acid may fall short of ideality

(12) L. H. Klemm, W. Hodes, and W. B. Schaap, *J. Org. Chem.*, 19, 451 (1954).

(13) The close similarity of the ultraviolet spectra of the various 1-substituted napthhalenes used here (*cf.* ref. 36) precludes studies on mixtures such as I and II by our analytical procedure. Though the ultraviolet spectra of III and IV differ to a larger extent analysis of such a mixture by this method would still present difficulties.

(14) A discussion of this will be found in H. G. Cassidy, *Adsorption and Chromatography*, Interscience Publishers, Inc., New York, N. Y., 1951, pp. 128–9. It seems to us, however, that the example of the diphenylpolyenes cited there is a poor choice since the adsorbabilities also fall in the order expected on the basis of relative extents of the conjugated systems present.

TABLE I

RELATIVE CHROMATOGRAPHIC ADSORBABILITIES ON PLAIN AND IMPREGNATED SILICIC ACID COLUMNS

	Binary Substrate Mixture[a]									
	α-Component				β-Component				Molar ratio influent	Retention Ratio,
Impregnant, A on Silicic Acid	Compound B_1	M. p. of B_1 °C.	M. p. of A·B_1 °C.	Conc. in influent[b]	Compound B_2	M. p. of B_2 °C.	M. p. of A·B_2 °C.	Conc. in influent[b]	(β/α)	Q_{max}[c] (β/α)
None	I	48	...	10.0	IV	61	...	10.0	1.00	1.21[d]
	Phenanthrene	98	...	10.0	Anthracene	215	...	10.0	1.00	1.02[d]
4.4% TNP	I	48	127[e]	5.64	IV	61	82[e]	5.53	0.98	1.62[d]
	II	<25[f]	76[e]	4.61	III	86	104[e]	4.59	1.00	2.1[g]
	V	<25[h]	...[i]	6.36	VI	103	...[j]	6.41	1.00	>1.03[k]
	Phenanthrene	98	133[l]	10.0	Anthracene	215	138[l]	10.0	1.00	0.92[d]
0.66% TNF	I	48	...[m]	3.37	IV	61	129[m]	4.86	1.44	4.0[g]
4.0% TNF	II	<25[f]	125[m]	4.61	III	86	149[m]	4.59	1.00	2.7[n]
	II	<25[f]	125[m]	9.21	IV	61	129[m]	7.38	0.80	1.8[n]
0.66% TNF	V	<25[h]	...[i]	6.01	VI	103	171[o]	5.72	0.95	2.2[g]
4.0% TNF	Phenanthrene	98	197[o]	10.0	Anthracene	215	194[o]	10.0	1.00	1.05[d]

[a] Dissolved in spectral grade isooctane. [b] In units of $10^{-4}M$. [c] Uncorrected for effect of layers of plain silicic acid in the cases of the impregnated columns. [d] Column apparently in a steady-state condition. [e] See ref. 17. [f] B.p. 121–122.5°/0.4 mm. [g] System not yet in a steady state. [h] B.p. 121–126°/0.5 mm. [i] It has been reported[5] that V fails to form a crystalline complex with either TNP or TNF. [j] M. Orchin and R. A. Friedel [*J. Am. Chem. Soc.*, **71**, 3002 (1949)] reported that the picrate of VI "is so unstable as to elude isolation." *Cf.* R. A. Friedel, M. Orchin, and L. Reggel, *J. Am. Chem. Soc.*, **70**, 199 (1948). [k] Quantitative measurements were conducted only so far as to be sure V was appearing in the filtrate considerably earlier than VI could be detected therein. From semiquantitative data, however, one can estimate a Q_{max} of 1.3 for steady state. [l] O. L. Baril and E. S. Hauber, *J. Am. Chem. Soc.*, **53**, 1087 (1931). [m] No crystalline TNF compound forms for I. See L. H. Klemm and J. W. Sprague, *J. Org. Chem.*, **19**, 1464 (1954). [n] Essentially in a steady-state condition. Value given is an average taken over fluctuations in the upper asymptotic part of the curve. [o] M. Orchin and E. O. Woolfolk, *J. Am. Chem. Soc.*, **68**, 1727 (1946).

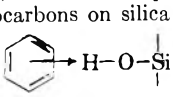
as a ground mass since it exhibits active sites (designated as G) for adsorption of B[15] in the absence of any molecules of A. Lending credence to the identity of molecular compound formation and adsorption (characteristic c) is the fact that in three cases a colored zone formed at the top of the impregnated adsorbent and gradually expanded downward as the experiment continued. From (c) it appears that one might be able to obtain relative steady-state constants for molecular compound formation on impregnated silicic acid which should be directly comparable to the corresponding relative equilibrium constants for the same reactions occurring in solution.

Efforts are underway in our laboratory to investigate further the characteristics of chromatographic columns impregnated with polynitroaromatic complexing agents and to develop, if possible, quantitative relationships thereon.

EXPERIMENTAL

Materials used. Alcoa grade F-20 alumina and Mallinckrodt reagent grade 100-mesh silicic acid were used as obtained. All solvents for recrystallization and chromatography were reagent or spectral grade. TNP (practical grade) was purified by recrystallization once from ethanol, air-drying, and then recrystallization from benzene–petroleum ether (30–60°), m.p. 120–121°. TNF (Dajac Laboratories[16]) was freed of a more strongly adsorbed brown impurity by elution chromatography using chloroform and silicic acid and was then recrystallized from chloroform, m.p. 172–173°. Naphthylcycloalkenes I–IV were prepared and purified as previously described.[17] 1-Phenylnaphthalene[18] was refluxed 4 hr. with Raney nickel[19] in ethanol, distilled *in vacuo*, heated with 30% palladium-on-charcoal for 4 hr. at 350°,[5] and redistilled, b.p. 121–126°/0.5 mm., $n_D^{25.5}$ 1.6637, log ϵ = 4.74 at 225 mμ in isooctane solution; reported[5] n_D^{20} 1.6646, log ϵ = 4.78 at 225 mμ in cyclohexane solution. 2-Phenylnaphthalene was prepared by dehydrogenation of IV (7 g.) by heating at 300–350° with 30% palladium-on-charcoal (0.4 g.) for 2.5 hr., extraction into benzene, and recrystallization from absolute ethanol to constant m.p., 101–102.5°, yield 80–90%.[20] C.p. anthracene was purified further by the method described by Fieser,[21] m.p. 214–215°. Technical grade phenanthrene was treated as described by Phillips[22] and then chromatographed as for anthracene, m.p. 97–98°.

Impregnation of silicic acid. Method A. Through a wet (with chloroform) column of 100 g. of silicic acid was percolated approximately 2. l. of 0.01*M* solution of TNP or TNF in chloroform (sufficient to ensure saturation of the column). The column was allowed to drain for 12 hr. and then the upper and lower sections were dug out and discarded. The central portion (50–60% of total length) was dried in air for a day and then at 100° for 2–3 hr., pulverized with a mortar and pestle, and stored in a brown bottle. Microanalysis for

(15) It has been proposed that adsorption of aromatic hydrocarbons on silica gel may involve a π-complex of the type  ; see A. V. Kiselev, *Doklady Akad. Nauk S. S. S. R.*, **106**, 1046 (1956).

(16) To which we are indebted for a gift of this chemical.

(17) L. H. Klemm and W. Hodes, *J. Am. Chem. Soc.*, **73**, 5181 (1951).

(18) R. Weiss, *Org. Syntheses*, Coll. Vol. III, 729 (1955).

(19) R. Mozingo, *Org. Syntheses*, Coll. Vol. III, 181 (1955); A. A. Pavlic and H. Adkins, *J. Am. Chem. Soc.*, **68**, 1471 (1946).

(20) We are indebted to Dr. Herman Ziffer for this preparation.

(21) L. F. Fieser, *Experiments in Organic Chemistry*, 2nd ed., D. C. Heath and Co., New York, N. Y., 1941, p. 344.

(22) D. D. Phillips, *Org. Syntheses*, **34**, 31 (1954).

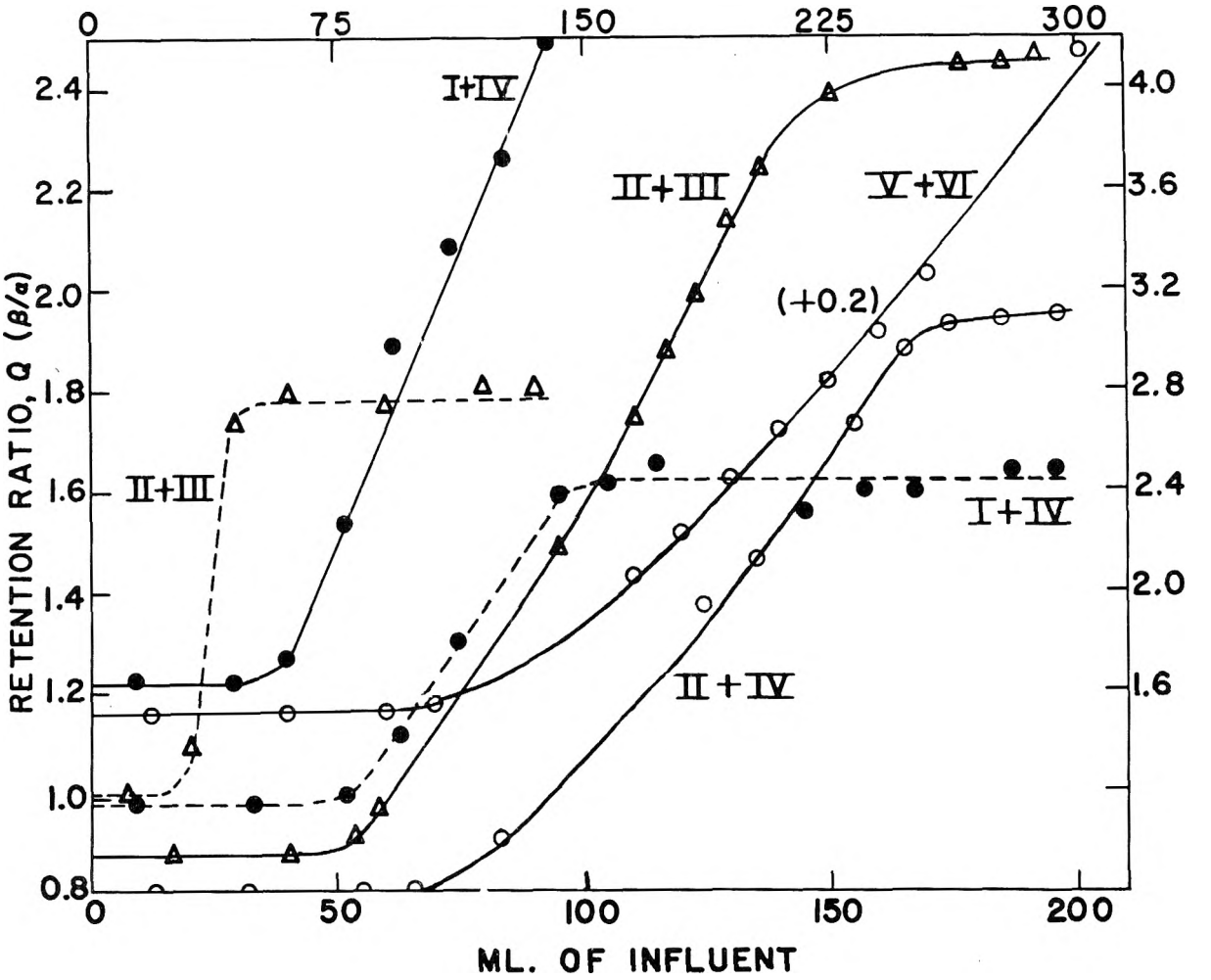


FIG. 1. RELATIVE CHROMATOGRAPHIC ADSORBABILITIES OF PAIRS OF α- AND β-MONOSUBSTITUTED NAPHTHALENES. Q is given in terms of total cumulated moles of β-compound adsorbed on the column to total cumulated moles of α-compound so adsorbed. Solid lines represent data for TNF-impregnated silicic acid as the adsorbent; broken lines, for TNP-impregnated silicic acid. The upper scale refers only to the run for II + III on TNF-silicic acid. The right hand scale refers only to the run for I + IV on TNF-silicic acid

carbon[23] indicated that the samples contained 4.4% (by weight) of TNP (1.9×10^{-4} moles of TNP per g.) and 4.0% of TNF (1.3×10^{-4} moles of TNF per g.), respectively.

Method B. This differed from method A only in that the TNF solution (TNP not used here) was ca. 0.085*M* and the impregnated silicic acid was dried only in air (but for several days) and then diluted by admixture with ten times its weight of plain silicic acid; found by analysis[23] to contain 0.66% (by weight) TNF (1.9×10^{-5} moles of TNF per g.).

Chromatography on impregnated silicic acid. Using the suction of a water aspirator a 2.5-cm. (diameter) column was packed dry with successive layers of 1 g. of plain silicic acid (to prevent possible elution of complexing agent), 4 g. of impregnated silicic acid, 0.5 g. of plain silicic acid, and a small wad of glass wool. The apparatus was all glass with nonlubricated ground joints[24] whereby were attached a receiver for effluent and a reservoir for influent. The column was prewashed with isooctane (50–300 ml.) until the effluent was spectrophotometrically clear. The experiment proper was conducted by continuous percolation under gravity of a standard isooctane solution, 4×10^{-4} to $1 \times 10^{-3}M$ in each of two hydrocarbon substrates, through the column and periodic spectrophotometric analysis (Beckman DU instrument) of cumulated samples (usually 10 ml. in size) of effluent at 2 to 4 selected wave lengths (I–IV, 224, 246, 282 mμ; II–III, 225, 249; II–IV, 225, 246; V–VI, 225, 250, 280; phenanthrene-anthracene, 274, 292, 356, 375).[25] Spontaneous evaporation of solutions during chromatography was kept as low as reasonably possible but could not be entirely eliminated. The measured cumulated volume of effluent was assumed equal to the cumulated volume of influent. About 9 ml. of solution was required to fill the interstices of the column. No control of temperature (room) or rate of flow (average 3.3–7.5 ml./hr.) was attempted.

The total quantity of each substrate retained on the column was calculated by difference and used to ascertain the retention ratio Q as a function of the total cumulated volume of solution passed. Pertinent data in this regard are recorded in Table I and plotted in Fig. 1. The column gradually became orange-red in color for the systems anthracene-phenanthrene-TNP (light color), anthracene-phenanthrene-TNF (very dark), and II–III-TNF (dark). In a few cases plots of concentration of one substrate *vs.* cumulated

(23) Conducted by Clark Microanalytical Laboratories, Urbana, Ill.

(24) Efforts to use rubber or neoprene stoppers or variously lubricated glass joints always produced extraneous chromophoric impurities in the effluent.

(25) L. H. Klemm, H. Ziffer, J. W. Sprague, and W. Hodes, *J. Org. Chem.*, 20, 190 (1955); R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1951.

total volume of effluent showed transient maxima, presumably as a result of displacement of the less strongly adsorbed substrate by the more strongly adsorbed one.[26]

Chromatography on plain silicic acid. The procedure was the same as with impregnated silicic acid except that a total of 5.5 g. of plain adsorbent was used instead. Data are also to be found in Table I.

Chromatography on alumina. Into a 2.5 × 11.5 cm. column of alumina (packed and prewashed as for silicic acid) was passed 200 ml. of isooctane solution *ca.* $5 \times 10^{-6}M$ in each of V and VI. The column was then eluted with 2% (by volume) acetone in isooctane and the effluent was analyzed as previously. Nearly all of V had been eluted before VI began to appear.

This procedure was repeated for use of I and IV except that the size of the column was 2.5 × 20 cm., 10 ml. of solution *ca.* $5 \times 10^{-3}M$ in each substrate was used, and elution was conducted with 300 ml. of isooctane. I attained a maximum concentration in the effluent at a cumulative volume of 150 ml. and dropped to an immeasurably low value at 250 ml. Meanwhile no concomitant effusion of IV was evident.

(26) Ref. 14, pp. 225–6.

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[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, UNIVERSITY OF FLORIDA]

Physical Properties of Aminoazobenzene Dyes. VI. Intramolecular Hydrogen Bonding and Tautomerism in 4-Hydroxyazobenzene Derivatives and Higher Homologs[1]

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The phenylhydrazone ⇄ azo dye tautomerism of 2′-methyl-, 4′-methyl-, 2′-methoxycarbonyl-, 4′-ethoxycarbonyl-, and unsubstituted derivatives of 4-phenylazo-1-naphthol and 5-phenylazo-8-hydroxyquinoline has been studied in alcoholic solution. In 5-(2′-methoxycarbonylphenylazo)-8-hydroxyquinoline the intramolecular hydrogen bond between the methoxycarbonyl ketonic oxygen and the azonium hydrogen involved in the 6-membered ring of the phenylhydrazone tautomer was of the same order of energy as the intramolecular hydrogen bond between the heterocyclic nitrogen and the hydroxyl hydrogen in the 5-membered ring of the azo tautomer. The 2′- and 4′-electron donor and electron attractor substituents studied in this paper were found to have similar qualitative effects on the tautomerism of 4-phenylazo-1-naphthol in alcohol and the tautomerism of the monocationic salt of 4-dimethylaminoazobenzene.

4-Hydroxyazobenzene has been shown to exist in alcohol in the azo form, λ_{max} 350 mμ.[3] Shingu[4] has shown that electron attractor substituents in the benzene ring of 1-phenylazo-4-naphthols increase the relative proportion of the phenylhydrazone tautomer while electron donor substituents in the 4′-position of the benzene ring increase the proportion of the azo tautomer. Each of these tautomers has a characteristic absorption spectrum with the azo tautomer absorbing at shorter wavelengths.[3] In this respect the 2′,4′-dinitro derivative of 4-hydroxyazobenzene acts like the 2,4-dinitrophenylhydrazone of *p*-benzoquinone in that it shows evidence of quinonoid character by its ability to undergo the Diels-Alder reaction with cyclopentadiene.[5] The discovery of the existence of a tautomeric equilibrium in solution between 4-phenylazonaphthol (I) and naphthoquinone monophenylhydrazone (II) by Kuhn and Bär[3] has been confirmed spectrally by Burawoy and Thompson,[6] Ospenson,[7] Badger and Buttery,[8] and Hadzi.[9] Ospenson has also given spectral evidence that 4-phenylazo-1-anthrol exists in alcohol almost completely in the phenylhydrazone form. From a study of the spectrum of 9-phenylazo-10-anthrol and appropriate derivatives in alcohol, Shingu[4] has concluded that the compound exists in solution only as anthraquinone monophenylhydrazone. These results parallel the reduction potentials[10] in alcohol of *p*-benzoquinone, 0.71*v*; 1,4-naphthoquinone, 0.49*v*; 1,4-anthraquinone, 0.40*v*; and 9,10-anthraquinone, 0.15*v*. *p*-Benzoquinone is the least stable of the *p*-quinones and the equilibrium Ph—NH—N=Ar=O ⇄ Ph—N=N—Ar—OH is displaced completely to the right; 9,10-anthraquinone is the most stable of these quinones and the equilibrium is displaced completely to the left.

The spectral data of Badger and Buttery[8] indicate that 4-phenylazo-1-naphthol exists in absolute alcohol solution as an equilibrium mixture of the

(1) This investigation was supported by research grant C-1308 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

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(3) R. Kuhn and F. Bär, *Ann.*, **516**, 143 (1935).

(4) H. Shingu, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **35**, 78 (1938).

(5) W. Lauer and S. Miller, *J. Am. Chem. Soc.*, **57**, 520 (1935).

(6) A. Burawoy and A. Thompson, *J. Chem. Soc.*, 1443 (1953).

(7) J. Ospenson, *Acta Chem. Scand.*, **5**, 491 (1951).

(8) G. Badger and R. Buttery, *J. Chem. Soc.*, 614 (1956).

(9) D. Hadzi, *J. Chem. Soc.*, 2143 (1956).

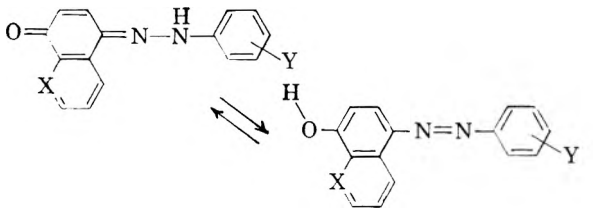
(10) J. B. Conant and L. F. Fieser, *J. Am. Chem. Soc.*, **45**, 2194 (1923).

azo and the phenylhydrazone tautomers, the former in slight excess. These authors have found that 5-phenylazo-8-hydroxyquinoline exists almost entirely in the azo form. This shift in the equilibrium has been attributed to the presence of a weak intramolecular hydrogen bond between the heterocyclic nitrogen and the hydroxyl hydrogen. This, of course, would tend to stabilize the azo tautomer. Badger and Buttery's results are confirmed and extended in Figure I and Table I.

I). This agrees with Shingu's results.[4] The substitution of an 8-aza group in these compounds and the consequent intramolecular hydrogen bonding has a buffering action on the equilibrium so that both the methyl and ethoxycarbonyl groups have a much weaker effect (Table I). The striking effect of analogous substitutions in the 2′- and 4′-positions on the I ⇄ II tautomerism of 4-phenylazo-1-naphthol in 95% ethanol and the III ⇄ IV tautomerism of 4-dimethylaminoazobenzene in 50%

TABLE I

PHENYLHYDRAZONE ⇄ PHENYLAZO TAUTOMERS

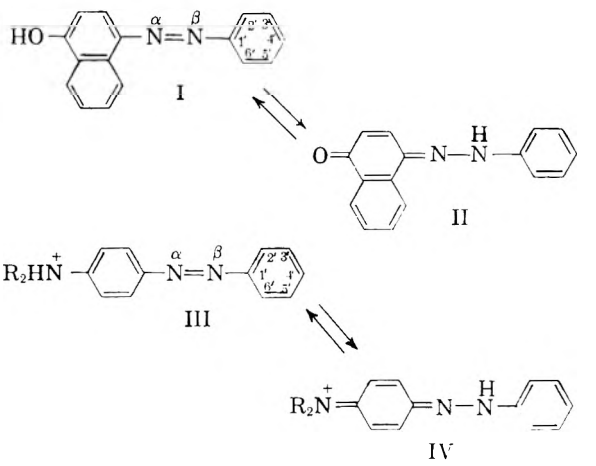


X	Y	$\lambda_{max}(\epsilon \times 10^{-3})$ P	A	P_ϵ/A_ϵ	DAB[a] Deriv.	C_ϵ/A_ϵ[b]
N	4′-CH_3	~(465)[c](4.8)	387(24.4)	0.20		
CH	2′-CH_3	~(465)(4.25)	403(17.7)	0.24	2′-CH_3	0.29
N	2′-CH_3	~(465)(5.7)	388(21.9)	0.26		
	H	(462)(5.5)	387(21.1)	0.26		
	4′-$COOC_2H_5$	~(465)(8.4)	402(23.7)	0.33		
CH	4′-CH_3	~(465)(10.5)	407(23.9)	0.44	4′-CH_3	2.6
	H	464(11.5)	409(15.4)	0.74	H	3.6
N	2′-$COOCH_3$	460(16.1)	395(14.4)	1.1		
CH	4′-$COOC_2H_5$	465(33.6)	~400[d](8.45)	~4	4′-$COOC_2H_5$	~6–8[e]
	2′-$COOCH_3$	466(31.9)	~400[d](5.00)	~6	2′-$COOCH_3$	13.1

[a] DAB is 4-Dimethylaminoazobenzene. [b] Reference 11. [c] Wave length values in parentheses are shoulders. [d] Not a λ_{max} or a definite shoulder. The main band at 465–466 mμ is unsymmetrical, sloping more gradually on the short wave length side. [e] Predicted value.

The P_ϵ/A_ϵ ratio in Table I gives an approximate idea of the relative proportion of phenylhydrazone to azo tautomer present in solution. P_ϵ is the molar extinction coefficient at the wave length maximum (or shoulder) of the phenylhydrazone tautomer; A_ϵ is the molar extinction coefficient at the wave length maximum of the azo tautomer. The ratio is approximate mainly because of the varying electronic and steric effects of diverse substituents. In 4-phenylazo-1-naphthol the presence of a 2′-methyl and/or an 8-aza group decreases the P_ϵ/A_ϵ ratio considerably (Table I). This effect of a 2′-methyl group is in line with the fact that the presence of this group in the 4-aminoazobenzene dyes has been shown to have a base-weakening effect on the adjacent β-nitrogen.[11] The same order of decrease is caused by the stabilization of the azo tautomer through the formation of an intramolecular hydrogen bond between the 8-aza nitrogen and the hydroxyl hydrogen. The electron donor 4′-methyl group decreases the P_ϵ/A_ϵ ratio while the electron attractor 4′-ethoxycarbonyl group increases this ratio in 4-phenylazo-1-naphthol (Table

alcoholic 1*N* hydrochloric acid is noticeably similar.

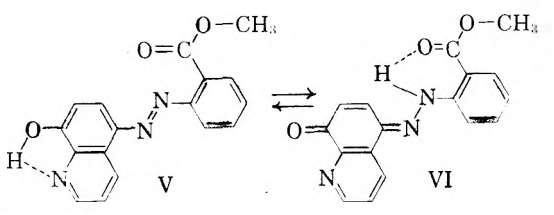


It has been shown[11] that in the monocationic salts of 4-aminoazobenzene derivatives the presence of a 2′-carboxy group considerably increases the proportion of the C tautomer (IV) involving proton addition to the β-nitrogen as compared to the A tautomer (III). This increase has been mainly attributed to the stabilization afforded by the in-

(11) E. Sawicki, *J. Org. Chem.*, 21, 605 (1956).

tramolecular hydrogen bonding involving the azonium hydrogen and the carboxy ketonic oxygen. In these monocationic salts the C_ϵ/A_ϵ ratio was found to give an approximate idea of the ratio of C to A tautomers present in acid solution. C_ϵ is the molar extinction coefficient at the long wave length maximum of the C tautomer; A_ϵ is the molar extinction coefficient at the long wave maximum of the A tautomer (e. g. III). As the I $\rightleftarrows$ II tautomeric system has evident geometrical and electronic differences from the III $\rightleftarrows$ IV tautomeric system one could not expect a strictly similar effect of all types of analogous substitutions on these two tautomeric systems. Just as in the 4-aminoazobenzene cationic salts the substitution of a 2′-methoxycarbonyl group into 4-phenylazo-1-naphthol strongly increases the P_ϵ/A_ϵ ratio. Part of this increase must be due to the electron attracting properties of the methoxycarbonyl group but the intramolecular hydrogen bond, involving a 6-membered ring, must also tend to stabilize the phenylhydrazone tautomer. An electron attracting substituent in the 4′-position of 4-aminoazobenzene causes an increase in the stability of the IV form, *i. e.*, the C_ϵ/A_ϵ ratio becomes larger. On the other hand an electron-donor substituent, such as the methyl, methoxy, or methylthio group, in the 4′-position decreases the C_ϵ/A_ϵ ratio.[12] This corresponds with somewhat similar effects of electron donor and electron acceptor substituents on the P_ϵ/A_ϵ ratio of 4-phenylazo-1-naphthol.[4]

In 5-(2′-methoxycarbonylphenylazo)-8-hydroxyquinoline the intramolecular hydrogen bond, involving a 5-membered ring, in the azo tautomer (V) is pitted against the intramolecular hydrogen bond, involving a 6-membered ring, of the phenylhydrazone tautomer (VI). The spectrum of 5-(2′-methoxycarbonylphenylazo)-8-hydroxyquinoline consists of two broad bands, with maxima at 395 mμ (associated with the azo tautomer, V) and 460 mμ (associated with the phenylhydrazone tautomer, VI. The relative intensities of these bands as compared to the relative intensities of the analogous bands in 5-phenylazo-8-hydroxyquinoline, 4-phenylazo-1-naphthol, and 4-(2′-methoxycarbonylphenylazo)-1-naphthol indicate that the intramolecular hydrogen bond involved in the 6-membered ring is somewhat stronger than the intramolecular hydrogen bond in the 5-membered ring (Fig. 1).



(12) E. Sawicki, *J. Org. Chem.*, **22**, 621 (1957).

EXPERIMENTAL[13]

5-(2′-Methoxycarbonylphenylazo)-8-hydroxyquinoline. All the compounds were essentially prepared by the following procedure. A diazotized solution of methyl anthranilate in aqueous hydrochloric acid was added to a stirred cold solution of 8-hydroxyquinoline in methanol. Enough potassium acetate was added to neutralize the hydrochloric acid. The mixture was kept below 5° for 12 hr. after which the mixture was filtered and washed thoroughly with water. Several crystallizations from methyl Cellosolve (2-methoxyethanol) gave an 80% yield of the dye, m.p. 164°.

Anal. Calcd. for $C_{17}H_{13}N_3O_3$. N, 13.7. Found. N, 13.5.

4-Phenylazo-1-naphthol,[14] m.p. 205° dec., 4-*o*-tolylazo-1-naphthol,[15] m.p. 146°, 4-*p*-tolylazo-1-naphthol,[15] m.p. 205–206° dec., 4-(4′-ethoxycarbonylphenylazo)-1-naphthol,[16] m.p. 247–248° dec., 5-*o*-tolylazo-8-hydroxyquinoline,[17] m.p. 181°, 5-*p*-tolylazo-8-hydroxyquinoline,[18] m.p. 191°, and 5-phenylazo-8-hydroxyquinoline,[19] m.p. 185–186°, were crystallized to constant melting point.[5]

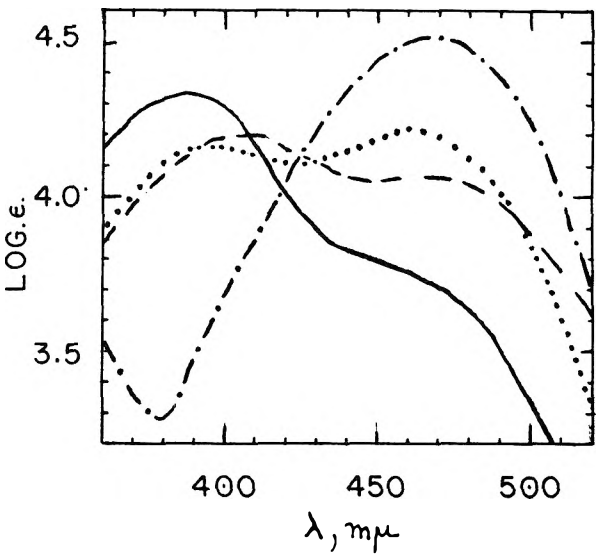


FIG. 1. VISIBLE ABSORPTION SPECTRA: 5-phenylazo-8-hydroxyquinoline (———); 4-phenylazo-1-naphthol (– – – –); 5-(2′-methoxycarbonylphenylazo)-8-hydroxyquinoline (. . . . .); and 4-(2′-methoxycarbonylphenylazo)-1-naphthol (– · – ·)

5-(4′-Ethoxycarbonylphenylazo)-8-hydroxyquinoline. This compound was crystallized several times from xylene to give orange cotton-like needles, m.p. 215–216°.

Anal. Calcd. for $C_{18}H_{15}N_3O_3$. N, 13.1. Found: N, 13.0.

4-(2′-Methoxycarbonylphenylazo)-1-naphthol. Several crystallizations from xylene gave orange crystals, m.p. 222°.

Anal. Calcd. for $C_{18}H_{14}N_2O_3$. N, 9.2. Found: N, 9.4.

Absorption spectral data. The spectra of all compounds were determined in commercial 95% ethanol containing 0.2% dioxane with a Beckman Model DU spectrophotometer. The dioxane was found to be necessary to facilitate solution of the dyes.

GAINESVILLE, FLA.

(13) All melting points are uncorrected.
(14) O. Witt and J. Dedichen, *Ber.*, **30**, 2655 (1897).
(15) T. Zincke and F. Rathgen, *Ber.*, **19**, 2486 (1886).
(16) R. Willstatter, E. Ulbrich, L. Pogany, and C. Maimeri, *Ann.*, **477**, 161 (1929).
(17) R. N. Shreve and R. B. Bennett, *J. Am. Chem. Soc.*, 65, 2243 (1943).
(18) J. Fox, *J. Chem. Soc.*, **97**, 1341 (1910).
(19) K. Matsumura, *J. Am. Chem. Soc.*, **52**, 4164 (1930).

[CONTRIBUTION FROM THE EMERYVILLE RESEARCH CENTER OF SHELL DEVELOPMENT CO.]

Reactions of Hydrogen Peroxide. I. A Novel Use of Selenium Dioxide as Catalyst for Oxidation of Acrolein to Acrylic Acid

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By a novel use of selenium dioxide as catalyst, hydrogen peroxide has been used to oxidize acrolein and methacrolein to monomeric acrylic and methacrylic acids. Systems with low water content gave highest yields of monomeric acids. Such solutions from 35% hydrogen peroxide in *tert*-amyl alcohol were produced by azeotropic removal of water. In all cases the peroxide content was kept below 15% by weight.

With the availability of acrolein and hydrogen peroxide as articles of commerce, means have been sought for combining them in the preparation of acrylic acid. In the absence of catalyst and in aqueous solution these materials showed little tendency to react. With standard peracid-forming catalysts such as formic, acetic, and tungstic, the aldehyde group was oxidized but polymerization and other reactions occurred so that only crude polymeric acids were obtained. After some searching, selenium dioxide was found to catalyze the formation of monomeric acrylic and methacrylic acids from acrolein and methacrolein.

Catalyst. Although selenium dioxide has been used as a reactant and catalyst in many other reactions, this is the first time it has been used in just this way. Oxidations of methylene groups adjacent to carbonyl groups with stoichiometric quantities of selenium dioxide to give α-diketones or ketoaldehydes are well known. Even certain methyl groups adjacent to aromatic rings can be oxidized to aldehydes, but the reaction apparently stops here. Thus these reactions leading to aldehydes or ketones are different from the present one producing acids. In another obviously different case[1] selenium dioxide with hydrogen peroxide has been used for the hydroxylation of cyclopentene and cyclopentadiene. The catalyst in this case is probably perselenic acid.

Reaction conditions. Conditions and results in the preparation of acrylic and methacrylic acids are closely analogous. The preparation of acrylic acid will be reviewed first and significant differences with methacrylic acid will then be given.

In the present oxidation of acrolein, tertiary alcohols containing only small amounts of water were used as solvents. At the optimum temperature, 40°, the reaction time was 3 hr. At the end of the reaction the catalyst precipitated as red elemental selenium. Anhydrous acrylic acid was obtained by distillation without further treatment. After the peroxide had been consumed and precipitation of selenium had started the temperature could be raised as high as 100° without causing polymerization. Apparently selenium inhibits the polymerization of acrylic acid.

Selenium dioxide is so far the only practical catalyst found for this reaction. At the concentrations used (5.0 g. SeO_2 per mole of H_2O_2) it was completely soluble in the reaction mixture. At concentrations of 1 g. of SeO_2 per mole of peroxide a much slower reaction occurred and poor yields of acrylic acid were obtained. Two other catalysts, phosphotungstic acid and selenotungstic acid, gave low conversions to distilled acrylic acid.

Two schemes were used for recovery of selenium. With excess acrolein the elemental selenium formed at the end of the reaction was collected on a filter. With a slight excess of peroxide the selenic acid was removed with a weakly basic, ion-exchange resin (Amberlite IR4B). Sodium selenate was recovered by leaching the resin with 10% sodium hydroxide.

Reaction intermediates. Although not established, the course of the present reaction is thought to involve oxidation of selenous to selenic acid with hydrogen peroxide. Acrolein then reacts with the selenic acid to give acrylic and selenous acids. As long as acrolein is present to react with selenic acid probably little if any perselenic acid is formed.

To evaluate the possibility that initial reaction is between the dioxide and acrolein, stoichiometric quantities of the two materials were allowed to react. The major product was not identified but no indication of acrylic acid could be found.

Solvent. The reaction was usually carried out with *tert*-butyl or *tert*-amyl alcohol as solvent. A simple expedient to obtain essentially anhydrous solutions of hydrogen peroxide without handling the hazardous 90% material was to remove water azeotropically from solutions of more dilute peroxide in the desired alcohol. To minimize possibilities for detonable mixtures, the concentration of peroxide in alcohol was not allowed to exceed about 15%. Little or no esterification of acidic products occurred during the reaction with the tertiary alcohols as solvents. With the primary and secondary alcohols as solvents, formation of acid is accompanied by esterification. However, combined conversions (90–100%) to acid and ester (as indicated by titration) were the same as to acid alone with the tertiary alcohols. Oxidation in methyl, ethyl, allyl, and *n*-

(1) Stoll, Lindenmann, and Jucker, *Helv. Chim. Acta*, **36**, 268 (1953).

butyl alcohols and in ethylene glycol gave some 15–40% of the corresponding acrylates. Unfortunately, the only quantitative study used for acrylic acid and esters in the flashed distillates was titration with base and saponification. In one case acrylic acid was isolated (but not quantitatively) by fractional distillation of the flashed distillate and identified by melting point and mixed melting of its crystalline derivative, β-anilinopropionanilide.

With increasing concentration of water an increased conversion to polymeric acid takes place. Thus with anhydrous or 90% hydrogen peroxide about a 5% conversion to polymer occurs; with 35% peroxide the conversion to polymer is 10% or higher. With water alone as the solvent, only polymer was obtained. In all these cases, the acidity as indicated by titration was 0.95–1.00 equivalent based on acrolein charged, only the conversion to polymer varied markedly. It seems probable that with increasing amounts of water an increase in ionization of the selenic and selenous acids takes place and this increased acidity causes polymerization of the acrolein and/or acrylic acid with a consequent decrease in conversion and yield of monomeric acrylic acid. This view may be supported by the observation that addition of 0.3% sulfuric acid to a standard reaction mixture increases polymer formation so that about equal amounts of monomeric acid (47.9%) and polymer (48.5%) were formed.

Methacrolein was oxidized to methacrylic acid in 93% yield under essentially the same conditions used with acrolein. Here a reaction temperature of 60–70° is possible without reducing the yield due to polymer formation. At this temperature a reaction time of about 1.5 hr. is sufficient. A few non-hydroxylic solvents were also investigated. In dioxane essentially the same conversion to monomeric methacrylic acid was obtained as in alcohol. The use of benzene and acetone as solvents lowered the conversions from 90–95% to 85% while in acetic acid the conversion was only 54%.

EXPERIMENTAL

Azeotropic removal of water from H_2O_2 in tert-amyl alcohol. A mixture of 198 g. (2.0 moles) of 34.7% H_2O_2 and 1000 g. of *tert*-amyl alcohol was distilled under a phase-separating stillhead at a pressure of 50 mm. The lower water phase was drawn off as it collected in the stillhead and the upper alcohol phase returned to the kettle. A maximum kettle temperature of 50° was reached. After about 110 cc. of water had been removed, reflux was discontinued and about 400–500 cc. of alcohol was collected. Titration of the residue in the kettle showed 12.09% H_2O_2 and 0.85% H_2O. This represents about a 95% recovery of H_2O_2.

Oxidation of acrolein to acrylic acid. In a four-neck flask having a stirrer, dropping funnel, thermometer, and condenser were placed 103 g. of *tert*-amyl alcohol, 5.0 g. of selenium dioxide, and 56 g. (1.0 mole) of acrolein. A solution of 281 g. (1.0 mole) of 12.09% H_2O_2 in *tert*-amyl alcohol was then added dropwise in 30 min. with cooling at 40°. Three hours from the start a titration indicated 0.925 equivalents of acid other than selenous or selenic had been produced. After standing overnight (about 20 hr. from start), another titration indicated the same amount of acid. The product was distilled rapidly from a Claisen flask directly into a large cold trap cooled in a dry ice-acetone mixture. A pressure of 100 mm. was used and the kettle was warmed with a hot water bath. Near the end the pressure was reduced to 1 mm. The distillate weighed 457 g. and contained 0.900 equivalents of acid by titration. The residue weighed 9.5 g. Analysis of the distillate showed 0.07% acrolein. The 0.900 equivalent of acid represents a 90.0% conversion of H_2O_2 to distilled acid and a 90.5% yield based on acrolein.

In a similar experiment, except that *tert*-butyl alcohol was used as solvent, the flashed distillate contained 0.696 equivalents of acid. This distillate was redistilled from a Claisen flask. The fraction boiling 53–87° (100 mm.), 98.1 g. was distilled through a 1 × 25 cm. glass-helices packed column after addition of a small amount of hydroquinone. When the head temperature reached 50° (100 mm.), the pressure was reduced to 10 mm. and the acrylic acid which flashed weighed 22.6 g. This represents a 45% recovery of the acrylic acid indicated to be present by titration. This lack of material balance is probably due to acrylic acid which distilled with the alcohol and to some polymer formation during distillation.

Anal. Calcd. for $C_3H_4O_2$: Neut. equiv., 72. Found: Neut. equiv. 75.

Heating the above product with aniline gave β-anilinopropionanilide which melted at 91–92° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 75.0; H, 6.7; N, 11.7. Found: C, 74.9; H, 6.8; N, 11.7.

β-Anilinopropionanilide prepared similarly from an authentic sample of acrylic acid melted at 93–93.5°. A mixture of the two materials melted at 93–93.5°.

Oxidation of methacrolein to methacrylic acid. A solution of 5 g. of selenium dioxide in 350 g. of *tert*-butyl alcohol was combined with 105 g. (1.5 moles) of methacrolein and stirred while 35 g. (1.0 mole) of 90% hydrogen peroxide was added dropwise in 17 min. Cooling was applied to keep the temperature at 60°. After 1.5 hr. a titration indicated 0.95 equivalents of acid had been generated. The product was stripped of all volatile material by warming in a water bath at 55–60° (80 mm.) and finally at 75° (1 mm.). This left 11 g. of red residue and took overhead 484 g. of distillate containing 0.937 equivalents of acid. A 434 g. portion of the distillate was redistilled through a small helices-packed column having 4 copper wires[2] running through the packing for the length of the column to act as a polymerization inhibitor. A piece of copper wire was also suspended in the stillhead. After the alcohol and a small intermediate cut of 4.5 g., methacrylic acid, 43.5 g., was collected at 69–71°, n_D^{20} 1.4298–1.4309. This center cut represents a 74% recovery of methacrylic acid indicated by titration to be present.

Anal. Calcd. for $C_4H_6O_2$: C, 55.80; H, 7.03; Br. No. 186 g. Br/100 g.; Neut. equiv. 86. Found: C, 55.81; H, 7.04; Br. No. 185 g. Br/100 g.; Neut. equiv. 87.

Heating the above product with aniline gave β-anilinoisobutyranilide which melted at 119–120°.

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.6; H, 7.1; N, 11.0. Found: C, 75.6; H, 7.6; N, 10.9. A mixture of the above derivative with β-anilinoisobutyranilide (m.p. 119–120°) prepared similarly from an authentic sample of *methacrylic acid* melted at 119–120°.

n-Butyl acrylate from oxidation of acrolein in n-butanol. A solution of 56 g. (1.0 mole) of acrolein and 5.0 g. of selenium dioxide in 350 g. of *n*-butanol was kept at 40° while 38 g. (1.0 mole) of 90% hydrogen peroxide was added in 10 min. After about 5 hrs. the clear yellow solution began turning red with precipitated selenium. After standing overnight at

(2) In his book "Vinyl and Related Polymer," John Wiley and Sons, Inc., New York 1952, p. 298, C. E. Schildknecht states that traces of copper salts of acrylic acid are effective inhibitors of polymerization of acrylic acid.

room temperature, the opaque red suspension was titrated. There was 0.791 equivalent of acid and 0.239 equivalent of ester. The product was flashed under vacuum using a hot water bath. There was taken overhead 70 g. of distillate leaving 15 g. of somewhat viscous liquid residue. Titration of the distillate showed 0.701 equivalent of acid and 0.194 equivalent of ester and 2.1 g. of acrolein.

Oxidation of acrolein with selenium dioxide. To a suspension of 55.5 g. (0.5 mole) of selenium dioxide in 350 g. of *tert*-butyl alcohol was added 56 g. (1.0 mole) of acrolein all at once. The reaction was warmed and maintained at 40°. The color changed from white to red in about 0.5 hr. After standing overnight at room temperature, filtration of the mixture gave 40.7 g. of selenium. The filtrate was distilled at 50° (25 mm.). The colorless distillate contained no acid as shown by titration.

Formic acid catalyzed oxidation of acrolein. A slow consumption of peroxide took place when 1.15 moles of acrolein, 1.15 moles of hydrogen peroxide, and 1.0 mole of formic acid in 500 cc. of water was left at room temperature. After 8 days 77.5% of the H_2O_2 was gone and 0.84 mole of acid had been generated. Evaporation of the solvents at less than 50° left 84 g. of a very viscous water-soluble polymer with analysis indicative of a crude poly(acrylic acid).

Anal. Calcd. for $C_3H_4O_2$: C, 50.00; H, 5.59; Neut. equiv. 72. Found: C, 49.25; H, 6.31; Neut. equiv. 109.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BUFFALO]

Studies in Organosilicon Chemistry. XXXIV. The Reaction of Trimethylsilylmethyl Metallic Compounds with Trichlorosilane

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Received November 14, 1956

Trichlorosilane and trimethylsilylmethylmagnesium bromide react in 2.5:1 molar ratio to form trimethylsilylmethyldichlorosilane, in 0.33:1 ratio to give bis(trimethylsilylmethyl)chlorosilane and in 0.30:1 ratio giving an 18.6% yield of tris(trimethylsilylmethyl)silane. Trichlorosilane and trimethylsilylmethyllithium react in 0.22:1 molar ratio forming tris(trimethylsilylmethyl)silane in 71% yield. The product undergoes bromination giving tris(trimethylsilylmethyl)bromosilane which can be hydrolyzed by aqueous ammonium hydroxide in acetone to form tris(trimethylsilylmethyl)silanol. Trimethylsilylmethyldichlorosilane undergoes hydrolysis to poly(trimethylsilylmethyl)siloxanes. Infrared absorption curves are presented for tris(trimethylsilylmethyl)silane, tris(trimethylsilylmethyl)silanol and poly(trimethylsilylmethyl)siloxanes, I(fraction 1), II(fraction 2), and III(fraction 3).

The steric effect of highly-branched groups in aliphatic organosilicon compounds is manifested in the reactivity or non-reactivity of certain functional groups attached to the silicon.[1,2,3,4,5] In line with some of this previously reported work, a series of compounds has been prepared and studied in which the trimethylsilylmethyl group has been substituted for one or more chlorines in trichlorosilane. Silanols containing large groups attached to silicon are quite stable toward condensation, in contrast with those with smaller groups.[6,7]

Trimethylsilylmethylmagnesium bromide reacts with trichlorosilane in various proportions, to form the mono-, the di-, and the trisubstitution products. Tris(trimethylsilylmethyl)silane reacts with bromine to form tris(trimethylsilylmethyl)bromosilane and this compound undergoes hydrolysis to form the corresponding silanol, isolable as such. (Trimethylsilylmethyl)dichlorosilane undergoes hydrolysis to give the trimeric and tetrameric forms of (trimethylsilylmethyl)siloxane. Trimethylsilylmethyllithium reacts with trichlorosilane to form tris(trimethylsilylmethyl)silane.

TABLE I

TRIMETHYLSILYLMETHYLSILANES

	B.P. °C	Mm.	n_D^{25}	d_4^{25}
$(CH_3)_3SiCH_2SiHCl_2$	52.0-53.5	24		
	146–148			
$[(CH_3)_3SiCH_2]_2SiHCl$	79–80	5		
$[(CH_3)_3SiCH_2]_3SiH$	108[a]	9[a]	1.4495[a]	0.8221[a]
	103–107[b]	8[b]	1.4498[b]	
$[(CH_3)_3SiCH_2]_3SiBr$	110	1.8	1.4725	
$[(CH_3)_3SiCH_2]_3SiOH$	112–113	5.0	1.4540	0.8594

[a] Through the Grignard reagent. [b] Through the organolithium compound.

Infrared absorption curves (Fig. 1) are presented for the first of the polymeric materials listed in Table II, as well as for tris(trimethylsilylmethyl)-silane, and for tris(trimethylsilylmethyl)silanol. The scanning speed was one micron per minute, with a normal slit, and a sample cell of 0.025 mm. The reference was air at 24° with no solvent.

(1) H. Gilman and R. N. Clark, *J. Am. Chem. Soc.*, **69**, 1499 (1947).

(2) L. H. Sommer and L. J. Tyler, *J. Am. Chem. Soc.*, **76**, 1030 (1954).

(3) L. J. Tyler, L. H. Sommer, and F. C. Whitmore, *J. Am. Chem. Soc.*, **69**, 981 (1947).

(4) L. J. Tyler, L. H. Sommer, and F. C. Whitmore, *J. Am. Chem. Soc.*, **70**, 2876 (1948).

(5) L. H. Sommer, R. M. Murch, and F. A. Mitch, *J. Am. Chem. Soc.*, **76**, 1619 (1954).

(6) P. D. George, L. H. Sommer, and F. C. Whitmore, *J. Am. Chem. Soc.*, **75**, 1585 (1953).

(7) J. F. Hyde, *J. Am. Chem. Soc.*, **75**, 2712 (1953).

TABLE II

POLYMERIC HYDROLYSIS PRODUCTS

	B.P., °C	Mm.	n_D^{25}	d_4^{25}	Mol. Wt.	MR
$[(CH_3)_3SiCH_2SiHO]_x$	105–108	1	1.4383	0.9027	368	115.2
$[(CH_3)_3SiCH_2SiHO]_y$	143	1	1.4433	0.9283	490 516	150.9
$[(CH_3)_3SiCH_2SiHO]_z$	166–168	1	1.4458	0.9355	517	150.4
Calculated for trimer					396	113.5
Calculated for tetramer					528	151.3

EXPERIMENTAL

Trimethylbromomethylsilane. This compound was prepared by the method of Speier,[8] and of Noller and Post.[9]

Trimethylsilylmethylmagnesium bromide was prepared in accordance with a procedure outlined by Willard Keeber[10] of the University of Buffalo, by the action of magnesium on trimethylbromomethylsilane, in absolute ether, under an atmosphere of dry nitrogen.

Lithium (6.9 g., 1.0 mole) and 250 cc. of mineral oil were placed in a dry 500 cc. three-necked flask and blanketed with dry oxygen-free, nitrogen. The flask was heated until the lithium had melted, then closed and shaken until the lithium had solidified in the form of a dry sand. After cooling, the mineral oil was decanted and the lithium was washed by repeated addition and decantation of 50 cc. portions of anhydrous ether, under a stream of nitrogen. Trimethylbromomethylsilane (73.5 g., 0.44 mole) dissolved in 200 cc. anhydrous ether was then added dropwise over a period of 3 hr. Cooling was provided to maintain the reaction temperature at −15° to −5°. After the addition had been completed, the reaction mixture was allowed to warm up to room temperature and stand overnight, forming trimethylsilylmethyllithium.

Trimethylsilylmethyldichlorosilane. Trimethylsilylmethylmagnesium bromide (0.2 mole) was prepared as described above and added to 50 cc. (0.5 mole) of trichlorosilane in 200 cc. of anhydrous ether, dropwise, over a 3-hr. period. The temperature was maintained below 10° by means of an ice bath but after addition had been completed, the mixture was allowed to warm to room temperature and stand overnight. The liquid was then decanted under an atmosphere of nitrogen and distilled yielding trimethylsilylmethyldichlorosilane, 24 g., 64% yield, b.p. 52.0–53.5° (24 mm.), 146–148° (760 mm.).

Anal. Calcd. for $C_4H_{12}Cl_2Si_2$: Cl, 37.94. Found: Cl, 34.50.

Bis(trimethylsilymethyl)chlorosilane. In a manner similar to that described above, 10 cc. (0.1 mole) of trichlorosilane was allowed to react with 0.3 mole of trimethylsilylmethylmagnesium bromide. Fractionation yielded only 0.8 g. (13.3% yield) of contaminated bis(trimethylsilymethyl)-chlorosilane, b.p. 79–80° (5 mm.).

Anal. Calcd. for $C_8H_{23}Si_3Cl$: Cl, 14.9. Found: Cl, 13.9. A higher fraction, 9.5 g., 32.7% yield, b.p. 100–106° (6 mm.), n_D^{25} 1.4501, was probably tris(trimethylsilylmethyl)-silane. It contained no chlorine.

Tris(trimethylsilylmethyl)silane. Trimethylsilylmethylmagnesium bromide (0.5 mole) in 300 cc. of absolute ether was prepared as before. Trichlorosilane (15 cc., 0.15 mole) dissolved in 100 cc. of absolute ether was then added dropwise over a period of 2 hr. A slightly positive nitrogen pressure was maintained throughout, and the reaction temperature was kept at between 0° and 5° by means of an ice bath. After addition had been completed the reaction mixture was allowed to warm to room temperature and stand overnight. After pouring into 100 cc. of cold water with 5 cc. of concentrated sulfuric acid the organic layer was separated. Fractionation yielded 27.3 g. of tris(trimethylsilylmethyl)silane, 18.6%, b.p. 100° (6 mm), 110–112° (10 mm), n_D^{25} 1.4489–1.4495, d_4^{25} 0.8221.

Anal. Calcd. for $C_{12}H_{34}Si_4$: C, 49.66; H, 11.7; Si, 38.68; Mol. wt., 290; M.R., 97. Found: C, 50.08; H, 11.62; Si, 37.8, 38.2; Mol. wt., 286, 283, 272; M.R. 96.

Trimethylsilylmethyllithium (0.44 mole) was prepared as described above and treated with 10 cc. (0.1 mole) of trichlorosilane in 10 cc. of absolute ether, added dropwise over a 2-hr. period. Cooling was required to maintain the temperature between −15° and −10°. A slight positive pressure of dry oxygen-free nitrogen was also maintained. After addition had been completed, the system was allowed to warm to room temperature and was stirred for 2 hr. After distillation of the ether, the temperature was kept at 70° for an additional hour, then poured into acidified water. The solids were washed with three 100 cc. portions of ether and the washings added to the decanted organic layer. Alcohol was added to the solids remaining in the reactor and the mixture slowly poured into water. There is danger of fire at this point. Organic layer and ether were stirred with water for 15 min., then separated and the organic layer dried over sodium sulfate. Fractionation gave 20.7 g. 71% yield, of tris-(trimethylsilylmethyl)silane, b.p. 103–107° (8 mm), n_D^{25} 1.4498.

Poly(trimethylsilylmethyl)siloxane. Trimethylsilylmethyldichlorosilane (24.0 g., 0.13 mole) was added dropwise, with stirring, to 200 cc. of ether containing 20 cc. of water. The *p*H of the resulting system was adjusted to approximately

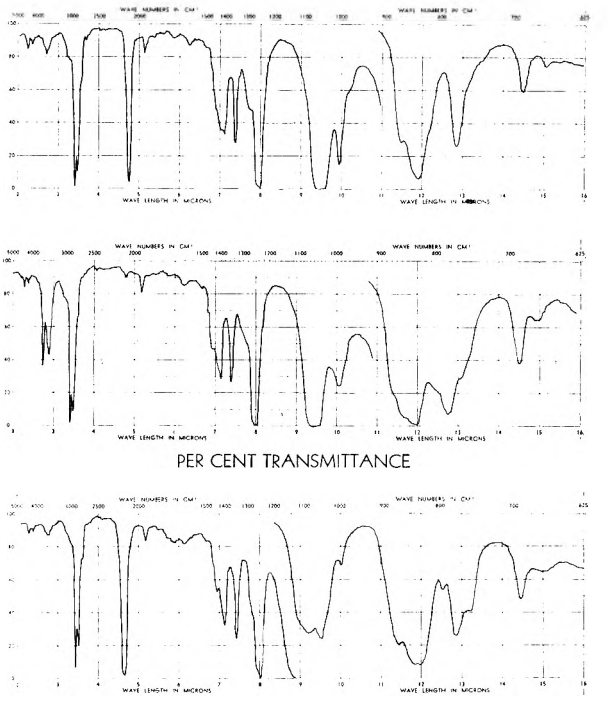

FIG. 1. INFRARED SPECTRA OF: $[(CH_3)_3SiCH_2]_3SiH$ (TOP), $[(CH_3)_3SiCH_2]_3SiOH$ (CENTER), AND $[(CH_3)_3SiCH_2SiHO]_4$ (BOTTOM)

(8) J. L. Speier, *J. Am. Chem. Soc.*, **73**, 826 (1951).

(9) D. C. Noller and H. W. Post, *J. Org. Chem.*, **17**, 1393 (1952).

(10) W. H. Keeber, Private Communication.

seven by the addition of 32.0 g. of two percent aqueous ammonium hydroxide. The ether layer was separated and dried over sodium sulfate. After removal of the ether by distillation, 18.2 g. of liquid remained. Fractionation produced 1.1 g. of product, b.p. 105–108° (1 mm) n_D^{25} 1.4383, d_4^{25} 0.9027, 3.0 g. of material, b.p. 143° (1 mm), n_D^{25} 1.4433, d_4^{25} 0.9283 and 1.8 g., b.p. 166–168° (1 mm), n_D^{25} 1.4458, d_4^{25} 0.9355.

Anal. Calcd. for trimer, Mol. wt., 396; M.R. 113; for tetramer, Mol. wt., 538; M.R., 151. Found: first fraction, Mol. wt., 368; M.R., 115.2. Second fraction, mol. wt., 503 (average); M.R., 150.9. Third fraction, Mol. wt., 517; M.R., 150.4.

The second fraction is probably a mixture of the first and third.

Tris(trimethylsilylmethyl)bromosilane. Tris(trimethylsilylmethylsilane (18 g., 0.06 mole), in 300 cc. of carbon tetrachloride was placed in a 500 cc. three-necked flask fitted with stirrer, reflux condenser, and dropping funnel. Bromine (13 g., 0.08 mole) in 100 cc. of carbon tetrachloride was added dropwise over a 2-hr. period. After approximately one half of the bromine had been added the reaction slowed up markedly. The flask was then illuminated with a 200 watt bulb, then allowed to stand for 50 hr. at room temperature with continued illumination. It was then heated to reflux and a stream of nitrogen passed through it for 1 hr. After cooling, a 5% aqueous solution of ammonium hydroxide (60 cc.) was then added and this mixture stirred for 30 min. The aqueous layer was then removed (*p*H approximately 10 by Alkacid test paper). Fractionation produced tris(trimethylsilylmethyl)bromosilane, 4.3 g., b.p. 110° (1.8 mm), n_D^{25} 1.4725, 20% yield.

Anal. Calcd. for $C_{12}H_{33}BrSi_4$: Br, 21.7. Found: Br, 22.1.

Tris(trimethylsilylmethyl)silanol. Tris(trimethylsilylmethyl)bromosilane (10 g., 0.03 mole) in 30 cc. of acetone was treated with 6.6 g. of 10% aqueous ammonium hydroxide (0.046 mole). The mixture was stirred for 2 hr. at room temperature, and the layers separated. The aqueous layer was slightly basic. The organic layer was dried over sodium sulfate and the acetone evaporated. There remained 9 g. of liquid which was fractionated yielding 3.7 g. of tris(trimethylsilylmethylsilyl)silanol, b.p. 112–113° (5.0 mm.), n_D^{25} 1.4540, d_4^{25} 0.8594, yield 40%.

Anal. Calcd. for $C_{12}H_{34}OSi_4$: C, 47.06, H, 11.11; Si, 36.68; Mol. wt., 306; M.R. 97. Found: C, 47.87; H, 10.93; Si, 35.8, 36.6, 36.5; mol. wt., 295; M.R., 96.

BUFFALO, N. Y.

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

Stable Organic Biradicals

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The preparations of seventeen glycols, two of the corresponding glycol ethers and eleven of the corresponding chlorides are described. While only somewhat more than half of these substances constitute new compounds, the present procedures are superior to previously reported methods of synthesis and are of general applicability to all compounds of this type, bis-triarylmethanol where the alcohol centers are separated by at least one aromatic ring. Ten of the chlorides were converted by treatment with "molecular" silver to potential biradicals of the bis-triarylmethyl type. Of these, seven had been previously prepared and declared to be non-radical in character. One of them, the Tschitschibabin hydrocarbon (XXIX A), however, has more recently been shown to possess radical character by its paramagnetic resonance (ESR) spectrum. All ten potential radicals were examined by the ESR technique, and all but one, the Thiele hydrocarbon (XVII), were shown to absorb micro waves of the resonant frequency. The results make it clear that if no interaction between the two "odd" electrons of a biradical (*e.g.*, quinoidation) can be envisioned in terms of Kekule structures, the substance will be a biradical. If interaction is possible, the detectability of radical character will depend upon the energy difference between the state involving interaction and the state in which the electrons are unpaired.

The problem posed by the possible interconversion of singlet (quinoid) and triplet (biradical) states in certain types of organic molecules is an intriguing one, and the type of compound potentially capable of such interconversion is very nearly as old as the stable free radical itself.[2] However, from the period 1904–1907 when the first attempts to prepare the quinoid forms (see below) were published until the late 1920's, no interest seems to have attached to the problem. As will become apparent in the sequel (see Discussion) early attempts to provide criteria for judging the radical character of biradicals were not altogether satisfactory. Of the ten potential biradicals selected for the present study seven had been examined before and considerable confusion is apparent in the literature as to the problem of quinoid-biradical interconvertibility and the nature of biradicals with "insulated" radical centers. It is the purpose of this paper and the previously published theoretical treatment of the paramagnetic resonance study[3] to provide an answer to the question posed by earlier work: When can one expect interaction between the "odd" electrons of a biradical? The present paper does not treat the theoretical findings in detail but is chiefly concerned with improved methods for the preparations of certain organic biradicals and the intermediates necessary for their syntheses, and with the general conclusions based upon the ESR data.

The species of biradical selected for study are of the bis-triarylmethyl type where the radical centers are separated by various groups which serve

(1) Abstracted from a portion of the Ph.D. Dissertation of Gilbert J. Sloan, University of Michigan, 1954.

(2) M. Gomberg, *J. Am. Chem. Soc.*, **22**, 757 (1900); *Ber.*, **33**, 3150 (1900).

(3) H. S. Jarrett, G. J. Sloan, and W. R. Vaughan, *J. Chem. Phys.*, **25**, 697 (1956).

either to insulate the radical electrons or to permit their interaction through quinoidation. The general mode of synthesis is presented in Chart I.

CHART I[a]

SYNTHESIS OF BIRADICALS

$$\underset{\text{I}}{\text{H—Y—H}} \longrightarrow \underset{\text{II}}{\text{Ac—Y—Ac}} \longrightarrow \underset{\text{III}}{\text{HO}_2\text{C—Y—CO}_2\text{H}}$$

$$\longrightarrow \underset{\text{IV}}{\text{CH}_3\text{O}_2\text{C—Y—CO}_2\text{CH}_3}$$

$$\text{III} \longrightarrow \underset{\text{V}}{\text{ClCO—Y—COCl}} \longrightarrow \underset{\text{VI}}{\text{H}_2\text{NCO—Y—CONH}_2}$$

$$\longrightarrow \underset{\text{VII}}{\text{N}\equiv\text{C—Y—C}\equiv\text{N}}$$

IV or VII + ArMgX ⟶ glycol (VIII–XVII)

glycol ⟶ dichloride (XVIII–XXIV)

⟶ biradical (XXVII–XXXII)

[a] The figure Y represents the bracketed structures appearing in the three series of compounds represented in Table I. For compounds I through IV see Table II (Experimental); for compounds VI, see Table III; and for compounds VII see Table IV.

The structures of the glycols, dichlorides, and biradicals are presented in Table I.

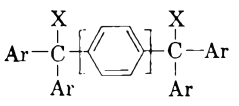
many of the compounds described have been prepared previously, the published methods were not generally applicable to all members of the series, and the yields obtained were poor.

The nitriles (VIIA through VIIE) are the most flexible intermediates, since they provide for the introduction of identical or different aromatic substituents; but the best previously reported syntheses of them involved six steps, with overall yields of the order of 3%.[4,5] In this work, the nitriles were conveniently prepared by treatment of the corresponding amides with phosphorus pentachloride, or more directly, by the pyrolysis of the zinc salts of the acids in the presence of lead thiocyanate. In no case was the overall yield below 25%.

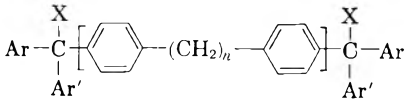
The latter reaction, which seems not to have been used for many years, was developed by Reid,[6] who applied it with excellent results to the preparation of many low-molecular weight nitriles. Its successful application to non-volatile, bifunctional acids indicates that it has considerable generality. It is interesting to note that the origin of the nitrile carbon is not certain. *A priori*, the most probable course of the reaction would involve decarboxylation of the salt, followed by attack of the resulting radical on

TABLE I

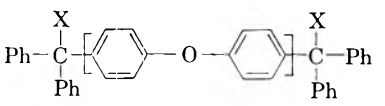
STRUCTURE OF GLYCOLS, CHLORIDES, AND RADICALS



Series 1



Series 2



Series 3

	Series	Glycols (X = OH) Substituents	n	Chlorides (X = Cl)	Glycol Ethers	Radicals (X = electron)
VIII[a,b]	1	Ar = phenyl		XVIII	XXV (X = OC_2H_5)	XXVII[c,d]
IXA[e]	2	Ar = Ar′ = phenyl	0	XIXA[e]		XXIXA[f,g]
B[b,h]	2	Ar = Ar′ = phenyl	1	B[h]		B[g]
C[h]	2	Ar = Ar′ = phenyl	2	C[h]		C[g]
D[i]	2	Ar = Ar′ = phenyl	3	D		D
E[j]	2	Ar = Ar′ = phenyl	4	E[j]		E[g]
X[k]	1	Ar = *p*-xenyl		XX[k]		XXVIII[g]
XIA[l]	2	Ar = Ar′ = *p*-xenyl	0	XXI[l]		XXX
B	2	Ar = Ar′ = *p*-xenyl	1			
C	2	Ar = Ar′ = *p*-xenyl	2			
D	2	Ar = Ar′ = *p*-xenyl	4			
XII[i]	1	Ar = *p*-tolyl		XXII		
XIII	2	Ar = Ar′ = *p*-tolyl	0			
XIV	1	Ar = *p*-anisyl			XXVI (X = OCH_3)	
XV	2	Ar = Ar′ = *p*-anisyl	0			
XVI	2	Ar = phenyl, Ar′ = 1-naphthyl	0	XXIII		XXXI
XVII[m,n]	3			XXIV[m]		XXXII[g]

[a] Reference 10. [b] Not previously analyzed. [c] Thiele hydrocarbon. [d] Non-radical. [e] Reference 11. [f] Tschitschibabin hydrocarbon; cf. ref. 18. [g] Previously reported non-radical; cf. ref. 19. [h] Reference 17. [i] Converted directly to chlorde. [j] Reference 18. [k] Reference 36. [l] Reference 16. [m] Reference 39. [n] Not isolated, but converted directly to XXIV (see Experimental).

SYNTHESES

The synthetic methods presented here constitute a general approach to a fairly large group of biradicals of considerable theoretical interst. Although

(4) J. N. Ashley, *et al.*, *J. Chem. Soc.*, 108 (1942).

(5) D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, **73**, 5691 (1951).

(6) E. E. Reid, *Am. Chem. J.*, **43**, 162 (1910).

the lead thiocyanate or on the decomposition products of the latter, somewhat as follows:

$$(RCO_2)_2Zn \longrightarrow 2R\cdot + Zn + 2CO_2$$

$$2R\cdot + Pb(SCN)_2 \longrightarrow Pb + 2RSCN$$

$$2RSCN + Pb + Zn \longrightarrow 2RCN + PbS + ZnS$$

If this is in fact the case, then the use of C^{14}-labeled acids should give inactive nitriles, and conversely, C^{14}-labeled thiocyanate should give active nitriles.[7] This latter reaction might prove useful in the "exchange" of C^{14} or C^{12} in biologically important acids.

The esterification of 4,4′-dicarboxybiphenyl presents an interesting problem. The acid cannot be esterified by the Fischer method, nor by treatment with diazomethane, probably because of its extremely low solubility in ordinary solvents. Prolonged refluxing with *n*-butanol and a strong acid, with removal of the water produced in the reaction, provides the butyl ester, but in rather poor yield. However, by treatment with phosphorous pentachloride, the acid can be converted to the acid chloride, which in turn affords the methyl ester in good yield on treatment with methanol.

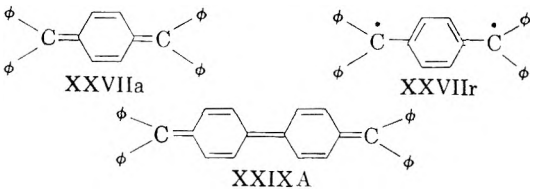
The reactions of the esters and ketones with Grignard reagents are, in general, straightforward. The resulting glycols, however, frequently are difficult to purify. Some of them form difficultly crystallizable oils which can be purified only by chromatography or conversion to the corresponding crystalline dichloride. The glycols VIII (Table I, series 1), and IXA (Table II, series 2) form solvates with many ordinary crystallizing solvents. The benzene solvate of VIII is remarkably stable; even extensive drying in high vacuum does not remove the benzene. It is interesting to note that the solvate is formed directly in the hydrolysis of the Grignard complex, presumably by reaction with the benzene liberated by hydrolysis of excess phenylmagnesium bromide. The absence of strongly polar functions from both moieties of the molecular compounds suggests that the source of their stability is geometrical, rather than electrical. Assuming that this is the case, it is still not clear whether the retention of the solvent molecules is due to the geometry of the glycol molecule, or that of the glycol crystal. Many cases of the latter type are known,[8] and some information might be gained by a careful study of the stoichiometry of the complexes, since the number of molecules of solvent retained per molecule of solvated species is frequently non-integral in complexes of the "clathrate" or crystalline type.

The dichlorides in this series of compounds become colored at elevated temperatures, even in ordinary organic solvents. That the colored thermochromic forms are ionic is strongly suggested by a qualitative similarity of the spectra obtained in hot acetic acid to those obtained in concentrated sulfuric acid. This effect would not be thought to render purification of the chlorides difficult, but it may be that the extensive decomposition which takes place during recrystallization involves the ion as a reactive intermediate. Such decomposition may be minimized by quickly dissolving the chloride in an excess of a low-boiling solvent, then quickly adding just enough of a second solvent, in which the chloride is insoluble, to cause rapid precipitation. Alternatively, the poor solvent can be allowed to distill isothermally into the solution in good solvent, resulting in slow precipitation at room temperature.

It should be noted that many of the Grignard reactions, especially those with *p*-xenylmagnesium bromide, were carried out in tetrahydrofuran, rather than in ether. The former solvent is excellent for this reaction, since it is readily purified (see p. 461), is much less hygroscopic than ether, and causes the formation of *p*-xenylmagnesium bromide to go nearly to completion in less than one-half hour. The biradicals were prepared *in vacuo* by reaction of the dichlorides with "molecular" silver[9] in benzene solution, and the extent of dehalogenation was checked in a number of cases and found to be 84–99% complete in two hours. Measurements of paramagnetic resonance absorption were made at intervals from a few minutes' treatment with silver to essentially complete dehalogenation, with positive results being observed in all but one case.

DISCUSSION

In 1904 Thiele prepared tetraphenylquinonedimethane, XXVIIa, in the course of an attempt to prepare the unsubstituted quinonedimethane. This substance is colored and very reactive; it can be considered to be an electromer of the biradical XXVIIr, but shows no reactivity toward oxygen.[10] A related hydrocarbon (XXIXA) prepared by Tschitschibabin,[11] however, is a violet solid, whose solutions absorb oxygen rapidly. It, then, is a substance with an even number of electrons, capable of formulation as a quinone, but giving every chemical evidence of free radical nature. At the time of Tschitschibabin's work, little could be said in favor of either structure on theoretical grounds, and experimental criteria for a decision were lacking.



XXVIIa XXVIIr

XXIXA

(7) A preliminary attempt to establish the fate of the C^{14} of $(RC^{14}O_2)_2Zn$ in this reaction has given some indication that the radioactivity does not appear in the nitrile. Work on the reaction mechanism is continuing.

(8) W. Schlenk, Jr., *Fortschr. chem. Forsch.*, 2, 92 (1951).

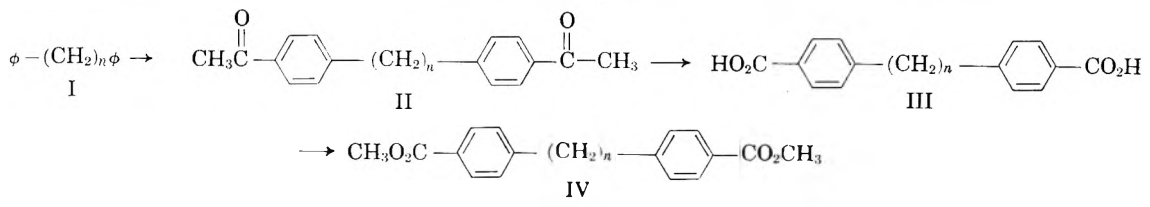
(9) M. Gomberg and L. H. Cone, *Ber.*, **39**, 3274 (1906).

(10) J. Thiele and H. Balhorn, *Ber.*, **37**, 1463 (1904).

(11) A. E. Tschitschibabin, *Ber.*, **40**, 1810 (1907).

TABLE II

PREPARATION OF α,ω-BIS(4-ACETOPHENYL)-, α,ω-BIS(4-CARBOXYPHENYL)-, AND α,ω-BIS(4-CARBOMETHOXYPHENYL)-ALKANES



n	Cpd.	Yield, %	M.P., °C.	Crystn. Solvent	Cryst. Form[a]	Cpd.	Yield, %	M.P., °C.	Cpd.	Yield %	Proc.	M.P., °C.	Crystn. Solvent	Cryst. Form[a]
0	IIA[b]	66	192–193	Dioxane	pl	IIIA[c]	90		IVA[d]	85	A	215–217	Chloroform	pl
1	IIB[e]	63	93.5–94.5	Dioxane	pl	IIIB[f]	92	329–332	IVB[g]	74	B	81–82	Methanol	nd
2	IIC[e]	41	167–168	Dioxane	pl	IIIC[h]	95		IVC[i]	74	B,C	117–118	Methanol	lv
3	IID[j]	79	84–86	Methanol	nd	IIID[k]	95	300–304	IVD[l]	86	B	90–92	Methanol	nd
4	IIE[m]	56	110–112	Methanol	nd	IIIE[n]	94	327–332	IVE[o]	82	C	91.5–93.0	Methanol	nd

[a] pl = plates, nd = needles, lv = leaves. [b] S. L. Silver and A. Lowry, *J. Am. Chem. Soc.*, **56**, 2429 (1934), report a yield of 43% and m.p. 191°. [c] O. Doebner, *Ber.*, **9**, 271 (1876). [d] M. Weiler, *Ber.*, **32**, 1063 (1899) reports m.p. 212–213° (uncor.) for IVA prepared in essentially the same way. Tschitschibabin, *Ber.*, **40**, 1810 (1907) reports m.p. 224° for IVA prepared in a different way. [e] R. E. Lutz, *et al.*, *J. Org. Chem.*, **12**, 617 (1948) report m.p.'s 92.5–93.0° and 167–168°, respectively. [f] P. Mitter, *Ber.*, **45**, 1207 (1912) reports a m.p. of 334–336° for IIIB prepared by a different method. [g] P. Mitter, *Ber.*, **45**, 1207 (1912) reports the same melting point. [h] C. Fischer and R. Wolffenstein, *Ber.*, **37**, 3215 (1904) report that IIIC does not melt at 320°. [i] C. Fischer and R. Wolffenstein, *Ber.*, **37**, 3215 (1904) report m.p. 119°. [j] D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, **73**, 5691 (1951) report a yield of 77% and m.p. 83–85°. [k] D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, **73**, 5691 (1951) report m.p. 304–307°. [l] D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, **73**, 5691 (1951) report a 77% yield, m.p. 85–88°, using essentially the same procedure. [m] An analytical sample was recrystallized three times from ethanol; m.p. 110–112°. Calcd. for $C_{20}H_{22}O_2$: C, 81.59; H, 7.53. Found: C, 81.52; H, 7.52. [n] An analytical sample was recrystallized from glacial acetic acid, m.p. 327–332°. Further recrystallization did not change the melting point, but the acid did not analyze satisfactorily for carbon. This difficulty appears to be a general one with these compounds.[c,f,h,k] Calcd. for $C_{18}H_{18}O_4$: C, 72.57; H, 6.08. Found: C, 73.08; H, 6.09. [o] An analytical sample was recrystallized twice from methanol, m.p. 92.0–92.5°. Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.80. Found: C, 73.94; H, 707.

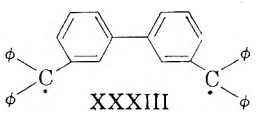
Of the techniques subsequently used to establish the free radical nature of the triarylmethyls, two, the determination of molecular weight and the study of deviations from Beer's law, are inapplicable to the Tschitschibabin hydrocarbon because the number of molecules present in a solution of this substance is the same regardless of whether the quinone or the biradical structure is correct. A determination of the magnetic susceptibility of the compound offered a solution to the problem, since the radical form would be expected to be paramagnetic, and the quinone form diamagnetic. An application of this method indicated that the quinone structure is correct.[12]

Aside from the reactivity of XXIXA toward oxygen, Bent and Gould have shown that it adds sodium more readily than does triphenylmethyl.[13] Now all radicals with essentially free electrons should have much the same electron affinity,[14] and one may therefore consider any observed difference in apparent electron affinity (*e.g.* sodium addition) to be due to a difference in degree of radicalness. Thus XXIXA is better formulated as the biradical XXIXAr.

XXIXAR

This formulation is supported by still another diagnostic for free radicals: it promotes the conversion of *para* to *ortho* hydrogen at a rate corresponding to 10% biradical, while XXVII is inactive.[15] Thus the physical and chemical evidence are in harmony for XXIXA.

Insulated compound such as the Schlenk[16] hydrocarbon XXXIII and the biphenyls XXIXE and



XXXIII

XXIXC (Table I), first prepared by Wittig and Leo[17] exhibit free radical chemistry, and the Schlenk hydrocarbon actually is paramagnetic (magnetic susceptibility method, see below). However, surprisingly XXIXE (Table I) exhibits no free radical character,[18] and XXIXC appears to be diamagnetic.[19] Thus the chemical and physical evidence can be contradictory.

Because the peroxides obtained from freshly prepared solutions of the radicals contain less than the expected amounts of oxygen, and since the colors of the solution are lasting, Wittig and Leo have attributed failure to observe radical properties in certain such compounds to disproportionation simultaneous with dehalogenation.[18] However, more recent work has shown that certain triarylmethyl solutions appear to retain their original colors (actually the absorption spectra do change, but not visually) while their paramagnetisms are falling to zero as a consequence of demonstrable disproportionation,[20,21] thus weakening the Wittig and Leo argument.

In an attempt to obtain an insulated biradical similar to those which appear to disproportionate but which is incapable of such degradation XXXII (Table 1) was prepared.[22] That it unhappily proved to be wholly diamagnetic (magnetic susceptibility method) was attributed to dimerization (or polymerization).

Two features of previous investigations of the type just cited seemed to us sufficiently questionable to justify a reexamination of the entire biradical problem. First, in view of the relatively slow disproportionation of alkyl substituted triarylmethyls and the steric problems posed by biradical dimerizations, it seemed highly unlikely that bis-triarylmethyls would disproportionate or dimerize so quickly as to prevent detection of paramagnetism. Second, serious doubt had recently been cast upon the validity of the magnetic susceptibility method for obtaining paramagnetic data on free radicals. In brief the suggestion that the over-all diamagnetism of a radical is much greater than the value calculated from Pascal constants or obtained from measurements on the hydrocarbons or halides[23,24] provides grounds for doubting any data relating to the paramagnetic properties of biradicals, since the diamagnetism must be subtracted from a measured susceptibility to give the paramagnetism.

The possibility of detecting paramagnetic species by the resonance absorption of microwaves[25] offered a new approach which is independent of assumptions regarding diamagnetism. The successful application of this technique to solutions of XXIXA, which in agreement with chemical (and as it happens magnetic) properties previously determined were shown to contain paramagnetic species at ordinary temperatures[26] encouraged us to undertake similar examination of the potential biradicals listed in the last column of Table I. It will be noted

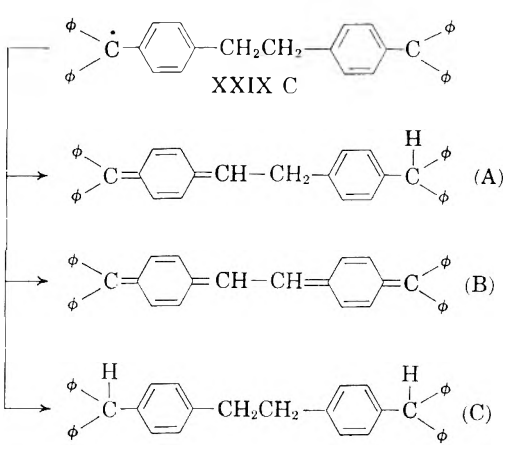
(12) E. Müller and I. Müller-Rodloff, *Ann.*, 517, 134 (1935).
(13) H. E. Bent and R. E. Gould, *J. Am. Chem. Soc.*, **57**, 1217 (1935).
(14) G. W. Wheland, *J. Chem. Phys.*, **2**, 474 (1934).
(15) G. M. Schwab and N. Agliardi, *Ber.*, **73**, 85 (1940).
(16) W. Schlenk and M. Brauns, *Ber.*, **48**, 716 (1915).
(17) G. Wittig and M. Leo, *Ber.*, **61**, 854 (1928).
(18) G. Wittig and M. Leo, *Ber.*, **62**, 1405 (1929).
(19) E. Müller, *Angew. Chem.*, **51**, 662 (1938).
(20) P. W. Selwood and R. F. Preckel, *J. Am. Chem. Soc.*, **65**, 895 (1943).
(21) C. S. Marvel, M. B. Mueller, C. M. Himel, and J. F. Kaplan, *J. Am. Chem. Soc.*, **61**, 2771 (1939).
(22) E. Müller and W. Bunge, *Ber.*, **69**, 2164 (1936).
(23) P. W. Selwood and R. M. Dobres, *J. Am. Chem. Soc.*, **72**, 3860 (1950).
(24) G. W. Wheland, *Advanced Organic Chemistry*, pp. 695–696, John Wiley and Sons, Inc., New York, 1949.
(25) For a recent review see J. E. Wertz, *Chem. Revs.*, **55**, 829 (1955).
(26) C. A. Hutchinson, Jr., A. Kowalksy, R. C. Pastor, and G. W. Wheland, *J. Chem. Phys.*, **20**, 1485 (1952).

that only three are new compounds (XXIXD, XXX, and XXXI), and that for XXVII, XVIII, XXX, and XXXI the same type of possibility for escape to diamagnetism through quinoidation exists as for XXIXA, which has been included for comparison, owing to the independent data available.[26] That XXIXA proves to be other than completely diamagnetic appears to constitute another situation such as is encountered in porphyrindine,[27] in which a diamagnetic ground state is in equilibrium with a paramagnetic excited state. That this situation is typical will appear in the sequel.

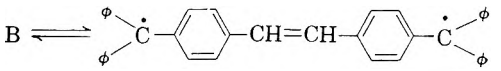
Consideration of Table V leads to some rather striking conclusions. First, it is evident that in all the cases in which no interaction between the two odd electrons of a potential biradical can be envisioned on the basis of classical organic chemistry, the substances are indeed paramagnetic. Even in the case of the Tschitschibabin hydrocarbon (XXIXA), where interaction can occur, paramagnetism is detectable. Whether the spins of the two odd electrons of the paramagnetic species are essentially independent (in which case the molecule would be a doubled doublet) or whether they are constrained to be parallel (in which case the molecule would be a triplet) is not conclusively established in this work. *A priori*, the fact that the biphenyl nucleus is non-coplanar[3,28] might lead one to suspect that the two halves of the molecule are uncoupled, and that the former situation obtains. However, it has been demonstrated that even appreciable twisting about the 1,1′-bond of biphenyl does not completely uncouple the halves of the molecule.[28] Concordant with this, convincing arguments can be adduced to support the contention that the two odd electrons couple through the distorted biphenyl nucleus to yield a triplet excited state lying only slightly higher than the diamagnetic ground state.[3]

The failure of the Thiele hydrocarbon (XXVII) to show similar properties is probably due to the increased separation of the singlet and triplet states.[28]

All of the molecules for which no interacting forms can be written show paramagnetic resonance. It should be noted, however, that even in the absence of light and oxygen, the paramagnetic species slowly disappear; there is little doubt that this must be attributed to some form of disproportionation. Although no attempt was made in this study to isolate degradation products, there is precedent for this conclusion. In a study of 1,2-bis[4′-(diphenylmethyl)phenyl]ethane (XXIXC), Müller reports the isolation of three degradation products, and gives a scheme whereby one of these might be formed by intramolecular and the others by intermolecular disproportionation:[19]



Of especial significance is the fact that compound B, although found to be diamagnetic, is reported to be deep purple and sensitive to oxygen. This is in accord with a second unexpected situation, seen in Table V. The degradation to colored, diamagnetic substances *which retain oxygen-sensitivity* is a fairly general occurrence in free radicals. The excitation of B to a triplet state presents an attractive explanation for the oxygen sensitivity of degraded solutions of XXIXC. But molecular orbital calculations[29] indicate that, even at room temperature, B should be in equilibrium with a detectable amount of the excited paramagnetic form:



If this were the case, the degraded solution would continue to show paramagnetism. That it does not is an indication that the disproportionation is essentially intramolecular. The retention of reactivity toward oxygen might then be explained as a result of a photo-excitation of A to a transient paramagnetic state. This hypothesis could be tested by exposing a sample of the degraded material to oxygen in the dark.

In the case of the diphenylmethane derivative XXIXB, both inter- and intramolecular disproportionation might lead to the same product. If this were so, it is difficult to see why the degraded solutions should differ in color from those of XXIXC. Further, it is not at all apparent why the diphenylpropane and diphenylbutane derivatives should behave so differently from the diphenylmethane and diphenylethane derivatives. It is of course possible that in the two former cases, the biradical form is in equilibrium with a monomeric diamagnetic ring compound, while in the two latter cases, the radical carbons do not approach within bonding distance of each other, and that this difference results in a different disproportionation mechanism. Work on the chemical properties of these compounds is continuing.

It is of extreme interest and importance to note

(27) E. Müller, *Fortschr. chem. Forsch.*, 1, 325 (1949).
(28) H. Suzuki, *Bull. Chem. Soc. Japan*, 27, 597 (1954).
(29) Private communication from Dr. H. S. Jarrett.

that in view of the demonstrated non-coplanarity of triphenylmethyl,[30] the systems under discussion here cannot be coplanar. They are, nevertheless, strongly (but not maximally) resonance stabilized. A similar situation has been shown to exist in triarylcarbonium ions by the elegant cryoscopic and spectroscopic work of Newman and Deno.[31] These authors demonstrated conclusively that even in cases where coplanarity is made impossible by large *ortho* substituents, resonance stabilization exists. Evidence is advanced to support the contention that the reduction of resonance which accompanies the distortion from planarity is accomplished by removal of one or two of the rings from resonance, rather than by an overall diminution of resonance throughout the system. The nonequivalence of the rings implied in this idea has not yet been adequately demonstrated.

EXPERIMENTAL

Melting points are uncorrected. Microanalyses by Goji Kodama, University of Michigan.

1. α,ω-Bis(4-acetophenyl)alkanes (II). A solution of 0.05 mole of the α,ω-diphenylalkane and 157 g. (2.0 moles, 142 ml.) of acetyl chloride in 100 ml. of carbon disulfide was added dropwise during 1 hr. to a vigorously stirred suspension of 267 g. (2.0 moles) of anhydrous aluminum chloride in 200 ml. of carbon disulfide. The reaction mixture was cooled in an ice-salt bath during the addition, after which it was refluxed, with continued stirring, for 2 additional hr. The condenser was then set down for distillation and the carbon disulfide removed. The mixture remaining in the flask was poured while still warm into a well-stirred mixture of ice and concentrated hydrochloric acid. The resulting solid was filtered off, washed well with water, and crystallized with a Norit treatment.

2. α,ω-Bis(4-carboxyphenyl)alkanes (III). To a solution of the appropriate diaceto compound (0.05 mole) in 500 ml. of methanol was added 500 ml. of 1*N* potassium hypochlorite. The resulting mixture was stirred for 2 to 3 hr. at 65–75°. The excess hypochlorite was destroyed by the addition of acetone and any undissolved solid was filtered off. The filtrate was cooled to room temperature and made acid to Congo Red by the careful addition of concentrated hydrochloric acid; the white precipitate was collected in a basket centrifuge and washed several times with warm water. The solid acid was air-dried, then dried thoroughly at 110°.

3. α,ω-Bis(4-carbomethoxyphenyl)alkanes (IV). *Procedure A.* A mixture of 48.4 g. (0.2 mole) of 4,4′-dicarboxybiphenyl, IIIA, 110 g. (0.53 mole) of phosphorus pentachloride, and 200 ml. of toluene was refluxed for 1 hr. The toluene was distilled on a steam bath at reduced pressure, leaving a brown crystalline residue, which was cooled in an ice bath. The reaction flask was again fitted with a reflux condenser, the top of which carried a dropping funnel with a pressure equalizing side-arm, containing 250 ml. of absolute methanol. The methanol was added during 0.5 hr., after which the mixture was refluxed for 2 hr., cooled and alkalized with 10% sodium carbonate solution. The solid which separated was collected, washed with water, dried, and recrystallized from chloroform, giving 46 g. (85% yield) of silvery white plates, m.p. 215–217°; reported 224°,[11] 214°.[32]

Procedure B. A mixture of 0.1 mole of the appropriate diacid, 300 ml. of absolute methanol, and 5 ml. of concentrated sulfuric acid was refluxed overnight. Most of the methanol was then distilled, the residue was poured into water and the mixture alkalized with 10% sodium carbonate solution. The resulting mixture was extracted with ether; the ether solution was washed with water, dried, and the ether distilled on a steam bath. The residue was then crystallized from methanol.

Procedure C. The diacid was treated with a 50% excess of diazomethane in ether. The mixture was allowed to stand for 0.5 hr. with occasional swirling; the excess diazomethane was then destroyed by glacial acetic acid. After removal of any insoluble material by filtration, the ether was evaporated under an air-jet, and the residue crystallized from methanol.

4. α,ω-Bis(4-chloroformylphenyl)alkanes (V). *1,3-Bis(chloroformylphenyl)propane* (VA). Compound IIID (5.68 g., 0.02 mole), was ground in a mortar with 12 g. of phosphorus pentachloride until reaction set in. The mixture was allowed to stand for 0.5 hr., then ground with ice, and the resulting solid was collected and dried in a vacuum desiccator, giving 7.09 g. of crude product. This was recrystallized from benzene and petroleum ether (b.p. 60–75°),[33] giving 4.45 g. (71% yield) of white needles, m.p. 75–76°. An analytical sample was recrystallized twice from benzene and petroleum ether, m.p. 76.0–76.5°.

Anal. Calcd. for $C_{17}H_{14}Cl_2O_2$: C, 63.57; H, 4.39; Cl, 22.08. Found: C, 63.66; H, 4.77; Cl, 22.10.

1,4-Bis(4-chloroformylphenyl)butane (VB). Compound IIIE (5.96 g., 0.02 mole) was treated with 12 g. of phosphorus pentachloride as in the preparation of VA above. The crude product was recrystallized from benzene and petroleum ether, giving 3.40 g. (51% yield) of white needles, m.p. 91–93°. An analytical sample was recrystallized twice from benzene and petroleum ether, m.p. 93.0–93.5°.

Anal. Calcd. for $C_{18}H_{16}Cl_2O_2$: C, 64.49; H, 4.81; Cl, 21.15. Found: C, 64.58; H, 4.93; Cl, 21.19.

These acid chlorides, as well as that of 1,2-bis(4-carboxyphenyl)ethane (IIIC) were also prepared by refluxing the acids for several hours with thionyl chloride in the presence of a trace of pyridine. The products were not purified for analysis, but were converted to the amides after removal of the excess thionyl chloride by distillation.

5. α,ω-Bis(4-carbamylphenyl)alkanes (VI). The crude acid chloride, prepared as in Section 4, was triturated with concentrated ammonium hydroxide and the mixture was allowed to stand for 1 hr. The granular solid was then collected, washed well with water, and dried. For conversion to the dinitrile, the diamide was used without further purification. For analysis, the diamide was recrystallized from glacial acetic acid. Although repeated recrystallization did not change the melting point, the amides did not analyze satisfactorily for carbon (see Table III).

6. α,ω-Bis(4-cyanophenyl)alkanes (VII). *Procedure D.* To a mixture of equal parts (by weight) of the appropriate diamide and phosphorus pentachloride was added approximately 5 parts of xylene. The mixture was refluxed for 1 hr.; the xylene was then evaporated in an air jet, and the mixture alkalized with 10% sodium carbonate solution. The solid which separated was collected, washed with water, and dried. The crude product was then sublimed and recrystallized once.

Procedure E. The diacid (0.010 mole) was neutralized with 0.5*N* potassium hydroxide solution; the resulting solution was heated to about 80° and added to a solution of 1.5 g. (0.011 mole) of zinc chloride in 10 ml. of hot water. The zinc salt was filtered off, washed several times with warm water, air dried, then dried overnight at 110°. The dry zinc salt was then ground thoroughly with 4.05 g. (0.0125 mole) of lead thiocyanate in a glass mortar. The resulting mixture was heated strongly in a sublimation

(30) H. S. Jarrett and G. J. Sloan, *J. Chem. Phys.*, 22, 783 (1954).

(31) M. S. Newman and N. C. Deno, *J. Am. Chem. Soc.*, 73, 3644 (1951).

(32) F. Ullmann, *Ann.*, 332, 38 (1904).

(33) Whenever petroleum ether is referred to in the remainder of this paper, it is of this boiling range.

TABLE III

α,ω-BIS(4-CARBAMYLPHENYL)ALKANES

Starting Material	Product	Yield, %[a]	Analyses: Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIC[b]	VIA	99	71.62	6.01	10.44	73.44	6.18	10.41
VA	VIB	95	72.31	6.43	9.92	73.43	6.07	10.02
VB	VIC	97	72.94	6.80	9.45	73.91	6.80	9.51

[a] The yields reported here are of crude product, based on the diacid. [b] Converted to the diacid chloride by thionyl chloride.

apparatus with a Bunsen burner until it became black, and for about 10 min. longer. The sublimate was collected, and the residue was extracted with several 20 ml. portions of hot absolute ethanol or acetonitrile. The combined extracts were treated with Norit, evaporated to a suitable volume, and cooled; the crystals which separated were collected and combined with the sublimate. The total yield was lowered if an attempt was made to sublime all of the product from the reaction mixture.

of phenylmagnesium bromide according to Procedure F. The reflux time was 2 hr., with stirring. The ethereal solution was dried over anhydrous sodium sulfate, stripped on a steam bath, and the residue fractionally crystallized from benzene and petroleum ether, giving 17.94 g. (42.3% yield, based on 15.8 g. of dimethyl terephthalate) of white crystalline powder, m.p. 170–171°. An analytical sample was recrystallized from benzene and petroleum ether, m.p. 170–171° dec., after sintering above 169°. The sample was

TABLE IV

α,ω-BIS(4-CYANOPHENYL)ALKANES

Starting Material	Product	Proc.	M.P., °C.	Crystn. Solvent	Cryst. Form	Yield, %
IIIA	VIIA[a]	E	232–234	Acetonitrile	Needles	59
IIIB	VIIB[b]	E	165–167	Methanol	Needles	43
IIIC	VIIC[c]	E	196–200	Ethanol	Prisms	79
VIA	VIIC[c]	D	196–200	Ethanol	Prisms	79
VIB	VIID[d]	D	94–95	Ethanol	Prisms	60
VIC	VIIE[e]	D	132–133	Ethanol	Plates	55

[a] This compound, was also prepared according to directions of T. S. Work, *J. Chem. Soc.*, 1315 (1940), with essentially the same results. [b] This compound was also prepared according to the directions of M. Schöpff, *Ber.*, **27,** 2321 (1894), with essentially the same results. [c] P. Kattwinkel and R. Wolffenstein, *Ber.*, **34,** 2423 (1901) report m.p. 198°. [d] J. N. Ashley, *et al.*, *J. Chem. Soc.*, 103 (1942) report the same melting point for VIID prepared by another method. [e] An analytical sample was recrystallized 5 times from ethanol, m.p. 133.5–134.0°. Calcd. for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.77. Found: C, 82.99; H, 6.14; N, 10.60.

7. α,ω-Bis[4-(diarylhydroxymethyl)phenyl]alkanes (VIII–XIV). *Procedure F.* Phenylmagnesium bromide in twofold excess was prepared from equivalent amounts of bromobenzene and magnesium in absolute ether, in a nitrogen atmosphere. The solution was then transferred through glass wool, under nitrogen pressure, to a flask containing the carbonyl compound. The resulting solution was refluxed in a nitrogen atmosphere for a period specified in the procedures for the individual compounds, then poured onto a mixture of ice and 10% sulfuric acid. The layers were separated; the ethereal solution was washed with 10% sulfuric acid, 10% sodium carbonate solution, and water.

Procedure G. A solution of *p*-xenylmagnesium bromide was prepared from 9.32 g. (0.04 mole) of 4-bromobiphenyl and 0.97 g. (0.04 atom) of magnesium in 40 ml. of tetrahydrofuran in a nitrogen atmosphere. The solution was then transferred through glass wool, under nitrogen pressure, to a flask containing 0.005 mole of diester. The resulting solution was refluxed in a nitrogen atmosphere for a period specified in the procedures for the individual compounds; most of the solvent was removed by distillation, and the residue was hydrolyzed with ice and 10% sulfuric acid. About 50 ml. of ether was added to the mixture, the organic layer was separated, filtered,[34] and washed with 10% sodium carbonate solution, and water.

α,α,α′,α′-Tetraphenyl-α,α′-dihydroxy-p-xylene (VIII). Dimethyl terephthalate (0.10 mole) was treated with 0.6 mole

(34) The insoluble material was quaterphenyl, in amounts varying from a few mg. to 1 g., m.p. and mixture m.p. with authentic material, 318–320°.

placed in an Abderhalden drying pistol at room temperature and a pressure of 0.05 mm. for 4 hr., before analysis.

Anal.[35] Calcd. for $C_{38}H_{32}O_2$: C, 87.66; H, 6.20. Found: C, 87.22; H, 6.46.

4,4-Bis(diphenylhydroxymethyl)biphenyl (IXA). To 13.5 g. (0.05 mole) of IVA was added phenylmagnesium bromide, according to Procedure F; the solution was refluxed for 4 hr. After hydrolysis, 100 ml. of benzene was added, and the organic layer was separated and filtered, giving 1.00 g. (after recrystallization from chloroform) of white solid, m.p., and mixture m.p. with IVA, 215–217°. The filtrate was washed and evaporated on a steam bath, leaving a yellow oil which solidified to an oily solid weighing 15.45 g. (70% yield). A small sample was recrystallized three times from benzene and petroleum ether, m.p. 177–178° dec., after sintering at 160–165°. Losses in crystallization were large; the crude glycol was therefore converted to the chloride without further purification.

Bis[4-(diphenylhydroxymethyl)phenyl]methane (IXB). Compound IVB (25.2 g., 0.10 mole) was treated according to Procedure F, with a reflux time of 4 hr. The ethereal solution was dried over sodium sulfate, and evaporated on a steam bath. The residue was an oil weighing 21.2 g. (80% yield) which was converted to the chloride without further purification. An attempt at purification of the chloride by chromatography of a benzene solution on alumina resulted in hydrolysis, and gave only glycol in the eluate, m.p. 92–94° dec., after sintering above 86°. The melting point did not change on crystallization from benzene-petroleum ether.

(35) For a discussion of this analysis see p. 752.

Anal. Calcd. for $C_{39}H_{32}O_2$: C, 87.94; H, 6.06. Found: C, 88.21; H, 6.35.

1,2-Bis[4'-(diphenylhydroxymethyl)phenyl]ethane (IXC). Compound IVC (9 g., 0.023 mole) was treated according to Procedure F, with a reflux time of 12 hr. The ethereal solution was evaporated on a steam bath, leaving a yellow oil which was crystallized from benzene and petroleum ether to give 9.6 g. (76% yield) of nearly white powder, m.p. 174–176° dec., after sintering above 170°. A second recrystallization gave 8.5 g. (67.5% yield) of white powder, m.p. 179–180° dec., after sintering above 174°. Wittig and Leo[19] report m.p. 176–178°, after sintering.

1,3-Bis[4'-(diphenylhydroxymethyl)phenyl]propane (IXD). Compound IVD (9.6 g., 0.0308 mole) was treated according to Procedure F. The product was an oil weighing 13.1 g. (77% yield) which was converted to the chloride without further purification.

1,4-Bis[4'-(diphenylhydroxymethyl)phenyl]butane (IXE). Compound IVE (4.18 g., 0.01 mole) was treated according to Procedure F with a reflux time of 4 hr. The ethereal solution was evaporated on a steam bath leaving an oil which was crystallized from benzene and petroleum ether to give 5.19 g. (90% yield) of light yellow powder, m.p. 120–130° dec., after sintering above 70°. A second recrystallization gave 4.45 g. (77.5% yield) of white powder, m.p. 128–130° dec., after sintering above 80°. Wittig and Leo[18] report m.p. 145–150°.

α,α,α',α'-Tetra-p-xenyl-α,α'-dihydroxy-p-xylene (X). Dimethyl terephthalate (0.97 g., 0.004 mole) was treated according to Procedure G. The ethereal solution was steam-distilled until the distillate was clear. On cooling, the residue solidified to a yellow solid, which on recrystallization from chloroform gave 2.36 g. (62.2% yield) of nearly white powder, m.p. 278–280° dec. An analytical sample was recrystallized 3 times from chloroform; white powder, m.p. 284–286° dec., after sintering above 282°. Wittig and Kröhne[36] report 289–291°.

4,4-Bis(di-p-xenylhydroxymethyl)biphenyl (XIA). Compound IVA (1.35 g., 0.005 mole) was treated according to Procedure G, with a reflux time of 6 hr., but the mixture was hydrolyzed before the removal of the tetrahydrofuran, which was then evaporated on a steam bath. The mixture was then cooled, and the solid which formed was collected, triturated with water in a glass mortar, filtered, and dried. The crude product was dissolved in about 100 ml. of boiling xylene, which was then distilled down to about 50 ml. and cooled, giving 3.4 g. of white powder, m.p. about 260° dec., after sintering above 220°. A second recrystallization from xylene gave 2.9 g. (70.5% yield), m.p. 283–288° dec., after sintering above 278°. Schlenk[16] reports the melting point as somewhat above 260°.

Bis[4-(di-p-xenylhydroxymethyl)phenyl]methane (XIB). Compound IVB was treated according to Procedure G, with a reflux time of 12 hr. The ethereal solution was allowed to stand at room temperature until it had evaporated to a volume of about 25 ml., and the solid which separated was collected; 3.61 g. of nearly white powder, m.p. 145–150° dec., after sintering above 90°. Recrystallization from ethyl acetate and petroleum ether gave 3.5 g. (86% yield), m.p. 97–100°.

Anal. Calcd. for $C_{63}H_{48}O_2$: C, 90.40; H, 5.78. Found: C, 90.11; H, 5.89.

1,2-Bis[4'-(di-p-xenylhydroxymethyl)phenyl]ethane (XIC). Compound IVC was treated according to Procedure G, with a reflux time of 6 hr. The ethereal solution was filtered, and the solid was washed with fresh ether, giving 3.56 g. of white powder, m.p. 256–260° dec. The filtrate was steam distilled until the distillate was clear, and the residue was recrystallized from chloroform, giving 0.36 g. of white powder, m.p. 256–260° dec. The two products were combined and recrystallized from chloroform, giving 2.30 g. (63% yield) of white powder, m.p. 258–260° dec., after sintering above 250°. An analytical sample was recrystallized from chloroform, m.p. 272.0–272.5° dec.

Anal. Calcd. for $C_{64}H_{50}O_2$: C, 90.32; H, 5.92. Found: C, 89.50, 91.00; H, 5.71, 6.10.

1,4-Bis[4'-(di-p-xenylhydroxymethyl)phenyl]butane (XID). Compound IVE was treated according to Procedure G, with a reflux time of 12 hr. The ethereal solution was evaporated on a steam bath, leaving a yellow oil which crystallized on cooling. It was recrystallized from ethyl acetate and petroleum ether, giving 1.28 g. (29% yield) of white powder, m.p. 232–234°, after sintering above 210°. An analytical sample was crystallized three times from chloroform, m.p. 241.5–242.0° dec.

Anal. Calcd. for $C_{66}H_{54}O_2$: C, 90.17; H, 6.19. Found: C, 90.31; H, 6.07.

α,α,α',α'-Tetra-p-tolyl-α,α'-dihydroxy-p-xylene (XII). A Grignard solution was prepared from 12.8 g. (0.075 mole, 9.25 ml.) of *p*-bromotoluene and 1.83 g. (0.075 atom) of magnesium in 50 ml. of tetrahydrofuran in a nitrogen atmosphere. To this was added a solution of 2.43 g. (0.0125 mole) of dimethyl terephthalate in 30 ml. of warm tetrahydrofuran, with stirring. The solution, which became deep red, was stirred under reflux for 8 hr., in a nitrogen atmosphere, during which time a light precipitate separated. The reaction mixture was hydrolyzed with ice and 10% sulfuric acid, and 100 ml. of ether was added. The ether layer was separated, washed, and dried; on distilling most of the ether and cooling, a white solid separated; this was collected, giving 0.62 g. of white needles, m.p. and mixed m.p. with authentic 4,4'-bitolyl, 121–122°. The filtrate from the initially precipitated bitolyl was evaporated on the steam bath leaving a yellow oil which became hard on cooling, but did not crystallize. The oil was converted directly to the chloride.

4,4'-Bis(di-p-tolylhydroxymethyl)biphenyl (XIII). A Grignard solution was prepared from 6.84 g. (4.92 ml., 0.04 mole) of *p*-bromotoluene and 0.97 g. (0.04 atom) of magnesium in 50 ml. of anhydrous ether, in a nitrogen atmosphere. To this was added 1.35 g. (0.005 mole) of IVA. The mixture was refluxed for 4 hr. with stirring, then 100 ml. of dry benzene was added and stirring under reflux was continued for 4 hr. longer in a nitrogen atmosphere. The reaction mixture was then hydrolyzed and worked up as in the preparation of XII above. The residue was crystallized from benzene and petroleum ether, giving 1.9 g. of light yellow powder, m.p. 110–114°. A sample (0.9 g.) of this material was chromatographed on a small alumina column, giving 0.53 g. of lustrous white powder, m.p. 204–205°, after sintering above 198°. An analytical sample from the eluate was recrystallized twice from benzene and petroleum ether, m.p. 204–205°.

Anal. Calcd. for $C_{42}H_{38}O_2$: C, 87.77; H, 6.66. Found: C, 87.68; H, 6.65.

α,α,α',α'-Tetra-p-anisyl-α,α'-dihydroxy-p-xylene (XIV). A Grignard solution was prepared from 56.1 g. (0.3 mole, 37.6 ml.) of *p*-bromoanisole and 7.29 g. (0.3 atom) of magnesium in 150 ml. of anhydrous ether. To this were added 100 ml. of benzene and 9.7 g. (0.05 mole) of dimethyl terephthalate, and the resulting mixture was refluxed for 8 hr., after which it was hydrolyzed with a saturated solution of ammonium chloride. The organic layer was separated, washed with water, and steam-distilled until the distillate was clear. The residue was recrystallized from benzene, giving 10.0 g. of light orange powder, m.p. 98–120°. This was recrystallized from acetone, giving 9.54 g. of light orange powder, m.p. 157–160°, sintering above 150°, which was taken up in 250 ml. of benzene and chromatographically adsorbed in 100 g. of alumina. Elution with 150 ml. of

(36) G. Wittig and H. Kröhne, *Ann.*, 529, 142 (1937).

benzene gave about 0.1 g. of a white solid, m.p. 270–274.[37] The alumina was then eluted with 2 l. of benzene containing 10 ml. of absolute ethanol. The solvent was evaporated from the eluate, and the residue was recrystallized from acetone to give 7.3 g. (26% yield) of cream-colored powder, m.p. 164–167°, after sintering above 158°. An analytical sample was recrystallized four times from acetone; short white needles, m.p. 170–171°. *Anal.* Calcd. for $C_{44}H_{34}O_6$: C, 76.85; H, 6.09. Found: C, 76.80; H, 6.07.

4,4'-Bis(di-p-anisylhydroxymethyl)biphenyl (XV). A solution of *p*-anisylmagnesium bromide was prepared from 7.5 g. (0.04 mole, 5.0 ml.) of *p*-bromoanisole and 0.97 g. (0.04 atom) of magnesium in 40 ml. of tetrahydrofuran, and transferred through glass wool, under nitrogen pressure, to a flask containing a suspension of 1.35 g. (0.005 mole) of IVA in 10 ml. of tetrahydrofuran. The resulting purple solution was refluxed for 6 hr., during which time the purple color disappeared, giving a clear amber solution. Most of the tetrahydrofuran was removed by distillation; the residue was hydrolyzed with ice and 10% sulfuric acid, and 100 ml. of ether was added. The mixture was worked up as in the preparation of XIV above. The residue was taken up in ether from which, on slow evaporation, a pale yellow solid separated; 0.75 g. (23% yield), m.p. 204–208° dec., after sintering above 190°. An analytical sample was recrystallized from acetone, then taken up in benzene and passed through a small column of alumina; from the eluate a white microcrystalline powder was isolated, m.p. 215.5–216.0° dec. The melting point was unchanged by further recrystallization. *Anal.* Calcd. for $C_{50}H_{36}O_6$: C, 78.98; H, 6.00. Found: C, 78.54; H, 5.74.

4,4'-Bis(phenyl-1-naphthylhydroxymethyl)biphenyl (XVI). A Grignard solution was prepared from 18.6 g. (0.09 mole, 12.6 ml.) of 1-bromonaphthalene and 2.19 g. (0.09 atom) of magnesium in 100 ml. of anhydrous ether. To this was added 10.86 g. (0.03 mole) of 4,4'-dibenzoylbiphenyl, m.p. 218.0–219.5°,[38] in several portions, followed by 100 ml. of dry benzene. After 3.5 hr. of refluxing, the mixture was hydrolyzed and the organic layer washed with 10% sulfuric acid, 10% sodium carbonate solution, and water. After distillation of most of the solvent, the residue was steam-distilled until no further organic material came over. The water was decanted from the residue, which was then taken up in 500 ml. of chloroform. The solution was filtered, evaporated to 75 ml., and cooled, giving 4.08 g. of nearly white powder, m.p. 242–246° dec. A second crop, consisting of 9.56 g. of brown solid, m.p. 170–180°, was collected; this was recrystallized twice from chlorobenzene, giving 6.05 g. of white powder, m.p. 260–262° dec. An analytical sample was recrystallized from chlorobenzene, m.p. 260–262° dec.

Anal. Calcd. for $C_{46}H_{34}O_2$: C, 89.29; H, 5.54. Found: C, 89.56; H, 5.89.

8. α,ω-Bis[4-(diarylchloromethyl)phenyl]alkanes (XVIII–XXIV). *Procedure H.* The glycol was dissolved in the minimum amount of anhydrous ether or benzene, and after addition of a few ml. of acetyl chloride, dry hydrogen chloride was passed in through a diffuser tube. The precipitation of the chloride almost always began within a few minutes after the first introduction of the gas, but was not complete until several hours had elapsed. The mixture was therefore allowed to stand overnight at about 5° before collection of the chloride, which was recrystallized from benzene by addition of just enough of a saturated solution of hydrogen chloride in acetic acid to cause the start of precipitation from the hot solution.

A second method of crystallization was used for the preparation of samples for analysis and dehalogenation to the radical. A centrifuge tube containing a nearly saturated solution of the chloride was placed in a jar containing petroleum ether. The closed jar was allowed to stand at room temperature until a volume of petroleum ether equal to the original volume of benzene had distilled into the centrifuge tube. The tube was removed, and the white, crystalline precipitate collected.

Procedure I. The glycol was treated with 10 ml. of thionyl chloride and 5 ml. of dry benzene per gram of glycol; the resulting solution was refluxed overnight, and evaporated on a steam bath. To the residue was added enough benzene to redissolve it, and the solution was again evaporated. The residue was then recrystallized.

α,α,α',α'-Tetraphenyl-α,α'-dichloro-p-xylene (XVIII). A solution of 2.6 g. (0.005 mole) of VIII and 5 ml. of acetyl chloride in 50 ml. of benzene was treated according to Procedure H, giving 2.30 g. (96% yield) of white powder, m.p. 256–258° dec., after sintering above 254°. An analytical sample was recrystallized three times from benzene and acetic acid saturated with hydrogen chloride; white powder, m.p. 262–264° dec., after sintering above 258°.

Anal. Calcd. for $C_{32}H_{24}Cl_2$: C, 80.16; H, 5.06. Found: C 80.27; H 5.36.

4,4'-Bis(diphenylchloromethyl)biphenyl (XIXA). The crude glycol (IXA) prepared from 0.04 mole of 4,4'-dibenzoylbiphenyl was dissolved in about 150 ml. of ether and 10 ml. of acetyl chloride and treated according to Procedure H, giving 14.4 g. (65% yield) of nearly white powder, m.p. 212–216° dec., after sintering above 202°. An analytical sample was recrystallized from benzene and acetic acid saturated with hydrogen chloride; nearly white powder, m.p. 223–225° dec., after sintering above 218°. Tschitschibabin[11] reports the melting point as 219°, "to a turbid liquid which becomes clear at 223°."

Bis[4-(diphenylchloromethyl)phenyl]methane (XIXB). The crude glycol (IXB) prepared from 0.05 mole of IVB was dissolved in 200 ml. of ether and 10 ml. of acetyl chloride and treated according to Procedure H, giving 15.85 g. (56% yield) of light yellow powder, m.p. 163–164° dec., after sintering above 160°. Fractional crystallization from benzene and acetic acid saturated with hydrogen chloride gave 13.42 g. (47% yield) of nearly white powder, m.p. 182–184° dec., after sintering above 174°. Wittig and Leo[17] report the melting point (no recrystallization) as 157–160°.

1,2-Bis[4-(diphenylchloromethyl)phenyl]ethane (XIXC). A solution of 1.5 g. (0.00274 mole) of IXC in 25 ml. of boiling glacial acetic acid was saturated with hydrogen chloride as the solution cooled. The mixture was allowed to stand overnight, giving 1.30 g. (81%) of pale yellow powder, m.p. 186–190°. Recrystallization from benzene and acetic acid saturated with hydrogen chloride gave 1.20 g. of nearly white powder, m.p. 192–194° dec. Wittig and Leo[17] report m.p. 184–186° dec.

1,3-Bis[4-(diphenylchloromethyl)phenyl]propane (XIXD). The crude glycol (IXD) prepared from 0.0308 mole of IVD was dissolved in about 200 ml. of ether and 10 ml. of acetyl chloride and treated according to Procedure H, giving 10.78 g. (59% yield) of pale yellow powder, m.p. 154–156° dec., after sintering above 150°. An analytical sample was recrystallized three times from benzene and acetic acid saturated with hydrogen chloride; nearly white powder, m.p. 154–156° dec., after sintering above 150°.

Anal. Calcd. for $C_{41}H_{34}Cl_2$: C, 82.40; H, 5.73. Found: C, 81.63; H, 5.66.

1,4-Bis[4'-(diphenylchloromethyl)phenyl]butane (XIXE). A

(37) The high-melting white solid obtained from the first (benzene) eluate was recrystallized twice from benzene, giving white leaflets, m.p. 276–278°. Unlike the glycols of this series, this compound gave no coloration with concentrated sulfuric acid. *Anal.* Found: C, 81.68; H, 6.15. This is consistent with the empirical formula $C_{36}H_{34}O_4$, whose calculated percentage composition is: C, 81.48; H, 6.46; the most probable structure then, is the reduction product of the glycol, α,α,α',α'-tetra-*p*-anisyl-*p*-xylene.

(38) W. Schlenk and M. Brauns, ref. 16, reported m.p. 216° and a yield of 60% in the Friedel-Crafts reaction of benzoyl chloride on biphenyl. Their yield could be achieved only by doubling the amounts of benzoyl chloride and aluminum chloride, and increasing reaction time to 12 hr.

solution of 4.45 g. (0.00775 mole) of IXE in about 50 ml. of ether and 3 ml. of acetyl chloride was treated according to Procedure H, giving 4.07 g. (86% yield) of pale yellow powder, m.p. 165–166° dec., after sintering above 161°. Wittig and Leo[18] report m.p. 159–161°.

α,α,α',α'-Tetra-p-xenyl-α,α'-dichloro-p-xylene (XX). To a solution of 1.26 g. (0.00169 mole) of X in 75 ml. of boiling benzene was added 5 ml. of acetyl chloride. Dry hydrogen chloride was passed into the solution for 0.5 hr. as it cooled. The hot solution became bright purple immediately on contact with the gas. The color became lighter on cooling, and a white precipitate formed: 0.95 g. (72% yield), m.p. 281–284° dec.; the sample started to discolor above 260° and to sinter above 270°. Wittig and Köhne[36] report 265–266° dec., with no carbon and hydrogen analysis. An analytical sample was recrystallized from xylene; white platelets, with no change in melting behavior. *Anal.* Calcd. for $C_{56}H_{40}Cl_2$: C, 85.81; H, 5.14. Found: C, 85.72; H, 5.07.

4,4'-Bis(di-p-xenylchloromethyl)biphenyl (XXI). The glycol IXA (0.5 g., 0.000607 mole), was treated according to Procedure I, giving 0.33 g. (63% yield) of pale purple powder, m.p. 278–280° dec., after sintering above 272°. The filtrate from this material was colorless, and on standing several hours gave a second crop, 0.05 g. of white powder, m.p. 254–256° dec., after sintering above 252°. Schlenk[16] reports the m.p. as "about 271°."

α,α,α',α'-Tetra-p-tolyl-α,α'-dichloro-p-xylene (XXII). The crude glycol (XII) from 2.43 g. of dimethyl terephthalate was dissolved in 50 ml. of benzene and 5 ml. of acetyl chloride, and treated according to Procedure H, giving a green solution from which 2.83 g. of nearly white needles separated. The filtrate was distilled down to about 20 ml. and resaturated with hydrogen chloride, giving a second crop; 0.31 g., nearly white needles, m.p. above 300°. Yield: 47%, based on dimethyl terephthalate. *Anal.* Calcd. for $C_{36}H_{32}Cl_2$: C, 80.74; H, 6.02. Found: C, 80.37; H, 6.11.

4,4'-Bis(phenyl-1-naphthylchloromethyl)biphenyl (XXIII). A suspension of 0.6 g. (0.0097 mole) of the glycol XVI in 25 ml. of chloroform was treated with 5 ml. of acetyl chloride; dry hydrogen chloride was then passed in for 3 hr., giving a clear deep blue solution. This was evaporated on a steam bath, leaving 0.5 g. of pale blue solid, m.p. 187–192°, after sintering above 175°. The solid was dissolved in 15 ml. of benzene and, after evaporation to 5 ml., 3 ml. of acetic acid saturated with hydrogen chloride was added to the hot benzene solution. From the resulting hot, purple-blue solution a white solid separated. On cooling, the color disappeared completely from the supernatant solution. The solid was filtered off: 0.36 g. (46%), m.p. 256–258° dec.

Anal. Calcd. for $C_{58}H_{44}Cl_2$: C, 85.80; H, 5.46; Cl, 8.73. Found: C, 85.41; H, 5.26; Cl, 8.70.

4,4'-Bis(diphenylchloromethyl)diphenyl ether (XXIV). A Grignard solution from 8.4 g. (0.08 mole, 5.5 ml.) of bromobenzene and 1.75 g. (0.08 atom) of magnesium, in 50 ml. of tetrahydrofuran, was added to a suspension of 7.56 g. (0.02 mole) of 4,4'-dibenzoyldiphenyl ether[39] in 25 ml. of tetrahydrofuran. The mixture was refluxed for 2 hr. and hydrolyzed with ice and 10% sulfuric acid. Ether was added and the organic layer was separated, washed with water, 10% sodium bicarbonate, and water. It was then dried over magnesium sulfate and concentrated on the steam bath to 9.65 g. (95%) of viscous, pale yellow oil (XVII), which was taken up in about 25 ml. of anhydrous ether. The resulting solution was saturated with anhydrous hydrogen chloride after addition of a few ml. of acetyl chloride. The white precipitate which formed was filtered off and washed twice with cold ether. The product became pale yellow on drying; yield 9.3 g. (82% based on ketone), m.p. 169–171° dec., after sintering above 162°. Recrystallization from benzene and acetic acid saturated with hydrogen chloride afforded 4.8 g. (42%) of pale yellow powder, m.p. 173–175° dec., after sintering above 172°. Dilthey[39] reports 165° after "decomposition" at 120°, and a yield of "about 75%."

9. α,ω-Bis[4-(diarylmethyl)phenyl]alkanes (XXVII–XXXII). The free radical solutions were prepared in the vacuum system shown in Figure 1(Top). Figure 1(Bottom) shows in detail the reaction vessel proper. Before each run, the reaction vessel and the flask A were cleaned thoroughly with a mixture of nitric and sulfuric acids. They were then rinsed several times with distilled water, dilute ammonia, and again with distilled water, dried in a vacuum oven at 150°, and cooled in a desiccator.

From a weighing funnel, 2×10^{-5} mole of the appropriate dihalide was poured into the reaction vessel; then 4×10^{-4} atom of "molecular" silver[9] was added. The constriction E was freed of solid particles by means of a pipe cleaner and the vessel was sealed onto the vacuum manifold. After the manifold had been swept out with nitrogen, 2 ml. of specially purified benzene was placed in flask A and frozen in liquid nitrogen. The entire apparatus was evacuated to less than 10^{-5} mm., stopcock B was closed, and the benzene distilled into the U-trap C. The system was then reevacuated and, with stopcock B again closed, the benzene was allowed to melt. Dry nitrogen (containing less than 25 ppm. of oxygen) was then admitted slowly through a bypass to a pressure slightly above atmospheric. The process of freezing and evacuation was repeated and the benzene was distilled into the reaction vessel D. Stopcock B was then opened, and the reaction vessel was sealed off the line at the constriction E.

The benzene was allowed to melt, and the vessel was shaken in the dark for a few minutes, then inverted, allowing the solution to filter into the thin-walled tip. After a measurement of the resonance absorption, the solution was returned to the compartment containing the silver, for continued shaking. After completion of the dehalogenation (see Section 10) the filtered solutions were stored in the dark, and removed only for the duration of the measurements. Some observations on the free radicals are summarized in Table V.

10. Determination of extent of dehalogenation. Accurately weighed samples of about 10^{-3} mole of each of several of the dihalides were converted to the corresponding radicals by means of a tenfold excess of "molecular" silver in 10 ml.

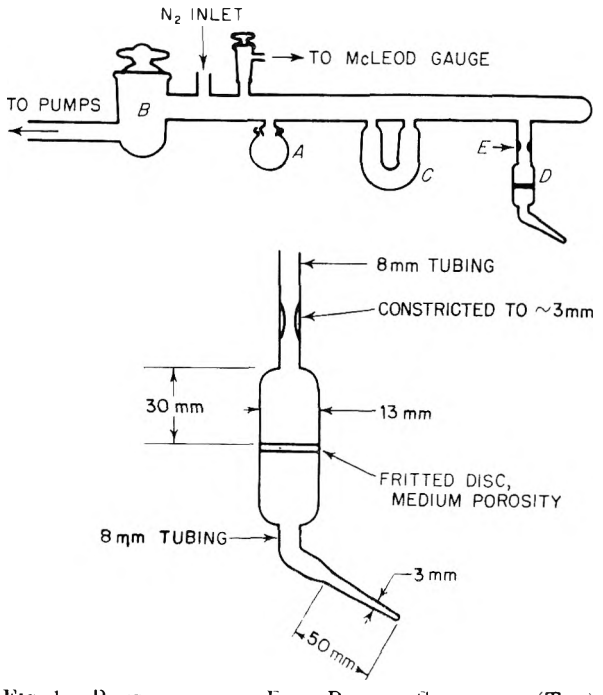


FIG. 1. PREPARATION OF FREE RADICAL SOLUTIONS. (TOP) VACUUM LINE ASSEMBLY. (BOTTOM) REACTION CELL

(39) W. Dilthey, E. Bach, H. Grütering, and E. Hansdörfer, *J. Prakt. Chem.*, [2], 117, 337 (1927).

TABLE V

OBSERVATIONS ON FREE RADICAL SOLUTIONS

Starting Material	Product	Initial Color	Color of Degraded Solution	Color after Exposure to Air	Paramagnetic Resonance Absorption Intensity[a]
XVIII	XXVII	Orange	Orange	Orange	–
XIXA	XXIXA	Deep purple	Deep purple	Colorless	+
XIXB	XXIXB	Bright red	Pale yellow	Colorless	++
XIXC	XXIXC	Wine red[b]	Pale blue	Colorless	++
XIXD	XXIXD	Yellow	Pale yellow	Pale yellow	++
XIXE	XXIXE	Yellow	Pale yellow	Pale yellow	++
XX	XXVIII	Brick red	Brick red	Brick red	+[c]
XXI	XXX	Royal blue	Royal blue	Colorless	+
XXIII	XXXI	Deep purple	Deep purple	Colorless	+
XXIV	XXXII	Yellow	Pale yellow	Pale yellow	++
ϕ_3CCl[d]	$\phi_3C\cdot$	Yellow	Colorless	Colorless	+

[a] *Cf.* ref. 3. [b] Green in thin layers. [c] Weak resonance, possibly due to partial dehalogenation to monoradical. [d] *Cf.* ref. 30.

of benzene. The preparations were carried out in the same manner as for the resonance experiments, in vessels 100 mm. long by 25 mm. in diameter. The end of the vessel containing the silver was scratched with a file, and a rubber tube through which pure nitrogen was flowing was slipped over the scratched tube. The tip of the tube was then broken off, whereupon the nitrogen pressure caused the radical solution to pass through the fritted disc. The thin-walled tip of the other end of the reaction vessel was the broken, and the radical solution forced out by the nitrogen stream. The silver was then washed with several 10 ml. portions of 6*N* ammonia. The aqueous ammoniacal washings were made slightly acid with dilute nitric acid, and 5 ml. of 0.1*N* silver nitrate was added. The silver chloride suspension was digested, cooled, and filtered. The weights of the samples used, durations of the dehalogenations, weights of silver chloride recovered, and percentages of the organic chlorine to which these weights correspond are assembled in Table VI.

TABLE VI

EXTENT OF DEHALOGENATION

Compound	Sample, Wt.	Shaking, Hr.	Silver Chloride, Wt.	Chlorine Recovered, %
XIXA	0.5593 g.	2	0.2669 g.	92.5
XIXC	0.5810	1.5	0.2546	89.2
XIXE	0.6221	2	0.2887	99.0
XXIV	0.5714	2	0.2416	84.0

11. Miscellaneous. 4,4'-Dicarbo-n-butoxybiphenyl (XXXIV). A mixture of 9.66 g. (0.04 mole) of IIIA, 200 ml. of *n*-butyl alcohol, and 10 ml. of methanesulfonic acid was refluxed for 2 days in a flask equipped with a Barrett moisture test receiver. The mixture was stripped on a steam bath at aspirator pressure; the residue was then taken up in ether, the solution was washed with 10% sodium carbonate and with water, and dried over calcium chloride. The ether was distilled off, and the residue was distilled at 1 mm. in a sausage flask, giving a pale yellow oil. This was crystallized from acetone by cooling the solution in dry ice and filtering quickly, giving 6.2 g. (44% yield) of pale yellow plates, m.p. 42.5–43.0°. An analytical sample was recrystallized five times from acetone; white plates, m.p. 47.7–48.0°. *Anal.* Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.40. Found: C, 74.34; H, 7.30.

α,α,α',α'-Tetraphenyl-α,α'-diethoxy-p-xylene (XXV). To 1.94 g. (0.01 mole) of dimethyl terephthalate was added 35 ml. of 1.3*N* phenylmagnesium bromide solution. The mixture was allowed to stand for several hours, with occasional swirling, then hydrolyzed with ice and 10% sulfuric acid. The layers were separated; the ethereal solution was washed with 10% sulfuric acid, 10% sodium carbonate, and water. The resulting solution was dried over sodium sulfate and evaporated on a steam bath. The residue was taken up in 95% ethanol, and the solution treated with Norit. A solid separated from the filtrate; this did not dissolve on prolonged refluxing with as much as 200 ml. of ethanol. The mixture was then cooled, and the solid recrystallized five times from ethyl acetate; white powder, m.p. 208–209°.

Anal. Calcd. for $C_{36}H_{34}O_2$: C, 86.71; H, 6.87. Found: C, 86.20; H, 7.11.

α,α,α',α'-Tetra-p-anisyl-α,α'-dimethoxy-p-xylene (XXVI). Dry hydrogen chloride was passed into a water-white solution of 0.45 g. (0.000853 mole) of XIV in 15 ml. of dry benzene. The solution became pink on first contact with the gas, then darkened until it was deep maroon. From it, a lustrous green solid separated. The solid was collected; on standing in air it became gray, but the green color returned in an atmosphere of hydrogen chloride. The green solid was then dissolved in 50 ml. of warm methanol, giving a clear red solution. On addition of one ml. of pyridine, the red color was instantly discharged, and a white precipitate formed. The mixture was refluxed for 0.5 hr., cooled, and filtered, giving 0.37 g. (70% yield), m.p. 175–176° dec. An analytical sample was recrystallized twice from benzene and petroleum ether; light orange powder, m.p. 175–176° dec.

Anal. Calcd. for $C_{38}H_{38}O_6$: C, 77.27; H, 6.48. Found: C, 77.02; H, 6.42.

Purification of tetrahydrofuran. Commercial tetrahydrofuran was distilled from sodium and mineral oil. Storage of this product over sodium always resulted in formation of dense, colored precipitates, and did not prevent formation of peroxides. A dry, peroxide-free product is obtained by distillation from phenylmagnesium bromide. It is convenient to prepare about 0.1 mole of the latter in 100 ml. of tetrahydrofuran, in a flask equipped with a take-off head, and then fill the flask with freshly distilled tetrahydrofuran.

Purification of benzene. Two liters of reagent grade benzene was stirred vigorously with 200 ml. of reagent grade concentrated sulfuric acid for 24 hr. The process was repeated until the acid no longer became yellow (4 times). The benzene was then stirred for 24 hr. with 200 ml. of 1% potassium permanganate solution, washed with water, 5% sodium bicarbonate, and water. It was dried over calcium chloride, distilled from sodium, and stored over sodium ribbon.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Orientation in the Nitration of ω-Styryltrimethylammonium Picrate[1]

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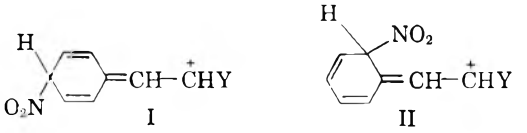
The preparation and characterization of ω-styryltrimethylammonium picrate is described. This compound is nitrated almost exclusively in the *ortho* and *para* positions with about 2% of the *meta* isomer being formed.

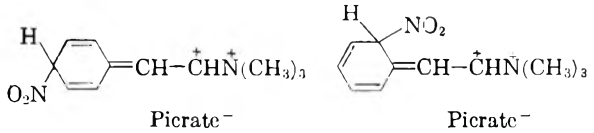
A number of ω-substituted styrenes have been nitrated, and in all instances, *ortho-para* orientation has been observed.[3,4,5] Nitration of ω-nitrostyrene[3] or of ω-styrenesulfonyl chloride,[6] for example, yields less than 2% of the *meta* isomer.

Bordwell and Rohde[6] concluded from competitive nitration experiments that cinnamic acid and ω-styrenesulfonyl chloride are less reactive than benene and compare to chlorobenzene in reactivity. One explanation[5,6] for the observed *ortho-para* orientation by the deactivating and negatively-substituted vinyl group is that the transition state is stabilized because of contributions from resonance forms such as I and II. Analogous forms for the attack at the *meta* position are not possible. The corresponding resonance forms for ω-styryltrimethylammonium picrate are:



I II

Y = —NO_2, —SO_2—, CO_2H, —C(=O)—



Picrate⁻ Picrate⁻

On the assumption that resonance forms involving adjacent like charges are often unimportant[7,8] it was hoped that this idea on orientation could be tested by nitrating ω-styryltrimethylammonium picrate (VI), and determining the quantity of *meta* isomer formed.[9] It should be noted that resonance forms I and II, also, would have adjacent like charges. However, in the case of the ammonium compound this would be more pronounced. Formation of an appreciable amount of *meta* isomer should indicate that the contribution of the side chain to the stabilization of the transition state is decreased by the violation of the adjacent charge rule.

ω-Styryltrimethylammonium picrate (VI) was prepared in 35% yield by the following sequence of reactions:

$$C_6H_5CHOHCH_2Br + N(CH_3)_3 \longrightarrow C_6H_5CHOHCH_2\overset{+}{N}(CH_3)_3\,\overset{-}{Br}$$

III IV

$$IV + 48\%\ HBr \longrightarrow C_6H_5CH{=}CH\overset{+}{N}(CH_3)_3\,\overset{-}{Br}$$

V

$$V + \overset{+}{Na}\ picrate \longrightarrow C_6H_5CH{=}CHN^{+}(CH_3)_3\ picrate^{-}$$

VI

The preparation of β-hydroxy-β-phenylethyltrimethylammonium bromide (IV) required the use of a sealed tube since the reaction was very slow at the reflux temperature of trimethylamine. The dehydration with 48% hydrobromic acid produced ω-styryltrimethylammonium bromide (V) in good yield, but also caused some cleavage to trimethylamine hydrobromide. A simple metathesis of V with sodium picrate produced VI quantitatively.

Compound V was characterized as ω-styryltrimethylammonium bromide on the basis of three facts. First, it was synthesized from a known compound, β-hydroxy-β-phenylethyl bromide through a known intermediate, β-hydroxy-β-phenylethyltrimethylammonium bromide.[9] Second, although all the hydrogenation catalysts investigated caused some hydrogenolysis, and a pure reduction product could not be obtained, the impure reduction product (m.p. 218.5–220.50°) gave a mixed melting point of 228–230° with β-phenylethyltrimethylammonium bromide (VII, m.p. 237°). Third, the infrared spectrum has absorption maxima at 13.25 μ and at 14.5 μ, which also occur in the spectra of styrene, α-methylstyrene, and β-methylstyrene.[10] Also, a band,

(1) Taken from Mr. Simms' Ph. D. Thesis, Purdue University, 1956.

(2) Dow Chemical Co. Fellow, 1954–1955.

(3) J. W. Baker and I. W. Wilson, *J. Chem. Soc.*, 842 (1927).

(4) H. W. Underwood and E. L. Kuchmann, *J. Am. Chem. Soc.*, 48, 254 (1926).

(5) L. N. Ferguson, *J. Chem. Ed.* 32, 42 (1955); this paper also gives reference to a number of papers pertaining to transition state resonance.

(6) F. G. Bordwell and K. Rohde, *J. Am. Chem. Soc.* 70, 1191 (1948); see also F. G. Bordwell and H. Stange, *J. Am. Chem. Soc.*, 77, 5941 (1955).

(7) L. Pauling, *The Nature of the Chemical Bond*, p. 199, Cornell University Press, Ithaca, New York, 1948.

(8) W. G. Wheland, *Advanced Organic Chemistry*, p. 424, John Wiley and Sons, Inc., New York, N. Y., 1950.

(9) H. J. Nienburg and G. Klein, Ger. Patent 633,983; *Chem. Abstr.*, 31, 7012 (1937).

(10) American Petroleum Institute, Research Project No. 44; Spectra 170, 329, 330, respectively.

which occurs at 10.40 μ, is probably indicative of *trans* olefinic hydrogens.[11]

The isomer distribution in the nitration of ω-styryltrimethylammonium picrate (VI) was determined by oxidizing the mixture of crude nitro picrates to a mixture of nitrobenzoic acids with potassium permanganate and then determining the nitrobenzoic acids by the method of Flurscheim and Holmes.[12] The assumption was made that unequal loss (because of destructive oxidation) of the isomeric nitro ω-styryltrimethylammonium picrates and the nitrobenzoic acids did not occur to an appreciable extent. This had been shown experimentally in determining the isomer distribution for the nitration of benzyltrimethylammonium picrate[13] and of β-phenylethyltrimethylammonium picrate.[14] It has also been shown that none of the three nitrobenzoic acids is selectively oxidized by alkaline potassium permanganate.[12] Analysis of mixtures of nitrobenzoic acids with known compositions showed that the presence of 2% of *m*-nitrobenzoic acid could be determined within ±0.5%.

The nitration of ω-styryltrimethylammonium picrate with concentrated nitric acid proceeded rapidly at 0°. The temperature was held below 5° during the addition of the picrate to the nitric acid and the solution was then allowed to warm to room temperature and stand for a few minutes. The yield of the nitro product varied between 75% and 96%. Some loss of the *ortho* isomer may have occurred during the isolation of the mixture of nitro-ω-styrltrimethylammonium picrates. The low *ortho* value shown in Table 1, analysis B, is probably due to this factor. The oxidation of the nitration product with alkaline potassium permanganate proceeded cleanly and rapidly.

The results from three nitrations of ω-styryltrimethylammonium picrate are tabulated in Table I. The percentage of *meta* isomer is consistently small and corresponds to 1.8 ± 0.5% of the starting ω-styryltrimethylammonium picrate.

It can be concluded from the above results that the $-CH{=}CH\overset{+}{N}(CH_3)_3$ grouping orientates *ortho-para* in much the same way as does the side chain in cinnamic acid, ω-nitrostyrene, and ω-styrenesulfonyl chloride. Hence, the increased positive charge adjacent to the β-carbon of the vinyl group, in this work as compared to the above, does not seem to alter the orientation appreciably. A possible explanation may be that the positive charge of the quaternary nitrogen is dissipated by the negatively charged picrate anion. In any case the adjacent charge rule is not an important factor in this reaction.

TABLE I

ISOMER DISTRIBUTION IN NITRATION OF ω-STYRYLTRIMETHYLAMMONIUM PICRATE

Experiment	*o*, %	*m*,[a] %	*p*,[a] %	*o*/*p* Ratio	Reagent	Temperature
A	12.8	1.6	64.1	0.2	HNO_3, 1.5 sp. gr.	3.5° during addition, 5–25° for 0.5 hr.
B	6.6	1.2	53.0	0.1	HNO_3, 1.5	0–3° during addition, 0–25° for 1 hr.
C	23.8	2.3	48.0	0.5	HNO_3, 1.5 sp. gr.	0–5° during addition, 5° for 0.5 hr.

[a] Determined by oxidizing the nitro picrates to a mixture of nitrobenzoic acids and analyzing the acid mixture. The values are based on the starting picrate, and are not normalized to 100% because of the wide variation in the *ortho* percentages.

EXPERIMENTAL[15]

β-Hydroxy-β-phenylethyl bromide (III). This compound, b.p. 102–104° (2 mm.), was prepared from styrene in 72% yield by method of Read and Reid.[16]

β-Hydroxy-β-phenylethyltrimethylammonium bromide (IV). Trimethyl (60 ml., 0.677 mole) was charged into a cooled Carius tube containing 25 g. (0.13 mole) of β-hydroxy-β-phenylethyl bromide; the tube was sealed, and then heated at 95° for 98 hr. The white solid product was washed from the tube with methanol. Most of the methanol was evaporated and the product, wt. 25.3 g. (77%) m.p. 200–210°, was precipitated by the addition of ethyl ether. It was recrystallized from methanol: (1) wt. 17.4 g. m.p. 225–226; (2) wt. 3.0 g., m.p. 213–216° (lit.[9] m.p. 228°).

Anal. Calcd. for $C_{11}H_{18}NOBr$: Br, 30.72. Found: Br, 30.60.

Similar results were obtained when the reaction mixture was allowed to stand at room temperature for 19 days.

ω-Styryltrimethylammonium bromide (V). β-Hydroxy-β-phenylethyltrimethylammonium bromide (15 g.) was dissolved in 100 ml. of 47% hydrobromic acid; the solution was refluxed for 45 min., and then allowed to stand at room temperature for 5 hr. The hydrobromic acid was stripped off at reduced pressure and the light pink solid residue was dissolved in hot methanol. Addition of a mixture of acetone and ether to the concentrated solution, and subsequent cooling yielded 12.6 g. (90%) of white solid, m.p. 173–178°. Two recrystallizations from 1-propanol yielded 7.0 g. of pure white crystals, m.p. 190–191°. This material decolorized dilute potassium permanganate immediately. It also decolorized bromine water (yielding a sticky yellow precipitate).

Anal. Calcd. for $C_{11}H_{16}NBr$: C, 54.65; H, 6.62; N, 5.79; Br, 32.95. Found: C, 54.38; H, 6.82; N, 5.84; Br, 32.89.

The infrared spectrum was determined, using the Nujol mull method, with the Perkin-Elmer model 21 double-beam spectrophotometer. The absorption peaks and their intensities are: 3.45 (s), 6.80 (s), 7.15 (w), 7.50 (v.w.), 8.20 (w), 9.30 (v.w.), 10.05 (m), 10.40 (s), 10.85 (m), 11.80 (w), 12.95 (m), 13.25 (s), 14.30 μ (s). The peak at 10.40 may indicate a *trans* arrangement of hydrogens at the double bond.

(11) F. A. Miller, in H. Gilman, *Organic Chemistry*, Vol. III, Chap. 2, p. 144, John Wiley and Sons, Inc., New York, N. Y., 1953.

(12) B. Flurscheim and E. L. Holmes, *J. Chem. Soc.*, **133**, 451 (1928). For a recent application of this method see: (b) W. Davey and J. R. Gwilt, *J. Soc. Chem. Ind.*, **69**, 330 (1950).

(13) F. R. Gross, C. K. Ingold, *et al.*, *J. Chem. Soc.*, 2440 (1926).

(14) C. K. Ingold, *et al.*, *J. Chem. Soc.*, 257 (1927).

(15) All melting points are uncorrected.

(16) J. Read and W. G. Reid, *J. Chem. Soc.*, 1489 (1928).

The ultraviolet spectrum of ω-styryltrimethylammonium bromide was determined on the Cary recording spectrophotometer, model 10-11M. The curve was very simple, with a single absorption maximum at 247 mμ, ϵ_{max} 15,350

Reduction of ω-styryltrimethylammonium bromide. The olefin (2.00 g.) was dissolved in 120 ml. of absolute ethanol and shaken with hydrogen at 39 p.s.i. in a Parr hydrogenator with 1 g. of 5% palladium chloride on charcoal[17] for 14 hr. at room temperature. The residue obtained by evaporating the solution under an air jet was recrystallized from 1-propanol to yield 1.14 g. of product, m.p. 184–200°. This material did not decolorize potassium permanganate and was evidently a mixture of trimethylamine hydrobromide and β-phenylethyltrimethylammonium bromide. It was purified by treating a water solution with silver oxide, filtering, and then acidifying the filtrate with hydrobromic acid. The residue obtained by evaporation of the solution weighed 0.54 g. (m.p. 218–220°), after one recrystallization from a mixture of 1-propanol and acetone. Two more recrystallizations raised the melting point to 224–226°.

This compound was also prepared using as catalyst: 10% palladium on charcoal.

β-Phenylethyltrimethylammonium bromide (VII). To 20 ml. of trimethylamine in a Carius tube cooled in a dry ice bath was added 12.3 g. of β-phenylethyl bromide[18] and the tube was sealed. After standing at room temperature for 5 days the tube appeared to contain only white solid. It was cooled, opened, and the product washed out with methanol. The mixture was concentrated and acetone was added in order to precipitate the product as a white crystalline solid, wt. 9.3 g. (m.p. 235–237°). A sample for analysis, after recrystallization from 1-propanol, melted at 237.5–238.0° (lit.[19] 220°). Chloroplatinate, m.p. 249–250° (lit.[20] 250°); picrate m.p. 130–131° (lit.[21] 131°).

Anal. Calcd. for $C_{11}H_{18}NBr$: B, 32.74. Found: Br, 32.62.

Analysis of the mixture formed by nitrating ω-styryltrimethylammonium picrate. The method of Flurscheim and Holmes[12] was used to determine the composition of the mixture of nitrobenzoic acids formed by oxidizing the crude nitration production with alkaline potassium permanganate. The *ortho* and *meta* acids are readily soluble in dilute alcohol (50% by volume), whereas *p*-nitrobenzoic acid has been found to be only 0.16% (w/v) soluble at 20°.[12b] The *para* isomer can therefore be separated and weighed as such. An empirically-determined correction of 0.2 g./100 ml. of solvent must be added to the weight found.[22] The soluble acids are then reduced with titanous chloride under strongly acidic conditions, and the mixture brominated with a slight excess of bromine water. The *o*- and *p*-aminobenzoic acids (the *para* acid was produced from the portion of the *p*-nitrobenzoic acid that dissolved in the extracting solvent) were simultaneously brominated and decarboxylated to yield 2,4,6-tribromoaniline. *m*-Aminobenzoic acid yields 2,4,6-tribromo-3-aminobenzoic acid. The two products are extracted from the aqueous mixture with ether and then separated by washing the ether with potassium bicarbonate solution. After correcting for the solubility of the *p*-nitrobenzoic acid, the amount of 2,4,6-tribromoaniline obtained is proportional to the *o*-nitrobenzoic acid in the original mixture. Similarly, the amount of 2,4,6-tribromo-3-aminobenzoic acid is proportional to the *m*-nitrobenzoic acid originally present.

The analytical method was checked with mixtures made from purified *o*-, *m*-, and *p*-nitrobenzoic acids (Eastman Organic Chemicals). The *p*-nitrobenzoic acid (m.p. 239.5–240°) was recrystallized twice from 95% ethanol and the *meta* (m.p. 141–142°) and *ortho* isomers (m.p. 146.5–147°) were recrystallized twice from 1% hydrochloric acid. The mixtures were analyzed as such or were heated for a few minutes with dilute alkaline potassium permanganate. The precipitate of manganese dioxide was filtered off, and the nitrobenzoic acid mixture recovered by ether extraction of the acidified solution. This preliminary treatment duplicated the potassium permanganate oxidation step in the nitration product analysis.

Table II shows the results of such a check and shows that this method can be used to determine small amounts of *m*-nitrobenzoic acid in the presence of much higher percentages of the *ortho* and *para* isomers.

TABLE II

ANALYSIS OF SYNTHETIC MIXTURE OF NITROBENZOIC ACIDS

Isomer	Starting Weight, G.	Starting Weight, %	Weight Found, G.	Recovery, %	% of Recovered	Total Starting Weight
o	0.810	33.3	0.830	102.5	34.5	34.1
m	0.0797	3.20	0.070	88.4	2.93	2.89
p	1.5482	63.5	1.5005	97.3	62.6	61.7
						98.7

Nitration of ω-styryltrimethylammonium picrate. In three nitrations of ω-styryltrimethylammonium picrate the above analytical method gave *meta* values which were fairly constant (1.8 ± 0.5% based on starting picrate), although the *o/p* ratio varied considerably from nitration to nitration. The following typical nitration is given in detail.

A. ω-Styryltrimethylammonium picrate (m.p. 183–184°, wt. 5.825 g.) was added to 50 ml. (sp. gr. 1.5) of nitric acid cooled in an ice bath. The temperature was maintained at 3–5° by the rate of addition of the picrate. After the light yellow solution was removed from the ice bath the temperature rose to 25° over a period of 0.5 hr. It was allowed to stand at 25° for 10 min. and was then poured into cracked ice. The picric acid that precipitated went back into solution as the mixture was neutralized with concentrated sodium hydroxide. After a slight excess of base had been added a yellow solid formed. The mixture was cooled, filtered, and after drying the product in a vacuum dessicator over phosphorous pentoxide, it weighed 5.14 g., and had m.p. 150–159° (1). Concentration of the filtrate under an air jet and extraction with 400 ml. of ethyl acetate in two portions yielded 0.615 g. of yellow solid, m.p. 135–155° (2). The water layer was evaporated to dryness, and the pulverized residue of salts extracted with ethyl acetate. Evaporation of the extract yielded 0.454 g. of brown solid, m.p. 120–125° (3).

Anal. Calcd. for $C_{17}H_{17}N_5O_9$: C, 46.90; H, 3.94. Found: (1) C, 46.79; H, 3.91; (2 and 3) C, 40.07; H, 2.63.

Fractions 1, 2, and 3 were combined and mixed with 200 ml. of 1*N* sodium hydroxide. The mixture was heated on the steam plate and an excess of 5% potassium permanganate (700 ml.) was slowly added until the color persisted. The residual permanganate was destroyed by the addition of sodium bisulfite and the precipitated manganese dioxide filtered off. After the filtrate had been acidified with dilute sulfuric acid, it was concentrated to 100 ml., cooled, and extracted with three 200 ml. portions of ethyl ether. The dried extract yielded 2.44 g. (96%) of mixed nitrobenzoic acids. This mixture was pulverized, placed in a tared Gouch crucible, and extracted as in the analytical example with 69 ml. of dilute (50% by volume) ethanol. The weight of the *p*-nitrobenzoic acid, after drying at 80° for 3 hr. and after correcting for solubility, was found to be 1.636 g., m.p. 237–240° (lit.[23] 238°).

(17) R. Monzingo, *Org. Syntheses*, **Coll. Vol. III**, 686 (1955).

(18) A. W. Dox, *J. Am. Chem. Soc.* 2844 (1924).

(19) V. Braun, *Ann.*, **382**, 45 (1911).

(20) H. Decker, P. Becker, *Ber.*, **45**, 2404 (1912).

(21) J. Reilly and P. J. Drumm, *J. Chem. Soc.*, 871 (1935).

(22) G. M. Bennett, *Analyst*, **73**, 191 (1948).

(23) S. M. McElvain, *Org. Syntheses*, **Coll. Vol. I**, 385 (1941).

TABLE III

ISOMER DISTRIBUTION IN NITRATION OF ω-STYRYLTRIMETHYLAMMONIUM PICRATE AS DETERMINED BY OXIDATION TO NITROBENZOIC ACIDS

Exp.	Isomer	Wt. Acid Found, G.	Based on Mixed Acids from $KMnO_4$ Oxidation, %	Based on Starting Picrate, %
A	*o*	0.328	13.50	12.80
	m	0.0432	1.78	1.64
	p	1.6367	67.20	64.10
			82.48	78.54
	o/p ratio 0.201			
B	*o*	0.139	9.15	6.60
	m	0.0254	1.66	1.20
	p	1.1139	73.50	53.00
			84.31	60.80
	o/p ratio 0.125			
C	*o*	0.528	27.90	23.80
	m	0.051	2.70	2.30
	p	1.063	56.40	48.00
			87.00	74.10
	o/p ratio 0.495			

The filtrate was reduced as usual and then brominated with 275 ml. of bromine water. 2,4,6-Tribromoaniline, wt. 0.9111 g., m.p. 114–118° (lit.[24] 120°), representing 0.328 g. of *o*-nitrobenzoic acid, and 2,4,5-tribromo-4-aminobenzoic acid, wt. 0.0966 g., m.p. 164–167° (lit.[25] 169°), representing 0.0432 g. of *m*-nitrobenzoic acid were recovered as indicated earlier. The results of this experiment are summarized in Table III, A.

B. The picrate (4.9340 g., m.p. 183–184°) was added over a period of 15 min. to 50 ml. of nitric acid (sp. gr. 1.5) cooled in an ice bath. The light yellow solution was then removed from the bath and allowed to stand for 1 hr. The usual workup yielded 4.133 g. (75%, m.p. 145–155°) of the mono nitration product.

Anal. Calcd. for $C_{17}H_{17}N_5O_9$: C, 46.90; H, 3.94. Found: C, 46.36; H, 3.88.

The filtrate was evaporated to dryness and the residue of salts extracted with ethyl acetate. The black tarry material recovered from the extract was discarded.

Oxidation as directed in experiment A yielded 1.521 g. of mixed acids. Analysis of this mixture gave the results shown in Table III, B.

C. The picrate (5.168 g.) was added to 50 ml. of nitric acid (sp. gr. 1.5) cooled in an ice bath. The yellow solution was allowed to stand at 5° for 30 min. The usual workup yielded (1) 5.26 g. (m.p. 138–160°, 90% yield) of yellow solid. Extraction of the concentrated filtrate with ethyl acetate offered (2) 0.303 g. (m.p. 130–160°) of brown solid.

Anal. Calcd. for $C_{17}H_{17}N_5O_9$: C, 46.90; H, 3.94; N, 16.09. Found: (1) C, 41.60; H, 4.40; N, 16.31. (2) C, 34.25; H, 3.27; N, 15.78.

Although both fractions were very impure, they were combined and oxidized as usual to yield 1.891 g. (89%) of mixed acids. Analysis of this mixture gave the results shown in Table III, C.

LAFAYETTE, IND.

(24) F. Asinger, *J. Prakt. Chem.*, **142**, 299 (1935).

(25) J. J. Sudborough, L. L. Lloyd, *J. Chem. Soc.*, **75**, 589 (1899).

[CONTRIBUTION FROM THE FULMER CHEMICAL LABORATORY, THE STATE COLLEGE OF WASHINGTON]

Alkylation of α-Enol-γ-butyrolactones Derived from Condensations of Ketones with Diethyl Oxalacetate[1]

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Alkylations of α-enol-γ-butyrolactones, derived from condensations of diethyl oxalacetate with cyclohexanone and acetone, respectively, are described. *p*-Nitrobenzyl chloride and 1-chloromethylnaphthalene are employed as alkylating agents with the sodium salts of the α-enol-γ-lactones dissolved in dimethylformamide. The structure of the resulting alkylation products has been shown to be that of an enol ether (II), as based on evidence relating to alkaline and acidic decomposition reactions and infrared absorption spectra.

The formation of *ketone-derived* α-enol-γ-butyrolactones has been reported recently from this laboratory.[3] In continuation of the investigation of these substances, the authors desired to study some alkylation reactions and the nature of the products derived therefrom. Schinz and Hinder[4] had observed methylation of an aldehyde-derived α-enol-γ-lactone either by reaction of the lactone with diazomethane or by reaction of the sodium salt of the lactone with methyl iodide in absolute ethanol. The structure was inferred to be that of an enol ether from the ultraviolet absorption spectrum and from its apparent nonidentity with a

(1) Presented in part before the Division of Organic Chemistry at the 121st Meeting of the AMERICAN CHEMICAL SOCIETY, Buffalo, N. Y., March 24, 1952, and in part before a Northwest Regional Meeting of the AMERICAN CHEMICAL SOCIETY, Eugene, Ore., June 10, 1955.

(2) Abstracted in part from theses submitted by James Wm. Cleary and Melvin J. Gortatowski in partial fulfillment of the requirements for the degrees of Doctor of Philosophy and Master of Science, respectively, the State College of Washington, February 1956 and June 1952.

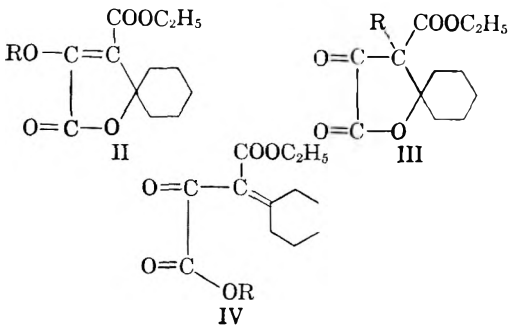
(3) G. W. Stacy, J. W. Cleary, and M. J. Gortatowski, *J. Am. Chem. Soc.*, **79**, 1451 (1957).

(4) H. Schinz and M. Hinder, *Helv. Chim. Acta*, **30**, 1349 (1947).

C-alkylation product (no direct comparison with this substance was made, however).

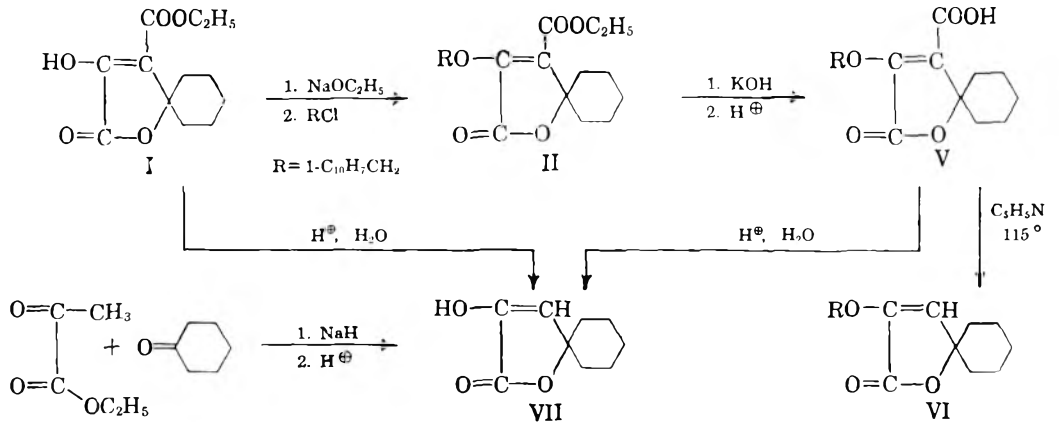
In an initial attempt to prepare an alkylation product, the sodium salt of the authors' cyclohexanone-derived α-enol-γ-lactone I[3] was heated under reflux in absolute ethanol with *p*-nitrobenzyl chloride in accord with the procedure described by Schinz and Hinder.[4] Under these conditions, it was not possible to obtain an alkylation product. However, when the same reactants were heated in dimethylformamide,[5] an excellent yield of an alkylation product was obtained. In like manner, the corresponding acetone-derived α-enol-γ-lactone[6] and an aldehyde-derived (isovaleraldehyde) α-enol-γ-lactone[7] were alkylated by *p*-nitrobenzyl chloride; the yield for the latter substance was not as good as those for the two ketone-derived α-enol-γ-lactones. As the presence of a nitro group was deemed disadvantageous in connection with some of the structure studies contemplated, the corresponding 1-naphthylmethyl derivative (II, R = 1-$C_{10}H_7CH_2$) was prepared in a similar manner by the reaction of I with 1-chloromethylnaphthalene. In later preparative runs, it was found that the crude sodium salt of I could be used just as well as the purified salt in obtaining the 1-naphthylmethyl derivative.

In respect to the structure of these alkylation products, it appeared desirable to consider several possibilities. In addition to the enol ether structure II, other logical possibilities were the *C*-alkylation structure III and the enoic ester structure IV.



C-Alkylation products, of course, are encountered frequently in the alkylation of β-keto esters.[8] The enoic ester structure IV would correspond to the type of product obtained in the Stobbe condensation.[9] Stecher and Clements have studied similar structures, which were β-bromobenzylidenepyruvic esters.[10]

In the structure proof of the authors' alkylation products, an initial observation, which argued against structures III and IV, was the lack of reactivity of the alkylation product with 2,4-dinitrophenylhydrazine. The next point of evidence involved the reaction of the alkylation product with alkali.



It has been observed that the α-enol-γ-lactone I, on being heated in alkaline solution, undergoes lactone ring opening followed by a reverse aldol condensation to yield cyclohexanone.[3] It might be anticipated that alkaline treatment of a structure such as III would result in a similar decomposition, while a structure such as IV would undergo a dual saponification with removal of both 1-naphthylmethyl and ethyl groups; on the other hand, structure II would be expected to undergo merely saponification of the carbethoxy group. By appropriate alkaline treatment of the alkylation product, therefore, it appeared that a choice among structures II–IV might be made. Accordingly, the alkylation product was heated with 20% potassium hydroxide solution, and an acid V was obtained. The acid V was decarboxylated by heating in pyridine to give a product VI, which did not react with ferric chloride solution or 2,4-dinitrophenylhydrazine.

(5) (a) J. C. Sheehan and W. A. Bolhofer, *J. Am. Chem. Soc.*, 72, 2786 (1950); (b) H. L. Rice and G. R. Pettit, *J. Am. Chem. Soc.*, 76, 302 (1954); (c) F. J. Marshall and W. N. Cannon, *J. Org. Chem.*, 21, 245 (1956).

(6) Minimal studies were carried out on the acetone-derived α-enol-γ-lactone because of the limited amount of this substance that was available (ref. 3).

(7) G. W. Stacy and G. D. Wagner, *J. Am. Chem. Soc.*, 74, 909 (1952).

(8) P. Karrer, *Organic Chemistry*, 4th English ed., Elsevier Publishing Company, Inc., New York, N. Y., 1950, p. 269.

(9) W. S. Johnson and G. H. Daub, *Org. Reactions*, VI, 1 (1951).

(10) E. D. Stecher and A. Clements, *J. Am. Chem. Soc.*, 76, 503 (1954).

These facts together with the infrared absorption spectra of these compounds strongly support an enol ether structure for II, V, and VI. Although the normal absorption for a γ-lactone carbonyl is about 1770 cm.$^{-1}$, it would be lowered by conjugation with the enol ether C=C.[11] This proved to be the case, for a strong absorption band was to be found at 1740–1750 cm.$^{-1}$. The conjugated double bond of the γ-lactone ring also was borne out in respect to the carbethoxy group of II and the carboxyl group of V. The carbonyl frequencies for these groups again were lowered in agreement with the fact that the carbonyl groups are part of a conjugated system. Davison and Bates[12] reported a doubling of the absorption for the C=C stretching frequency at about 1610 cm.$^{-1}$ and 1635 cm.$^{-1}$ for a number of vinyl ethers. For the authors' enol ethers, similar absorptions were observed at about 1600 cm.$^{-1}$ and 1640–1650 cm.$^{-1}$, respectively. Finally, a strong absorption band corresponding to the carbon-oxygen single bond stretching frequency of an enol ether was found at about 1190–1215 cm.$^{-1}$.

Although decarboxylation of the acid V had been accomplished in low yield by heating in pyridine, it occurred more readily when V was heated in aqueous acid. At the same time hydrolytic removal of the 1-naphthylmethyl group occurred, so that the product was the α-enol-γ-lactone VII. The hydrolytic removal of the 1-naphthylmethyl group constituted further evidence for the enol ether structure of V and, therefore, of the alkylation product II because the facile acid hydrolysis of vinyl and enol ethers is, of course, well known.[13]

The α-enol-γ-lactone VII gave a blood-red color with ferric chloride solution and failed to react with 2,4-dinitrophenylhydrazine. The infrared absorption spectrum of VII was found to be similar to those of the α-enol-β-carbethoxy-γ-lactones previously reported,[3] except for the absorption band corresponding to the conjugated β-carbethoxy group, which, of course, was missing in the present case. The α-enol-γ-lactone VII also was converted to a *p*-nitrobenzoate (enol ester), and again the infrared absorption spectrum of this derivative was in good agreement with the assigned structure.[3] Further, VII could be prepared by an alternate and more direct approach. Preparation of α-enol-γ-lactones similar to VII has been accomplished by condensation of aldehydes with pyruvic acid under alkaline conditions.[4] When such a procedure was applied in the present case, however, formation of VII was not observed. On the other hand, condensation of ethyl pyruvate with cyclohexanone in the presence of sodium hydride did succeed. This constitutes a new example of the Stobbe-type condensation.[9] The product obtained in this manner was proved to be identical with that produced from V by a mixed melting point determination and by identity of the infrared absorption spectra.

It had been noted by Schinz and Hinder that aldehyde-derived α-enol-β-carbethoxy-γ-lactones suffered loss of the carbethoxy group when heated under acidic conditions.[4] Excellent yields were obtained by heating with aqueous acids in the presence of a trace of hydroquinone over a period of several hours. Particularly since V could be readily converted to VII, it seemed that our cyclohexanone-derived α-enol-β-carbethoxy-γ-lactone I could also be converted to VII in parallel with the results reported[4] for the aldehyde-derived products. This was realized, but only after the heating period was extended to 15 hr. and a larger quantity of hydroquinone was used. When a 2-hr. period was employed, only starting material was isolated from the reaction mixture. When long heating periods were employed, but only a trace of hydroquinone was added to the reaction mixture, only very small amounts of the product VII were obtained.

EXPERIMENTAL[14]

Alkylation of α-enol-γ-butyrolactones. Ethyl β-(1-hydroxycyclohexyl)-α-(1-naphtylmethoxy)fumarate γ-lactone (II). To 50 ml. of absolute ethanol was added 1.73 g. (0.075 gram atom) of sodium; 18.0 g. (0.075 mole) of I was dissolved in 50 ml. of hot absolute ethanol and added slowly with swirling to the sodium ethoxide solution. A white precipitate formed immediately, and the mixture was heated under reflux for 0.5 hr., after which the ethanol was removed by evaporation under reduced pressure leaving the sodium salt of I. To this was added 100 ml. of dry dimethylformamide, and the mixture was heated at 90° to expel any remaining ethanol and to effect the complete solution of the sodium salt. 1-Chloromethylnaphthalene, 13.2 g. (0.075 mole), was added to the mixture, which then was heated on a steam bath for 4.5 hr. During the course of the reaction the solution turned red and sodium chloride precipitated. The mixture was poured slowly with stirring and cooling into 300 ml. of water, and the resulting mixture was allowed to stand in an ice bath overnight. The precipitate was collected by filtration and dried to yield 24.9 g. (87%) of crude II, m.p. 104–107°. Recrystallization from dilute ethanol accompanied by treatment with Norit gave 18.1 g. (63% yield) of fine, colorless needles, m.p. 117.5–118.5°. Further purification for preparation of an analytical sample was accomplished by sublimation, m.p. 119–120°.

Anal. Calcd. for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.35; H, 6.51.

The sodium salt of I, as obtained directly from the reaction mixture involving the condensation of cyclohexanone with sodium diethyl oxalacetate,[3] could be used in the preparation of alkylation products. In this way, 1.31 g. (5.0 mmoles) of the sodium salt of I and 0.88 g. (5.0 mmoles) of 1-chloromethylnaphthalene in dimethylformamide re-

(11) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley and Sons, Inc., New York, N.Y., 1956, pp. 171–6.

(12) W. H. T. Davison and G. R. Bates, *J. Chem. Soc.*, 2607 (1953).

(13) A. W. Johnson, *et al.*, in E. H. Rodd, ed., *Chemistry of Carbon Compounds*, Vol. I (A), Elsevier Publishing Company, Inc., New York, N.Y., 1951, p. 324.

(14) All melting points are corrected, and boiling points are uncorrected. The microanalytical work was performed by Galbraith Laboratories, Knoxville, Tenn. For details on determination of the infrared absorption spectra see ref. 3.

acted to form 0.88 g. (46% yield) of II, m.p. 118.5–119.5°.

The infrared absorption spectrum of II showed bands that were assignable to conjugated γ-lactone (1750 cm.$^{-1}$, s), conjugated ester (1690 cm.$^{-1}$, s), C=C (1640 cm.$^{-1}$, m; 1598 cm.$^{-1}$, w), and enol ether (1190 cm.$^{-1}$, s).

Ethyl β-(1-hydroxycyclohexyl)-α-(p-nitrobenzoxy)fumarate γ-lactone. The procedure for this and following alkylations was essentially the same as that described for II above. From reaction of 1.55 g. (5.9 mmoles) of the sodium salt of I and 0.51 g. (3.0 mmoles) of *p*-nitrobenzyl chloride in 50 ml. of dimethylformamide was obtained 0.94 g. (84% yield) of the crude alkylation product, m.p. 128.0–128.5°. Recrystallization from 95% ethanol afforded colorless, flat plates, m.p. 131–132°.

Anal. Calcd. for $C_{19}H_{21}NO_7$: C, 60.79; H, 5.63; N, 3.73. Found: C, 60.79; H, 5.66; N, 3.78.

The infrared absorption spectrum of this alkylation product showed bands that were assignable to conjugated γ-lactone (1757 cm.$^{-1}$, s), conjugated ester (1708 cm.$^{-1}$, s), C=C (1650 cm.$^{-1}$, m; 1600 cm.$^{-1}$, w), and enol ether (1193 cm.$^{-1}$, s).

Ethyl β-(2-hydroxyisopropyl)-α-(p-nitrobenzoxy)fumarate γ-lactone. From 0.50 g. (2.5 mmoles) of the α-enol-γ-lactone,[3] from which the sodium salt was prepared by reaction with 0.059 g. of sodium, and 0.43 g. (2.5 mmoles) of *p*-nitrobenzyl chloride in 10 ml. of dimethylformamide, there was obtained 0.59 g. (71% yield) of light yellow crystals, m.p. 108–110°. This was recrystallized from benzene-ligroin with charcoal treatment to yield 0.37 g. (45%) of alkylation product as colorless crystals, m.p. 113–114.5°.

Anal. Calcd. for $C_{16}H_{17}NO_7$: C, 57.31; H, 5.11; N, 4.18. Found: C, 57.56; H, 5.03; N, 4.23.

The infrared absorption spectrum showed bands that were assignable to conjugated γ-lactone (1755 cm.$^{-1}$, s), conjugated ester (1690 cm.$^{-1}$, s), C=C (1647 cm.$^{-1}$, m; 1600 cm.$^{-1}$, m), and enol ether (1212 cm.$^{-1}$, s).

Ethyl β-(1-hydroxyisoamyl)-α-(p-nitrobenzoxy)fumarate γ-lactone. From reaction of 1.48 g. (5.9 mmoles) of the sodium salt of the α-enol-γ-lactone[7] and 0.51 g. (2.9 mmoles) of *p*-nitrobenzyl chloride in 50 ml. of dimethylformamide was obtained 0.32 g. (36% yield) of an alkylation product, m.p. 95–96°. An analytical sample was prepared by repeated recrystallization from 95% ethanol, m.p. 97–98°.

Anal. Calcd. for $C_{18}H_{21}NO_7$: C, 59.49; H, 5.82; N, 3.85. Found: C, 59.39; H, 5.87; N, 3.68.

STRUCTURE PROOF

β-(1-Hydroxycyclohexyl)-α-(1-naphthylmethoxy)fumaric acid γ-lactone (V). A mixture of 0.28 g. (0.75 mmole) of II and 10 ml. of 20% potassium hydroxide solution was heated under reflux for 2.5 hr. With cooling the resulting reaction mixture was acidified slowly with concentrated hydrochloric acid. To insure complete precipitation, the acidified mixture was allowed to stand for 8 hr. in an ice bath, after which the precipitate was collected by filtration to yield 0.24 g. (91%). Recrystallization from dilute ethanol accompanied by Norit treatment gave 0.17 g. (64% yield) of a colorless, microcrystalline product, m.p. 149° (dec.).

Anal. Calcd. for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.77; H, 5.79.

The infrared absorption spectrum revealed bands that were assignable to conjugated γ-lactone (1752 cm.$^{-1}$, s), conjugated carboxyl group (1672 cm.$^{-1}$, s), C=C (1640 cm.$^{-1}$, w; 1598 cm.$^{-1}$, w), and enol ether (1188 cm.$^{-1}$, s).

β-(1-Hydroxycyclohexyl)-α-(1-naphthylmethoxy)acrylic acid γ-lactone (VI). In a decarboxylation procedure quite similar to a number that have been reported,[15] 5.63 g. (0.016 mole) of V (with a trace of hydroquinone) in 50 ml. of anhydrous pyridine was heated under reflux for 0.5 hr. The pyridine was removed by distillation under reduced pressure leaving a viscous, brown residue, which then was stirred for 0.5 hr. with 20 ml. of 3*N* hydrochloric acid. The supernatant acid was removed, and the residue was taken up in ether, which then was washed with 5% sodium hydroxide solution and saturated sodium chloride solution, respectively. (The sodium hydroxide extract was later acidified to give 1.35 g of the starting material V.) The ether was removed leaving 2.54 g. of a brown, semisolid residue. This was crystallized from ethanol to yield 0.52 g. (10%) of coarse, round crystals, m.p. 114–116°. A sample for analysis was recrystallized several times from dilute ethanol to give fine, colorless platelets, m.p. 119–120°.

Anal. Calcd. for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.80; H, 6.32.

The infrared absorption spectrum showed bands that were assignable to conjugated γ-lactone (1742 cm.$^{-1}$, s), C=C (1638 cm.$^{-1}$, m; 1599 cm.$^{-1}$, w), and enol ether (1181 cm.$^{-1}$, s).

α-Hydroxy-β-(1-hydroxycyclohexyl)acrylic acid γ-lactone (VII). *A. By heating the acid* V *under acidic conditions.* A mixture of 2.18 g. (6.2 mmoles) of V, 50 ml. of ethanol, and 35 ml. of 20% sulfuric acid, to which a trace of hydroquinone had been added, was heated under reflux for 5.5 hr. This was poured into 300 ml. of ice water and allowed to stand overnight; a small amount of heavy, red oil separated and was discarded. The aqueous phase was extracted with portions of ether until the extracts were colorless. The ether was evaporated to give 0.90 g. of a viscous, brown residue which contained a few crystals. This was taken up in hot benzene and filtered; the benzene was removed leaving 0.85 g. of a glassy solid. This crude product was extracted with hot, olefin-free ligroin, and the extract was filtered and allowed to stand at room temperature for a day. The resulting precipitate was collected by filtration to yield 0.36 g. (34%) of colorless crystals, which melted partially at 118–120° and completely at 127°. A sample of this was recrystallized several times from a mixture of benzene and ligroin to give pure VII, m.p. 134.4–135.0°.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.07; H, 7.24.

The infrared absorption spectrum revealed bands that were assignable to enolic hydroxyl (3150 cm.$^{-1}$, s), conjugated γ-lactone (1730 cm.$^{-1}$, s), and C=C (1640 cm.$^{-1}$, m; 1610 cm.$^{-1}$, w).

B. By condensation of cyclohexanone with ethyl pyruvate. A 200-ml three-necked flask, equipped with a reflux condenser and stirrer, was flushed with a stream of dry nitrogen. A mixture of 3.60 g. (0.15 mole) of sodium hydride in 25 ml. of benzene was placed in the flask, and with stirring a mixture of 17.4 g. (0.15 mole) of ethyl pyruvate[16] and 4.91 g. (0.05 mole) of cyclohexanone was added in portions of 0.5 ml. at intervals of about 1 min. After the addition of several milliliters of this mixture, 0.5 ml. of absolute ethanol was added. The exothermic reaction which ensued was moderated by cooling the flask in a pan of cold water, which was removed near the end of the addition. When the addition had been completed, another 25-ml. quantity of anhydrous benzene was added, and the stirring was continued. The mixture soon soldified and had to be broken into small lumps. After a total of 2 hr. of stirring, 15 ml. of concentrated hydrochloric acid in 60 ml. of water was added slowly. The mixture was extracted with ether, and the combined ether extracts in turn were extracted with 5% sodium bicarbonate solution and washed with saturated sodium sulfate solution. After removal of the ether, an orange semisolid weighing 4.28 g. (51% yield) was obtained. Recrystallization accompanied by Norit treatment afforded 1.16 g. (14% yield) of VII as colorless crystals, m.p. 135.5–136.5°.

C. By heating the ester I under acidic conditions. A mixture of 2.40 g. (0.01 mole) of I, 5 ml. of water, 20 ml. of glacial acetic acid, and 20 ml. of concentrated hydrochloric acid, to

(15) H. R. Snyder and E. L. Eliel, *J. Am. Chem. Soc.*, 71, 663 (1949).

(16) C. L. Stevens and A. E. Sherr, *J. Org. Chem.*, 17, 1228 (1952).

which 0.10 g. of hydroquinone had been added, was heated under reflux for 15 hr. The reaction mixture was poured into 100 ml. of water and allowed to stand overnight. The precipitate was separated by filtration, washed with several portions of hot water, and discarded. The filtrate and washings were extracted with ether, and the ether was in turn extracted with 5% sodium bicarbonate solution. Removal of the ether resulted in a residue of 1.23 g. (65% yield) of crude product VII. Recrystallization from benzene accompanied by charcoal treatment yielded 0.34 g. (20%) of colorless crystals, m.p. 136–137°.

The identity of VII, as obtained by these three different methods, was established by the identity of the infrared spectra and mixed melting point determinations.

When I was treated under acidic conditions for short periods of time, only starting material was obtained from the reaction mixture. A sample of 1.00 g. (4.2 mmoles) of I with a trace of hydroquinone was dissolved in a mixture of 10 ml. of glacial acetic acid 2 ml. of concentrated hydrochloric acid, and 5 ml. of water. The solution was heated under reflux for 1.5 hr. and then was cooled in an ice bath. There was obtained 0.65 g. (65%) of I (Identity with the starting material was established by a mixed melting point determination). None of the expected product VII could be isolated from the reaction mixture.

Longer heating (12 hr.) in the absence of hydroquinone resulted in intractable reaction mixtures from which only traces of product and no starting material could be isolated. The necessity of having hydroquinone present to prevent resinification of some of the substances involved was clearly demonstrated.

p-Nitrobenzoate of VII. In a procedure similar to those previously described,[3] 1.00 g. (5.4 mmoles) of *p*-nitrobenzoyl chloride and 0.42 g. (2.5 mmoles) of VII in 10 ml. of pyridine reacted to yield 0.90 g. of crude enol ester. Recrystallization from a benzene-ligroin mixture accompanied by charcoal treatment gave 0.39 g. (39% yield). An analytical sample was prepared by recrystallizing twice from benzene to give clear, colorless platelets, m.p. 174–176°.

Anal. Calcd. for $C_{16}H_{15}NO_6$: C, 60.57; H, 4.77; N, 4.41. Found: C, 60.60; H, 4.98; N, 4.46.

The infrared absorption spectrum revealed bands that were assignable to enol ester (1760 cm.$^{-1}$, s), conjugated γ-lactone (1737 cm.$^{-1}$, s), and C=C (1646 cm.$^{-1}$, m; 1607 cm.$^{-1}$, m).

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PULLMAN, WASH.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF RHODE ISLAND]

Hunsdiecker Reaction of Silver Salts of *Cis*- and *Trans*-1,2-Cyclohexanedicarboxylic Acid[1]

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The Hunsdiecker reaction was carried out on the silver salts of *cis*- and *trans*-1,2-cyclohexanedicarboxylic acid. The same product, *trans*-1,2-dibromocyclohexane, was obtained from both salts. The isomerization appears to take place at an intermediate stage in the reaction. The mechanistic implications are discussed briefly.

The Hunsdiecker reaction, by which metal salts of carboxylic acids, usually the silver salts, are decarboxylated to the organic halide by the action of halogen, has attracted considerable attention in the past few years both as a method of synthesis of halogen compounds and mechanistically.[2] The present study was initiated from the former point of view in connection with a study of routes to the synthesis of alicyclic vicinal dihalides. The synthesis of the *cis* isomers of 1,2-dihalocycloalkanes was the principal interest, and accordingly it was decided to determine whether the Hunsdiecker reaction was capable of yielding *cis* dibromides from *cis* dicarboxylic acids.

The problem of isomerization was immediately apparent. A review of the literature disclosed that isomerization is not uncommon in the Hunsdiecker reaction. It was obvious from an examination of the literature that racemization of optically active compounds is to be expected when the carboxylic acid salt group is attached to the asymmetric carbon.[3] Little or no optical activity is preserved in the alkyl halides resulting from Hunsdiecker reactions of this type. However, the work in this laboratory was to be undertaken using geometrical isomers rather than optical isomers, the materials chosen being the silver salts of *cis*- and *trans*-1,2-cyclohexanedicarboxylic acid. It was not so evident from the literature that isomerization would take

(1) This work was performed under Contract No. DA-19-020-ORD-3171, OOR Project 1037, of the Office of Ordnance Research, U. S. Army. Support for this work is gratefully acknowledged.

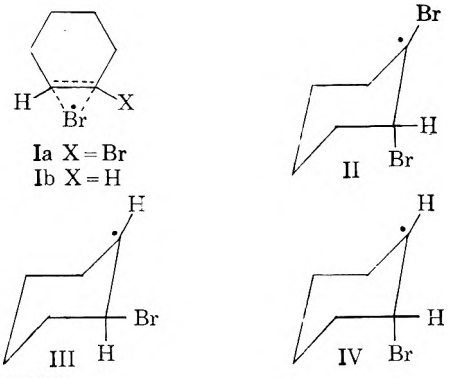
(2) For an extensive review see: R. G. Johnson and R. K. Ingham, *Chem. Revs.*, 56, 219 (1956).

(3) (a) C. L. Arcus, A. Campbell, and J. Kenyon, *J. Chem. Soc.*, 1510 (1939). (b) R. T. Arnold and R. Morgan, *J. Am. Chem. Soc.*, 70, 4248 (1948). (c) J. Cason, M. J. Kalm, and R. H. Mills, *J. Org. Chem.*, 18, 1670 (1953). (d) Heintzeler, *Ann.*, 569, 102 (1950). (e) R. G. Johnson and R. K. Ingham, Ref. (2), cite also: C. E. Berr, Doctoral Dissertation, University of California, Los Angeles (1952).

place with geometric isomers. Prelog and Zalan[4] obtained an optically active bromide by the bromine decarboxylation of the silver salt of *cis*-1,2-diethyl-4-cyclohexanecarboxylic acid, but the configuration at carbon atom number four was not investigated in either starting acid or subsequent bromide.

Similarly Hunsdiecker, Hunsdiecker, and Vogt[5] prepared ethyl 1-bromo-2-cyclohexanecarboxylate from the silver salt of the monoethyl ester of 1,2-cyclohexanedicarboxylic acid, but apparently without establishing configurations. A more careful examination of the steric nature of some Hunsdiecker reaction products was made in a study by Price and Berman[6] on the bromine decarboxylation of both the *cis* and *trans* isomers of silver cinnamate. Both isomers produced *trans*-β-bromostyrene. Wieland and Fischer[7] actually decarboxylated the silver salts of both *cis*- and *trans*-1,2-cyclohexanedicarboxylic acid using iodine, but failed to recover anything except small amounts of the starting acids.

It thus appeared likely, but not certain, that both the *cis* and *trans* isomers of silver 1,2-cyclohexanedicarboxylate would yield the more stable *trans*-dibromide. It was of interest to compare the latter reaction to a reaction involving a rather similar free radical intermediate: the addition of hydrogen bromide to 1-bromocyclohexene under the influence of ultraviolet light. It has already been established that this reaction produces almost exclusively *cis*-1,2-dibromocyclohexane.[8] The presumed free radical intermediates in the two reactions are not the same, but have interesting points of similarity. The intermediate in the hydrogen bromide reaction has been described as either a bridged free radical of structure Ia[8], or of conformation II.[9]



If the bridged free radical, Ia, is the intermediate, then the approach of the hydrogen atom donor must be from the side opposite the bromine bridge and *cis*-1,2-dibromocyclohexane is produced. If the more classical structure, II, is the intermediate, then the approach of the hydrogen bromide to give up its hydrogen atom is to be expected from the side opposite the axial bromine to yield, again, *cis*-dibromide. The latter explanation assumes that II is either a preferred conformation of the intermediate free radical or that isomerization to the alternate conformation with equatorial halogen is much slower than attack by hydrogen bromide. In either case the product, *cis*-1,2-dibromocyclohexane, is the result of the geometry or conformation of the intermediate free radical. In the case of the Hunsdiecker reaction the intermediate after one silver carboxylate group has been converted to bromide would presumably have structure Ib, III, or IV. *Trans*-1,2-dibromocyclohexane would result from the reaction of Ib with bromine. Probably a mixture of *cis* and *trans* isomeric dibromides would be produced from III since both sides of the ring at the free radical carbon are about equally accessible. Finally, the *trans* isomer would arise from IV, the bromine molecule being less hindered in its approach to the ring from the side away from the axial bromine.

In order to test the hypothesis on the stereochemistry of the Hunsdiecker reaction as outlined in the preceeding paragraph, both the *cis* and *trans* isomers of the silver salts of 1,2-cyclohexanedicarboxylic acid were treated with bromine under anhydrous conditions in carbon tetrachloride. Two different temperatures were employed to determine effect on yield and to find the most satisfactory reaction time. The temperatures chosen were room temperature or below and reflux temperature. The reactions at reflux temperature were very fast whereas the reactions run at room temperature were very slow, but the yields were independent of temperature. In all reactions the only saturated dibromide obtained was *trans*-1,2-dibromocyclohexane. The *trans* configuration was established by comparison of the infrared spectrum with the spectra of known *cis*- and *trans*-dibromides. While the spectra of the two isomers are quite similar, there are sufficient differences to detect any appreciable contamination of one isomer with the other. (The *cis* isomer has a moderately strong absorption band at 7.75 μ which is absent in the *trans* isomer.) No evidence of the *cis*-1,2-dibromocyclohexane was found in any of the decarboxylations.

The observation that anhydrous silver bromide and bromine in carbon tetrachloride can cause isomerization of initial products[10] was also considered, inasmuch as it might be possible that *cis*-dibromide had been formed which was then re-

(4) V. Prelog and E. Zalán, *Helv. Chim. Acta* **27**, 535 (1944).

(5) C. Hunsdiecker, H. Hundsdiecker, and E. Vogt, German Patent 730,410 [*Chem. Abstr.*, **38**, 374 (1944)].

(6) C. C. Price and J. D. Berman, Unpublished work. Cited by Johnson and Ingham, ref. (2).

(7) H. Wieland and F. G. Fischer, *Ann.*, **446**, 49 (1926).

(8) H. L. Goering, P. I. Abell, and B. F. Aycock, *J. Am. Chem. Soc.*, **74**, 3588 (1952).

(9) H. L. Goering and L. L. Sims, *J. Am. Chem. Soc.*, **77**, 3465 (1955).

(10) D. C. Abbott and C. L. Arcus, *J. Chem. Soc.*, 3195 (1952).

arranged to the more stable *trans* isomer. Neither *cis*- nor *trans*-1,2-dibromocyclohexane was altered in configuration by such isomerization conditions, even after much more prolonged treatment than the Hunsdiecker reactions received. Also, addition of *cis*-1,2-dibromocyclohexane to a typical Hunsdiecker reaction of the *cis*-dicarboxylic acid gave a product containing about the expected percentage of *cis*-dibromide. Again, the lack of isomerization was established by examination of the infrared spectra of the recovered dibromides.

Although there was no reason to suspect that isomerization had taken place in the formation of the silver salts from the acids, or that they were unstable on standing, they were checked by conversion back to the free acids. The configurations were unchanged. Likewise, the action of silver bromide and bromine in carbon tetrachloride under anhydrous conditions was without effect on configuration of the free acids.

The conclusion was reached that the isomerization of the *cis*-1,2-cyclohexanedicarboxylic acid to the *trans*-dibromide was taking place in the course of the reaction and was not a prior isomerization of the acid or a postreaction isomerization of the dibromide. As a consequence of these findings the assumption must be made that either Ib or IV represents the structure of the intermediate radical if kinetic and steric control of the reaction prevails. Structure *III* is plausible only if complete thermodynamic control of the reaction is assumed.

EXPERIMENTAL

All melting points are uncorrected.

The *cis*-1,2-cyclohexanedicarboxylic anhydride was furnished through the courtesy of the National Aniline Division of Allied Chemical and Dye Corp.

The bromine used was analytical reagent grade, dried just before use by shaking with concentrated sulfuric acid. The carbon tetrachloride was analytical reagent grade, dried and stored over phosphorus pentoxide.

cis-1,2-Cyclohexanedicarboxylic acid. Hydrolysis of *cis*-1,2-cyclohexanedicarboxylic anhydride in boiling water gave the acid, m.p. 191–194° (lit.[11] m.p. 191°).

trans-1,2-Cyclohexanedicarboxylic acid. Isomerization of *cis*-1,2-cyclohexanedicarboxylic acid in a sealed tube with a small amount of aqueous hydrochloric acid at 170–180° for 8 hours gave a 61.5% yield of *trans*-1,2-cyclohexanedicarboxylic acid after recrystallization from ethyl alcohol. M.p. 228.5–230.5° (lit.[12] m.p. 227–229°).

Silver salts of cis- and trans-1,2-cyclohexanedicarboxylic acids. The silver salts were prepared by adding an exactly equivalent quantity of aqueous silver nitrate solution to a carefully neutralized solution of the sodium salt of the acid. Filtration of the white precipitate followed by careful washing with water, alcohol, and ether gave a quantitative yield of the silver salt. Drying for several days under vacuum over phosphorus pentoxide, followed by screening to 100 mesh gave the salts in a form suitable for the reaction with bromine. The salts were white and remained white even after storage for several months in brown bottles.

Reactions of the silver salts with bromine. The method selected was the inverse addition procedure described by Conly[13] in which the dry silver salt is added to the carbon tetrachloride solution of bromine. All runs were made and worked up in exactly the same manner with the exception of the temperature at which the reaction was run. The procedure is described as follows.

All apparatus was oven-dried at 110° just before assembly A 300 ml. three necked flask was fitted with a condenser, a pressure equalized addition funnel and a bent-tube adapter which could be rotated to allow the dry silver salt to drop into the reaction flask from a small auxiliary flask. Stirring was performed by a magnetic stirrer. A heating mantle was employed for those reactions carried out a reflux temperature, while a cooling bath was provided for the reactions carried out at 0–25°. The top of the condenser was connected *via* a drying tube to a gas collecting system in order to follow the speed and extent of the reaction by observation of the carbon dioxide evolved. The small auxiliary flask was filled with 38.6 g. (0.10 mole) of the silver salt of the dicarboxylic acid and connected to the reaction flask. A slight excess of dry bromine (11.0 ml., 0.215 mole) was mixed with 200 ml. of anhydrous carbon tetrachloride and placed in the addition funnel over a layer of phosphorus pentoxide on a bed of glass wool. The bromine–carbon tetrachloride mixture was allowed to pass slowly through the drying bed into the flask. This mixture was brought to reflux or cooled to 0° depending on the conditions selected, and then the silver salt was added in small portions. At the lower temperature the reaction started slowly and proceeded very slowly for about 8 hr. as evidenced by the evolution of carbon dioxide. At reflux temperatures the reaction started immediately, was very exothermic, and proceeded as rapidly as the silver salt could be added safely, being complete in less than an hour. As soon as the carbon dioxide evolution was complete the reaction was discontinued. The silver bromide was removed by filtration and the carbon tetrachloride and excess bromine removed by distillation at atmospheric pressure through a short packed column. The residue was fractionated through a short all-glass semimicro column at water pump vacuum. Only one low boiling fraction was found. A residue remained which could not be distilled without decomposition. The distillate was washed several times with cold concentrated sulfuric acid. The acid-insoluble material was separated, treated with dry sodium carbonate, filtered, and refractionated. The products are described in Table I.

TABLE I

PRODUCTS OF THE HUNSDIECKER REACTION WITH THE SILVER SALTS OF *cis*- AND *trans*-1,2-CYCLOHEXANEDICARBOXYLIC ACIDS

Silver Salt	Temp., °C.	% Yield	M.P. °C.	n_D^{25}	I.R. Spectrum
cis	0–25	43	−4.8	1.5503	All *trans*
cis	Reflux	47	−4.7	1.5505	All *trans*
trans	0–25	48	−4.5	1.5507	All *trans*
trans	Reflux	37	−2.5	1.5510	All *trans*

Establishment of absence of isomerization. In order to establish whether isomerization of products was taking place, the known *cis*- and *trans*-1,2-dibromocyclohexanes, prepared according to previously described methods[8], were each subjected to treatment with bromine and silver bromide in anhydrous carbon tetrachloride at reflux for 12 hr. The results are presented in Table II.

That the reaction intermediates did not isomerize product was also established by carrying out a completely typical Hunsdiecker reaction on the silver salt of *cis*-1,2-cyclohexane-

(11) E. F. Jenkins and E. J. Costello, *J. Am. Chem. Soc.*, 68, 2733 (1946).

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

(13) J. C. Conly, *J. Am. Chem. Soc*, 75, 1148 (1953).

TABLE II

ATTEMPTED ISOMERIZATION OF THE ISOMERIC 1,2-DIBROMOCYCLOHEXANES WITH SILVER BROMIDE AND BROMINE

Dibromide	Before Treatment		After Treatment			
	M.p., °C.	n_D^{25}	% Recovery	M.p., °C.	n_D^{25}	I.R. spectrum
cis	10.0	1.5512	60	6.5	1.5511	All *cis*
trans	−4.5	1.5505	94	−4.5	1.5505	All *trans*

dicarboxylic acid (using reflux temperature) to which was added a sample of known *cis*-1,2-dibromocyclohexane. The product, worked up in the usual fashion, showed a melting point depression of about 30° and gave an infrared spectrum completely identical with that of a synthetic mixture made up of authentic *cis*- and *trans*-dibromides. The data could not distinguish partial isomerization from complete retention of configuration, but there could be no doubt that a very large portion of the *cis*-1,2-dibromocyclohexane survived the reaction.

cis-*1,2*-Cyclohexanedicarboxylic acid was also subjected to the treatment with bromine and silver bromide in anhydrous carbon tetrachloride at reflux for 12 hr. The acid was recovered quantitatively with no change in melting point indicating that no isomerization had taken place.

All infrared spectra were obtained using a Baird Associates recording spectrophotometer with a sodium chloride prism. The samples were run as pure liquid films.

KINGSTON, R. I.

[COMMUNICATION NO. 1875 FROM THE EASTMAN KODAK RESEARCH LABORATORIES]

Hydrogenolysis of Acylhydroquinones

J. L. R. WILLIAMS

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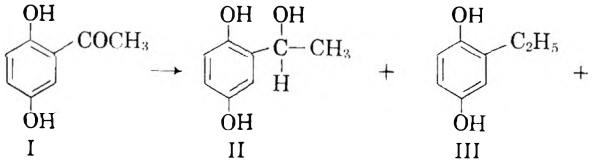
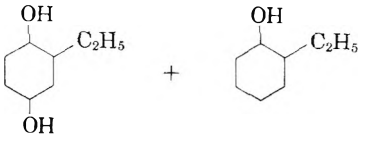
Four acylhydroquinones have been hydrogenated to the corresponding dialkylhydroquinones at 140–150° and 3000–4000 p.s.i. In the case of 2,5-dihydroxycaprylophenone, the hydrogenation either was stopped at the intermediate carbinol stage or was carried to completion, yielding *n*-octylhydroquinone, by the use of suitable operating conditions.

In an earlier work[1] when acetylhydroquinone (I) was hydrogenated using Adams' catalyst, W-6 Raney nickel, or W-7 Raney nickel catalysts at room temperature and 25–50 p.s.i., the products included 2,5-dihydroxyphenylmethylcarbinol (II), ethylhydroquinone (III), ring hydrogenated products, and possibly some of the corresponding hydrogenolysis products, such as IV and V.



I II III



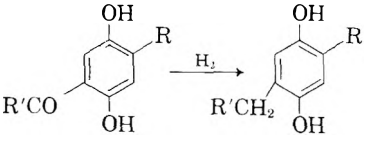
IV V

The use of copper chromite-type catalysts, such as HJS-2 and Harshaw Cu-X, with proper temperature control made possible the stepwise hydrogenation at about 2000–4000 p.s.i. of acetylhydroquinone (I) to 2,5-dihydroxyphenylmethylcarbinol (II) and ethylhydroquinone (III) in excellent yields.[2]

(1) D. D. Reynolds, J. A. Cathcart, and J. L. R. Williams, *J. Org. Chem.*, 18, 1709 (1953).

(2) J. L. R. Williams, *J. Org. Chem.*, 19, 1205 (1954).

Since the above work was completed, further examples of the hydrogenolysis reaction have been carried out, using other acylhydroquinones.



R = alkyl or H

Table I summarizes the results obtained when four acylhydroquinones underwent hydrogenolysis at 140–150° and 3000 – 4000 p.s.i.

TABLE I

HYDROGENOLYSIS OF ALKYLACYLHYDROQUINONES

Ketone	Product
2,5-Dihydroxy-4-methylacetophenone	2-Methyl-5-ethylhydroquinone
2,5-Dihydroxy-4-methylpalmitophenone	2-Methyl-5-hexadecylhydroquinone
2,5-Dihydroxy-4-*n*-octylcaprylophenone	2,5-Di-*n*-octylhydroquinone
2,5-Dihydroxycaprylophenone	*n*-Octylhydroquinone

2,5-Dihydroxycaprylophenone can also be hydrogenated under milder conditions to 2,5-dihydroxyphenylheptylcarbinol in low yield. While these hydrogenations require the use of medium-pressure equipment (2000–4000 p.s.i.), the reaction times are convenient, being of the order of 1–2.5 hours.

Others[3,4] have carried out the hydrogenolysis of acylhydroquinones using 10% palladium on charcoal at atmospheric pressure and low pressures (25–50 p.s.i.). Although the yields were good, the hydrogenolysis times were excessive, of the order of 4 to 20 hours. The advantages of the present method at 2000–4000 p.s.i. are: shorter reaction times, less noncrystallizable by-product, and complete hydrogenolysis of the ketone (less than 0.2% residual carbonyl by ultraviolet absorption analysis).

EXPERIMENTAL

Hydrogenation of 2,5-dihydroxycaprylophenone. α-(2,5-Dihydroxyphenyl)octanol-1. In a stainless-steel reactor were placed 46.7 g. (0.19 mole) of 2,5-dihydroxycaprylophenone,[5] 4 g. of copper chromite catalyst (Harshaw Cu-X-647-57-P) and sufficient ethanol to make a final volume of 150 ml. Hydrogenation at 100–106° and 3800 p.s.i. for 40 min. was carried out. Pressure drop at room temperature, 450 p.s.i.; calcd., 350 p.s.i.

The cooled reaction mixture was filtered and the ethanol evaporated under reduced pressure (water aspirator). The solid residue was recrystallized from 200 ml. of hexane and 25 ml. of ether to give 8.3 g. of α-(2,5-dihydroxyphenyl)-octanol-1, m.p., 77–78°.

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.6; H, 9.3. Found: C, 70.1; H, 9.2.

The hexane-ether mother liquors were evaporated to dryness (yield, 34 g.) and 1 g. of the residue was recrystallized from a mixture of 15 ml. of benzene and 10 ml. of hexane to give material, m.p., 81.5–82.0°.

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.6; H, 9.3. Found: C, 72.2; H, 9.0.

This is a mixture of carbinol and *n*-octylhydroquinone.

α-(2,5-Diacetoxyphenyl)octanol-1-acetate. A solution of 34 g. (0.142 mole) of the carbinol mixture, m.p. 81.5–82.0°, in 50 g. of acetic anhydride was allowed to stand at room temperature 48 hr. The volume was reduced to one-half the original, at reduced pressure and at 35°. After the addition of 50 g. of acetic anhydride, the reaction mixture was heated at 60° for 6 hr. Two hundred milliliters of benzene was added, and the whole extracted twice with water. The organic layer was separated and dried over anhydrous magnesium sulfate. Distillation gave 30.2 g. (62%) of 2,5-diacetoxyphenylheptylcarbinol acetate, b.p., 148° (0.2 mm.).

Anal. Calcd. for $C_{20}H_{28}O_6$: C, 66.6; H, 7.8; acetyl, 31.2. Found: C, 66.7; H, 7.8; acetyl, 31.3.

n-Octylhydroquinone. A mixture of 47.2 g. (0.2 mole) of 2,5-dihydroxycaprylophenone,[5] 4 g. of copper chromite catalyst (Harshaw Cu-X-649-57-P), and 110 ml. of absolute ethanol was hydrogenated at 103–115° and 3800 p.s.i. until the absorption of hydrogen ceased (40 min.). The temperature was raised to 150–160° (3380 p.s.i.) and maintained at that value for 1.25 hr. (Pressure drop at room temperature, 940 p.s.i.; calcd., 960 p.s.i.). Filtration and evaporation of the reaction mixture gave crude *n*-octylhydroquinone, m.p., 90–94°. Recrystallization from hexane gave material melting at 96–97°. Literature[3] m.p., 96.5–98°.

Hydrogenation of 2,5-dihydroxy-4-methylacetophenone. A mixture of 163 g. (0.78 mole) of toluhydroquinone diacetate and 330 g. (2.5 moles) of anhydrous aluminum chloride was divided into three portions. One portion was placed in a 1-l. beaker surrounded by an oil bath maintained at 125–130°. The reaction mixture was stirred vigorously until the reaction subsided. The second and third portions were added using the same procedure, after which time (5 min.) the reaction mixture was allowed to stand at 115–120° for 15 min. The reaction mixture was cooled, ground in a mortar, and poured into a rapidly stirred mixture of 300 ml. of concentrated hydrochloric acid and 4 l. of ice. After stirring for 1 hr., the solid was filtered and dissolved in 600 ml. of benzene. The solution was dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The residue was stirred with 150 ml. of a 7% hydrogen chloride in methanol solution for 1 hr. The resulting solution was poured into 2 l. of ice water and the solid filtered. Recrystallization from a mixture of 100 ml. of ethanol and 300 ml. of water yielded crude 2,5-dihydroxy-4-methylacetophenone, m.p., 141.5–144.0°. Recrystallization again from 2 l. of benzene yielded 50 g. (38.5%) of pure ketone, m.p. 146–147°. Evaporation of the mother liquors to 200 ml. yielded an additional 3.8 g. of ketone.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.0; H, 6.1. Found: C, 65.3; H, 6.1.

2-Ethyl-5-methylhydroquinone. A mixture of 25 g. (0.15 mole) of 2,5-dihydroxy-4-methylacetophenone, 4 g. of copper chromite catalyst (Harshaw Cu-X-649-57-P), and 130 ml. of absolute ethanol was hydrogenated at 105–115° and 3700 p.s.i., at which temperature one molar equivalent of hydrogen was absorbed. The temperature was then maintained at 140° for 1 hr. The filtered reaction mixture was evaporated to yield a white solid, m.p. 160–164°. By recrystallization from a mixture of 200 ml. of ether and 400 ml. of benzene, there was obtained 11.7 g. of 2-ethyl-5-methylhydroquinone, m.p., 170–171°. The mother liquors were treated with Norit, and evaporated to 250 ml. Cooling in ice gave an additional 5 g. of 2-ethyl-5-methylhydroquinone, m.p. 169.5–170.5°. The total yield was 16.7 g. or 70%.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.0; H, 7.9. Found: C, 70.8; H, 8.1.

Diacetate, m.p., 114–115°.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.0; H, 6.8. Found: C, 66.4; H, 6.8.

Hydrogenation of 2,5-dihydroxy-4-methylpalmitophenone. 2-Methyl-5-hexadecylhydroquinone. A mixture of 36.2 g. (0.1 mole) of 2,5-dihydroxy-4-methylpalmitophenone,[5] 4 g. of copper chromite catalyst (Harshaw Cu-X-649-57-P), and 130 ml. of absolute ethanol was treated with hydrogen at 145–155° and 3850 p.s.i. for 1.25 hr. The pressure drop at room temperature was 550 p.s.i., calcd., 480 p.s.i. A sample of the cooled material from the bomb, after drying on a porous plate for a few minutes, melted at 123–127°. The solid was dissolved in acetone and the catalyst was filtered. The acetone was evaporated, and the residue recrystallized from 250 ml. of glacial acetic acid to which there was added a small amount of zinc dust. There was obtained 29.5 g. (85%) of 2-methyl-5-hexadecylhydroquinone, m.p., 125–127°. Ten grams of the material, when recrystallized again from 100 ml. of acetic acid, gave 8 g. of pure 2-methyl-5-hexadecylhydroquinone, m.p., 126.5–127.5°. Literature[4] m.p., 127–128°.

2,5-Dihydroxy-4-n-octylcaprylophenone. A charge consisting of 15 g. (0.43 mole) of 2,5-dihydroxy-4-*n*-octylcaprylophenone,[5] 2.5 g. of copper chromite catalyst (Harshaw Cu-X-649-57-P), and absolute ethanol to give a final volume of 150 ml. was hydrogenated at 150–160° and 4200 p.s.i. during 1 hr. Pressure drop at room temperature was 260 p.s.i., calcd., 210 p.s.i.

The catalyst was removed by filtration, and the ethanol evaporated at reduced pressure to give 13.4 g. of material,

(3) A. Loria, J. R. Thirtle, and A. Weissberger (Eastman Kodak Co.), U. S. Patent 2,728,659 (Dec. 27, 1955).

(4) J. R. Thirtle, P. W. Vittum, and A. Weissberger (Eastman Kodak Co.), U. S. Patent 2,732,300 (Jan. 24, 1956).

(5) The author is indebted to R. J. Thirtle for supplying these ketones.

m.p., 104–109°. Recrystallization from 100 ml. of cyclohexane gave 11.3 g. (79%) of 2,5-di-*n*-octylhydroquinone, m.p. 109.0–109.5°. An additional recrystallization from 80 ml. of hexane gave 8 g. of pure product, m.p. 110.5–111.5°. Literature[3] m.p. 109.5–110.5°.

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[CONTRIBUTION FROM THE BALLISTIC RESEARCH LABORATORIES]

Reaction of *t*-Butyl Peroxide with Acetals

LESTER P. KUHN AND CARL WELLMAN

Received January 21, 1957

The decomposition of *t*-butyl peroxide in 1,1-diethoxybutane and in 1,1-diisopropoxybutane has been studied in the liquid phase. From the ethyl acetal the major products are ethane, *t*-butyl alcohol, acetaldehyde, ethyl butyrate, ethyl *n*-butyl ether, *n*-butyraldehyde, and 4,5-diethoxyoctane. From the isopropyl acetal the corresponding isopropyl derivatives were obtained. On the basis of the products obtained and their yields a mechanism is proposed which involves the abstraction of a hydrogen atom by a *t*-butoxy radical from a carbon atom of the acetal which is adjacent to oxygen. The new radical which is thus formed decomposes to yield an alkyl radical and a carbonyl-containing compound.

$$R_2\dot{C}OEt \longrightarrow R_2C{=}O + Et\cdot$$

The object of this work was to determine the mode of reaction between alkoxy radicals and acetals. To this end, *t*-butyl peroxide was decomposed in the acetal at 120–140° at an initial concentration of 10 mole % peroxide. On the basis of the products formed a reasonable mechanism is presented which accounts for the experimental results and which is consistent with the known reactions of alkoxy radicals.

From the decomposition of *t*-butyl peroxide in 1,1-diethoxybutane a complex mixture of products was obtained which was successfully separated and analyzed by means of gas chromatography. The results are shown in Table I. The variation in yields from run to run was about ±5%.

TABLE I

PRODUCTS FROM THE DECOMPOSITION OF *t*-BUTYL PEROXIDE IN 1,1-DIETHOXYBUTANE

Compound	Yield[a] Observed	Calcd.
Methane	0.32	0.32
Ethane	1.07	1.25
Butane	0.09	0.09
Acetaldehyde	2.86	2.86
Acetone	0.32	0.32
t-Butyl alcohol	1.7	1.61
n-Butyraldehyde	0.54	0.54
Ethyl *n*-butyl ether	0.61	0.61
Ethyl butyrate	0.92	0.90
4,5-Diethoxyoctane	0.88	0.88

[a] The yield is expressed in moles per mole of peroxide decomposed.

The following reactions satisfactorily account for the products and the observed yields:

$$(t\text{-BuO})_2 \longrightarrow 2t\text{-BuO}\cdot$$
$$1 \qquad 2$$

$$t\text{-BuO}\cdot + C_3H_7CH(OC_2H_5)_2 \longrightarrow$$
$$0.9 \qquad 0.9$$
$$t\text{-BuOH} + C_3H_7\dot{C}(OC_2H_5)_2$$
$$0.9 \qquad 0.9 \qquad \text{I}$$

$$C_3H_7\dot{C}(OC_2H_5)_2 \longrightarrow C_3H_7COOC_2H_5 + C_2H_5\cdot$$
$$0.9 \qquad 0.9 \qquad 0.9$$

$$t\text{-BuO}\cdot + C_3H_7CH(OC_2H_5)_2 \longrightarrow$$
$$0.72 \qquad 0.72$$
$$t\text{-BuOH} + C_3H_7CH(OC_2H_5)O\dot{C}HCH_3$$
$$0.72 \qquad 0.72 \qquad \text{II}$$

$$C_2H_5\cdot + C_3H_7CH(OC_2H_5)_2 \longrightarrow$$
$$1.25 \qquad 1.25$$
$$C_2H_6 + C_3H_7CH(OC_2H_5)O\dot{C}HCH_3$$
$$1.25 \qquad 1.25 \qquad \text{II}$$

$$C_3H_7CH(OC_2H_5)O\dot{C}HCH_3 \longrightarrow$$
$$2.9$$
$$CH_3CHO + C_3H_7\dot{C}H(OC_2H_5)$$
$$2.9 \qquad 2.9 \qquad \text{III}$$

$$C_3H_7CH(OC_2H_5)\cdot \longrightarrow C_3H_7CHO + C_2H_5\cdot$$
$$.54 \qquad .54 \qquad .54$$

$$C_3H_7CH(OC_2H_5)\cdot + C_3H_7CH(OC_2H_5)_2 \longrightarrow$$
$$0.61 \qquad 0.61$$
$$C_3H_7CH_2OC_2H_5 + C_3H_7CH(OC_2H_5)O\dot{C}HCH_3$$
$$0.61 \qquad 0.61$$

$$2C_3H_7CH(OC_2H_5)\cdot \longrightarrow$$
$$1.76$$
$$C_3H_7CH(OC_2H_5)CH(OC_2H_5)C_3H_7$$
$$0.88$$

$$t\text{-BuO}\cdot \longrightarrow CH_3COCH_3 + CH_3\cdot$$
$$0.32 \qquad 0.32 \qquad 0.32$$

$$CH_3\cdot + C_3H_7CH(OC_2H_5)_2 \longrightarrow$$
$$0.32 \qquad 0.32$$
$$CH_4 + C_3H_7CH(OC_2H_5)O\dot{C}HCH_3$$
$$0.32 \qquad 0.32$$

$$2C_2H_5\cdot \longrightarrow C_4H_{10}$$
$$0.18 \qquad 0.09$$

The arabic numbers under each reactant and product were so chosen that the yield of each product would be as close as possible to the yield observed and that each unstable intermediate formed in a particular step would be completely consumed in a subsequent step. The calculated yield of products

obtained in this way which are listed in Table I can be seen to check very well with the observed yield.

The only products derived from the *t*-butoxy radical are *t*-butyl alcohol, methane, and acetone which indicated that the butoxy radical reacts either by hydrogen abstraction from the acetal or by decomposition to yield methyl radical and acetone. It does not combine with another radical. The fact that acetone and methane are obtained in equivalent amounts is evidence that they are derived from the same radical. The sum of the yields of acetone and *t*-butyl alcohol 2.02 checks well with the moles of *t*-butoxy radicals, 2.0, formed from the decomposition of a mole of peroxide. The yield of acetone, 0.32 mole, is comparable to the yield of acetone, 0.39 mole, obtained by previous workers[1] from the decomposition of *t*-butyl peroxide in cumene at 125°.

The *t*-butoxy radical always abstracts a hydrogen from a carbon atom which is adjacent to oxygen. This susceptibility to transfer, of hydrogen atoms on carbon adjacent to oxygen, has also been demonstrated in reactions of radicals derived from benzoyl peroxide with alcohols and aldehydes.[2] The abstraction of a hydrogen from the aldehydic carbon yields radical I which decomposes to give an ethyl radical and ethyl butyrate. The abstraction of hydrogen from methylenic carbon gives radical II which decomposes to give acetaldehyde and radical III. Radical III reacts in three ways: (1) It can decompose to give an ethyl radical and butyraldehyde, (2) It can dimerize to give 4,5-diethoxyoctane, and (3) It can abstract a hydrogen from the solvent to yield ethyl *n*-butyl ether. The hypothesis that these various products are derived from radical II in the manner shown is substantiated by the fact that the yield of acetaldehyde is equal to the sum of yields of butyraldehyde, plus ethyl butyl ether plus twice the yield of diethoxyoctane. There are four hydrogens on methylenic carbon available for abstraction and one hydrogen on the aldehydic carbon. If these hydrogens were of equal reactivity the ratio of acetaldehyde to ethyl butyrate in the products would be 4. The fact that this ratio is actually 3.3 indicates that the hydrogen on the aldehydic carbon is slightly more reactive than the hydrogen on the methylenic carbon. Although, in the sequence of reactions shown above, the hydrogen on the aldehydic carbon is abstracted only by *t*-butoxy radicals (step 2) whereas the alkyl radicals abstract only the hydrogen on methylenic carbon (steps 5, 8, and 11), it is not our intention to imply that the relative reactivities of these hydrogen atoms is any different for reaction with alkyl than for reaction with butoxy radicals.

(1) J. H. Raley, F. F. Rust, and W. E. Vaughan, *J. Am. Chem. Soc.*, 70, 1336 (1948).

(2) A. V. Tobolsky and R. B. Mesrobian, *Organic Peroxides*, Interscience, N. Y. (1954), p. 84.

Several experiments were performed in which *t*-butyl peroxide was decomposed in butyraldehyde diisopropyl acetal. These reactions were carried out at a temperature range which was 10 to 20° higher than the reactions with the diethyl acetal, hence the results are not strictly comparable. The following products and yields were obtained: methane 0.64, propane 1.90, propylene 0.09, acetone 2.25, *t*-butyl alcohol 2.0, butyraldehyde 0.33, isopropyl *n*-butyl ether 0.36, isopropyl butyrate 0.7 and 4,5-diisopropoxyoctane 0.30. The material balance in this reaction is not as good as that obtained in the reaction with the ethyl acetal. It is evident, however, that the same sequence of reactions occurs in both cases. Replacement of the ethyl acetal by isopropyl acetal results in the formation of propane instead of ethane, acetone instead of acetaldehyde, isopropyl butyrate instead of ethyl butyrate, isopropyl butyl ether instead of ethyl butyl ether, and diisopropoxyoctane instead of diethoxyoctane.

The conclusion to be drawn from the above results is that the attack by an alkoxy or an alkyl radical upon an acetal results in the transfer of hydrogen and the production of a new radical with its odd electron on a carbon atom adjacent to oxygen. This new radical can decompose to yield an alkyl radical and a carbonyl-containing molecule. These reactions can be represented as follows:

$$X\cdot + R_2'CHOR \longrightarrow XH + R_2'\dot{C}OR \qquad (1)$$

$$R_2'\dot{C}OR \longrightarrow R_2'CO + R\cdot \qquad (2)$$

This type of radical decomposition, which does not appear to have been previously reported, yields the same products as the decomposition of the isomeric alkoxy radical:

$$R_2'R\dot{C}O \longrightarrow R_2'CO + R\cdot \qquad (3)$$

The inability of vinyl ethers to yield homopolymers of high molecular weight when the reaction is catalyzed by free radical initiators[3] has been vaguely attributed to their electron-rich double bonds and to a low degree of resonance. A more plausible reason is the occurrence of reaction 2. The free radical polymerization of vinyl ethyl ether would be propagated by the step

$$RCH_2\text{—}\dot{C}HOEt + CH_2{=}CHOEt \longrightarrow RCH_2CH(OEt)CH_2\text{—}\dot{C}HOEt$$

in which the radical intermediate has its odd electron on a carbon atom adjacent to oxygen. Since this radical can also react according to equation 2 the growth of the polymer is effectively halted.

EXPERIMENTAL

The decompositions were carried out by heating a solution of *t*-butyl peroxide (0.01 mole) in the acetal (0.1 mole) in an apparatus which consisted of a reaction flask, a 12-inch

(3) C. E. Schildknecht, *Vinyl and Related Polymers*, John Wiley and Sons, N. Y., 1952, p. 593.

Vigreux column, a still-head containing a cold-finger reflux condenser, a dry ice trap and a liquid nitrogen trap. The system was first purged with helium and a slow stream of helium was maintained during the reaction. The reaction flask was heated so as to maintain a slow reflux at the base of the Vigreux column but the temperature in the still-head did not exceed 30°. The temperature of the reaction mixture in the runs with diethoxybutane was initially 120° and rose to 140° during the course of the reaction. The temperature of the runs with diisopropoxybutane was about 10° higher. After 4 to 5 hr. of heating the reaction flask was allowed to cool and the flow of helium was increased to ensure the complete transfer of volatile products to the traps. At the conclusion of a run the contents of the liquid nitrogen trap were transferred to an evacuated 1-l. flask and brought to atmospheric pressure with helium. The gaseous products were analyzed with a mass spectrometer. The dry ice trap was connected to an evacuated flask and allowed to come to room temperature. The contents were thus separated into a gaseous and a liquid fraction. The gaseous fraction which was analyzed by means of gas chromatography and the mass spectrometer was at least 98% acetaldehyde. The reaction mixture was distilled at atmospheric pressure through a 12-inch Vigreux column until the temperature reached the boiling point of the acetal. The distillate was combined with the liquid fraction of the dry ice trap and analyzed by means of a Perkin-Elmer "Fractometer" using their column "A" which is supplied with the instrument. Helium was used as the carrier gas. The temperature was 50° and the pressure was 25 p.s.i. The chromatogram from the run with the ethyl acetal contained a number of well-separated bands which were identified as acetaldehyde, acetone, ethanol, *t*-butyl alcohol, *n*-butyraldehyde, ethyl *n*-butyl ether, *t*-butyl peroxide, ethyl butyrate, and the acetal in that order. The ethyl alcohol was not a reaction product but was an impurity of the acetal. The products were identified by trapping each fraction from the gas chromatography apparatus in a Dry Ice trap and transferring the condensate to an infrared cell and obtaining the infrared spectrum. The identification of each fraction was confirmed by showing that the retention time in the gas chromatogram of the known material was identical with the unknown in the reaction mixture. For quantitative analysis of the reaction mixture, a synthetic mixture was made which contained equal molecular amounts of the different substances which were found to be present. This mixture was run on the fractometer and the peak heights measured. It was found that the relative peak heights were independent of the sample size. Dividing each relative peak height of the chromatogram of the unknown mixture by the corresponding relative peak height of the known mixture gave the relative amounts of each constituent of the reaction mixture. To convert these relative amounts to absolute concentrations it was necessary to determine the concentration of any one of the constituents. For this purpose the concentration of *t*-butyl peroxide was determined from the intensity of its infrared band at 11.4 microns using a calibration curve that had previously been prepared using solutions of *t*-butyl peroxide in carbon tetrachloride in a 0.1-mm. cell. This band was chosen because there was no interference from the other constituents. The residue from the distillation of the reaction mixture was further distilled at reduced pressure. The unreacted acetal distilled at 55° to 60° at 40 mm. and a high boiling product (0.8 gram) was obtained, b.p. 72–76° at 2 mm. Its infrared curve showed no bands due to hydroxyl or carbonyl groups.

Anal. Calcd. for $C_{12}H_{26}O_2$: C, 71.29; H, 12.87; mol. wt. 202. Found: C, 71.12; H, 12.75; mol. wt. 196.

In a similar manner the decomposition of the diisopropyl acetal yielded 0.6 gram of a product, b.p. 75–80° at 2 mm.

Anal. Calcd. for $C_{14}H_{30}O_2$: C, 73.04; H, 13.04; mol. wt. 230. Found: C, 72.88; H, 12.70; mol. wt. 224.

Acknowledgment. We are indebted to Mr. Roger Bowman for the mass spectrometer analyses.

ABERDEEN PROVING GROUND, MD.

[CONTRIBUTION NO. 243 FROM THE DEPARTMENT OF CHEMISTRY, TUFTS UNIVERSITY]

Conversion of 4-Bromo-2-heptene to Conjugated Diene[1]

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4-Bromo-2-heptene has been converted to a mixture of 1,3- and 2,4-heptadiene by dehydrobromination with *s*-collidine and by the Hofmann exhaustive methylation procedure. The mixtures obtained by the two procedures differed both in the ratio of structural isomers and in the distribution of geometrical isomers.

For another study a straight-chain, unsymmetrical, conjugated diene without terminal unsaturation was desired. Not many such dienes are recorded in the literature, and of those that have been reported the usual method of preparation (dehydration of an allylic alcohol prepared from a Grignard reagent and an α,β-unsaturated aldehyde) leaves the structure assignment somewhat doubtful. For instance, 2,4-heptadiene has been reported at least ten times. The boiling point reported for this diene has varied from 103° to 109.7°, and agreement of literature values for the refractive index is no better. Dumoulin[3] carried out a permanganate oxidation on his 2,4-heptadiene, and the acids obtained led him to conclude that the diene contained some of the 1,3-isomer. He appears to be the only worker to have indicated that the 2,4-heptadiene might contain some of the 1,3-diene. Owens[4] did some work on the dehydration of *n*-butylvinylcarbinol which indicated that a mixture of structural isomers was obtained. The distillation curve of the dehydration product

(1) Presented before the Division of Organic Chemistry, ACS, Atlantic City Meeting, September, 1956.

(2) From the master's thesis of J.A.S. and work of F.L.G.

(3) J. Dumoulin, *Compt. rend.*, 182, 974 (1926).

(4) G. R. Owens, Ph.D. thesis, Ohio State University, 1937.

showed two plateaus. On the basis of the differences in the values of the exaltation of the molar refractivity the lower boiling material (b.p. 100.0–100.5°) was assigned the 1,3-heptadiene structure and the higher boiling material (b.p. 103.8–108.3°) was designated as 2,4-heptadiene.

In their original paper on allylic bromination Ziegler *et al.*[5] advocated the reaction of an alkene with *N*-bromosuccinimide followed by dehydrobromination as a method for the preparation of conjugated dienes. A branched-chain heptadiene, and straight-chain nonadiene and dodecadiene were reported as having been prepared in fairly good yield. No experimental work on the structures of these dienes was reported; the only evidence offered for the nature of the products were diene numbers[6] which were about 95% of the theoretical values. These high diene numbers are surprising in light of later work[7] on the reaction of maleic anhydride with conjugated dienes, where it has been shown that the high yield of adduct is obtained only when the carbon-carbon double bonds of the diene are of the *trans*-configuration. It is not likely that the dienes obtained by Ziegler *et al.* were of high steric purity, and the high diene numbers can be explained by the long reflux time employed, during which the maleic anhydride was involved in a polymerization reaction.[8]

In the years since 1942 the procedure suggested by Ziegler *et al.* has been highly successful and widely used for the introduction of a conjugated diene system into cyclic compounds, but the method has seen little application in open-chain compounds. The open-chain compounds that have been used[9] have been of high molecular weight, and the conversion to conjugated diene has been only moderately successful.

Heptadiene was chosen as the final product, for ultraviolet and infrared absorption should enable one to establish the diene as the 1,3- or 2,4-isomer. Hurd and Ensor[10] reported that 4-bromo-2-pentene was dehydrobrominated by trimethylamine at a low temperature. On the basis of this report it was hoped that 4-bromo-2-heptene could be converted to 2,4-heptadiene under these mild conditions. The bromoheptene was treated with various amines under a variety of reaction conditions; but to obtain a bromine-free product it was necessary to keep the reaction mixture at a rather high temperature for a fairly long period of time. The procedure finally adopted was to drop the bromoheptene into hot (165°) *s*-collidine which was stirred. The diene distilled from the reaction flask through a small, helix-filled column. After washing, the crude distillate was distilled through a spinning-band column. This distillation gave fractions amounting to a 78% yield of diene. The distillation curve exhibited two plateaus, one at b.p. 101.9–103° (22% yield of diene) and the other at b.p. 108.2–109.1° (26% yield of diene.)

In establishing the identity of the two principal products, the diene number of each material was determined. The lower boiling compound gave a diene number (220) which was 83% of the theoretical value (264), whereas the higher boiling material had a diene number (165) which was but 62% of theory. These data may be explained by the steric requirements[7] of the diene reaction. Both of these materials had an ultraviolet absorption maximum at 226 mμ with $\epsilon_{max.}$ 24,800 and 25,700, respectively. These $\epsilon_{max.}$ values would indicate that both materials are essentially pure conjugated diene.[11]

Maleic anhydride adducts of the low - and high-boiling materials were prepared. The amounts of crystalline adducts isolated correlated well with the values for diene number. The two adducts had identical melting points, but differences in crystal form and marked depression in a mixed melting point determination showed the adducts to be different compounds. Elemental analyses of the hydrocarbons and of the maleic anhydride adducts agreed with the theoretical values for heptadiene and for the maleic anhydride adduct of heptadiene.

The infrared curve of the lower boiling material had a doublet at 10.00 and 11.16μ which is associated with terminal unsaturation.[12] A strong band at 10.53μ indicated a *trans*-configuration of the carbon-carbon double bond.[13] Medium bands at 6.03 and 6.22μ also supported a highly unsymmetrical conjugated diene structure.[13] These data were consistent with a 1,3-diene structure for the lower boiling material, and in conjunction with the diene number the data indicated the material to be predominantly the *trans*-1,3-heptadiene.

The doublet at approximately 10 and 11μ was missing from the infrared curve of the higher boiling material. Very weak bands at 6.05 and 6.23μ indicated a fairly symmetrical conjugated diene.[13] These data indicated the absence of terminal unsaturation, and since the ultraviolet

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(6) H. P. Kaufmann, J. Baltes, and H. Büter, *Ber.*, **70**, 903 (1937).

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(12) J. N. Coker, A. S. Bjornson, T. E. Londergan, T. F. Martens, and J. R. Johnson, *J. Am. Chem. Soc.*, **77**, 5546 (1955).

(13) R. S. Rasmussen and R. R. Brattain, *J. Chem. Phys.*, **15**, 131 (1947).

absorption showed this material to be conjugated diene, the higher boiling material must be the 2,4-heptadiene.

Another method for converting an alkyl halide to an alkene is the Hofmann exhaustive methylation procedure. Some years ago we carried 4-bromo-2-heptene through this procedure. The infrared absorption of the final product showed the presence of terminal unsaturation, indicating that rearrangement had occurred during the transformations. Since that time Young *et al.*[14] have shown that the conversion of an allylic halide to the quaternary salt was accompanied by considerable rearrangement.

4-Bromo-2-heptene was subjected to the Hofmann procedure, and distillation of the final product gave fractions amounting to an 84% yield (based on the quaternary salt) of diene. The distillation curve had two plateaus, one at b.p. 68.1–68.5°/230 mm. (47% yield of diene) and the other at b.p. 75.3–76.0°/230 mm. (20% yield of diene). The lower boiling material proved to be identical with the 1,3-heptadiene and the higher boiling material identical with the 2,4-heptadiene obtained by the collidine dehydrobromination procedure. Differences in diene numbers and slight differences in infrared curves showed the geometric isomer composition of the various materials to be different.

EXPERIMENTAL

Chemicals. 4-Bromo-2-heptene was prepared as described previously.[15] The material used had b.p. 70–71°/32 mm., n_D^{25} 1.4710.

Trimethylamine (anhydrous) was purchased from Distillation Products, Rochester, N. Y., and used as received.

Triethylamine, *2,6-lutidine*, *s-collidine*, *quinoline*, and *lepidine* were the best grades available from Distillation Products. The materials were distilled just before use, and the higher boiling ones were vacuum distilled.

Maleic anhydride (Distillation Products) was recrystallized three times from chloroform and stored in a desiccator over calcium chloride.

Dioxane was the best grade available from Distillation Products. The material was refluxed with sodium and distilled in a nitrogen atmosphere.

Preliminary experiments. To establish desirable experimental conditions for the dehydrobromination, 0.028 mole of 4-bromo-2-heptene was heated with 0.056 mole of an amine in a nitrogen atmosphere for varying periods of time. Precipitates formed in all cases except with quinoline, where a lower, dark, liquid layer was formed. To the reaction mixture ligroin (b.p. 30–60°) was added, and this mixture extracted successively with 5% acetic acid, 10% sodium bicarbonate, and water. The organic layer was dried and distilled through a column (14 × 140 mm.) which was packed with helices. A bromine-free distillate could be obtained only if a temperature of at least 140° and 2 hr. reaction time were used. The following procedure was used for the larger scale experiments.

Dehydrobromination of 4-bromo-2-heptene with s-collidine. In a 250 ml. flask fitted with a dropping funnel, Hershberg stirrer, and helix-filled column (packed portion, 14 × 170 mm.) was placed 93.2 g. (0.77 mole) of *s*-collidine (b.p. 63.5°/16 mm.). The apparatus was flushed with nitrogen and the reaction system protected from air during the course of the reaction. The reaction flask was placed in a metal bath, the temperature of which was maintained at 165–170° during the reaction. 4-Bromo-2-heptene (54.5 g., 0.31 mole) was added dropwise to the reaction flask over a period of 2 hr. When the rate of distillation decreased, the temperature of the metal bath was raised until the boiling point of the distillate suddenly rose, indicating collidine was coming into the distillate. The reaction was discontinued at this point. The distillate (30.3 g.) came over at 102–106°. A portion of the distillate gave a negative test for bromine.

The residue in the reaction flask was filtered, the precipitate washed with ligroin (b.p. 30–60°) and dried. This precipitate was collidine hydrobromide (58.7 g.; 95% yield).

The distillate was washed into a separatory funnel with 400 ml. of ligroin (b.p. 30–60°). This solution was extracted with three 130-ml. portions of 5% acetic acid, once with 100 ml. of 10% sodium bicarbonate, and finally with 100 ml. of water. Hydroquinone was added to the organic layer and it was then dried with freshly heated sodium sulfate overnight.

The ligroin solution was filtered from the sodium sulfate, the drying agent washed three times with ligroin, and the washings added to the main solution. Some hydroquinone was added to the solution and the ligroin distilled from the solution through a Fenske column (18 plates) under a nitrogen atmosphere. The distillation was discontinued when the temperature of the distilling liquid reached 85°. The residue was transferred to a smaller flask, some hydroquinone was added, and the liquid was distilled under nitrogen through a Nester spinning-band column (7 mm. I.D. × 600 mm.). After removal of solvent 27 fractions were collected which were combined to give the following: Forerun, 0.98 g., b.p. 96–102°/752 mm., n_D^{25} 1.4321–1.4425; Liquid I, 6.49 g., 22% yield of diene, b.p. 101.9–103°/752 mm., n_D^{25} 1.4438–1.4445, d^{25} 0.722; Intermediate Fraction, 8.11 g., 27% yield of diene, b.p. 103–108°/755 mm., n_D^{25} 1.4452–1.4529, d^{25} 0.726; Liquid II, 7.66 g., 26% yield of diene, b.p. 108.2–109.1°/755 mm., n_D^{25} 1.4542–1.4549, d^{25} 0.737. The total weight of distillate (23.24 g.) corresponded to a 78% yield of diene from the bromoheptene. Vacuum distillation of the product in another preparation gave essentially the same results.

Liquid I was identified as a mixture of *cis*- and *trans*-1,3-heptadiene. In the ultraviolet the material had $\lambda_{max.}^{EtOH}$ 226 mμ, ε 24,800. The infrared curve had the following peaks (microns): 3.24(m), 3.34(sh), 3.41(vs), 3.47(vs), 5.56(w), 6.03(ms), 6.22(ms), 6.85(s), 7.24(m), 7.68(w), 10.00(vs), 10.53(s), 11.16(vs), 13.14(m). The curve indicated terminal unsaturation, conjugated diene and *cis*- and *trans*-configurations with a preponderance of the *trans*-isomer.

Anal. Calcd. for C_7H_{12}: C, 87.4; H, 12.6; diene number, 264. Found[16]: C, 87.4; H, 12.5; diene number[5] (1 hr. reflux), 220.

A maleic anhydride adduct of the material was prepared by refluxing a benzene solution of the reactants for 2 hr.; 1.01 g. of diene gave 1.80 g. of solid, m.p. 58–65°. Considerable waxy material was present in the solid. One crystallization from ligroin (b.p. 60–90°) gave 1.28 g. of plates, m.p. 67.6–68.3°. Two more crystallizations gave material of m.p. 68.8–69.5°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.3. Found: C, 67.6; H, 6.9.

Liquid II was identified as a mixture of geometric isomers of 2,4-heptadiene. In the ultraviolet the material had $\lambda_{max.}^{EtOH}$ 227 mμ, ε 25,700. The infrared curve had the following peaks (microns): 3.34(s), 3.41(vs), 3.48(sh), 5.59(vw),

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(15) F. L. Greenwood and M. D. Kellert, *J. Am. Chem. Soc.*, 75, 4842 (1953).

(16) Elemental analyses by Dr. Carol Fitz, Needham Heights, Mass.

6.05(w), 6.23(vw), 6.90(s), 7.27(m), 7.67(w), 9.35(w), 10.18(vs), 10.58(vs), 10.78(m), 11.15(vw), 11.53(vw), 12.18(m). The curve indicated a fairly symmetrical conjugated diene,[13] absence of terminal unsaturation and *cis*- and *trans*-configurations.

Anal. Calcd. for C_7H_{14}: C, 87.4; H, 12.6; diene number, 264. Found: C, 87.5; H, 12.6; diene number, 165.

The diene (1.08 g.) gave 1.58 g. of waxy maleic anhydride adduct, m.p. 61.8–67°. One crystallization from ligroin (b.p. 60–90°) gave 0.83 g. of needles, m.p. 67.9–69.0°. Two more crystallizations gave material of m.p. 68.8–69.5°. Mixed m.p. with adduct of Liquid I, 35.6–42.8°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.3. Found: C, 67.8; H, 7.0.

The Intermediate Fraction must be a mixture of 1,3- and 2,4-heptadiene. The material had an ultraviolet absorption maximum at 226 mμ, $\epsilon_{max.}$ 25,900. The material (1.02 g.) gave 1.46 g. of gummy maleic anhydride adduct. Fractional crystallization of the adduct gave 0.51 g. of plates, m.p. 68–69°. This material gave no depression in a mixed melting point determination with the adduct of Liquid I. This proves the presence of the 1,3-diene in this fraction. Attempts to isolate the adduct of the 2,4-diene from the Intermediate Fraction adduct were unsuccessful.

Reaction of 4-bromo-2-heptene with trimethylamine. A pressure bottle containing 100 ml. of dioxane was placed in an ice bath. To this flask was added 10.1 g. (0.171 mole) of trimethylamine which was passed through a drying tube containing potassium hydroxide pellets before entering the dioxane. The reaction flask was kept cold during the dropwise addition of 15.0 g. (0.0847 mole) of 4-bromo-2-heptene. Three reaction mixtures were prepared as above, and the bottles placed in the refrigerator overnight. The bottles were then placed in a water bath (75–80°) for 8 hr. The white solid which was initially present melted to a colorless, lower layer on warming. The reaction flasks were shaken occasionally during the 8 hr. heating period. The bottles were cooled, and the reaction mixtures were combined in a 500 ml. wide-mouth Erlenmeyer flask.

The liquid was removed from the reaction mixture with a filter stick, and the residue washed twice with dry ether. The ether was also removed with the filter stick. The quaternary salt was extremely hygroscopic and had to be protected from moisture at all times. We were unsuccessful in finding a suitable solvent for crystallization of the salt. The flask containing the quaternary salt was kept in a vacuum desiccator over phosphorus pentoxide until it came to a constant weight. Yield, 58.1 g., 97%.

Anal. Calcd. for $C_{10}H_{22}BrN$: Br, 33.8. Found: Br, 34.6.

The quaternary salt was surely a mixture of normal and rearranged product.[14] The bromine analysis showed that the reaction product was predominantly the desired quaternary salt and did not contain much trimethylamine hydrobromide which would have resulted from a dehydrobromination reaction.

Conversion of quaternary salt to heptadiene. Into a 2-l. flask fitted with a Hershberg stirrer and dropping funnel were placed 250 ml. of water and silver oxide which had been freshly prepared from 249.1 g. (1.466 moles) of silver nitrate and 58.6 g. (1.466 moles) of sodium hydroxide. Into the dropping funnel was placed a solution of 172.1 g. (0.729 mole) of the quaternary salt in 250 ml. of water. This solution was added dropwise to the reaction flask over a period of 40 min. The reaction mixture was allowed to stir overnight. The reaction mixture was filtered, the residue washed twice with water, and the washings and filtrate were combined to give 1 l. of water-white solution.

A 500 ml. Claisen flask was fitted with a dropping funnel, downward condenser, and receiver which was immersed in an ice bath. The apparatus was flushed with nitrogen and protected from air during the course of the reaction. The reaction flask was immersed in a metal bath which was maintained at 170–180° during the pyrolysis. The solution of the quaternary base was added at such a rate that the decomposition flask was essentially dry during the pyrolysis. The addition of the base solution required 7.5 hours. Acetic acid (50.0 g., 0.833 mole) was added to the distillate, and the organic layer was separated. The aqueous layer was extracted with 2 100-ml. portions of ligroin (b.p. 30–60°), and the extracts combined with the organic layer. The organic layer was extracted with 100 ml. of 5% sodium bicarbonate and with 50 ml. of water. The organic layer was placed in a flask containing some hydroquinone and some freshly heated sodium sulfate.

The drying agent was removed by filtration and washed three times with ligroin. The combined washings and filtrate were placed in a flask with some hydroquinone, and the solvent removed through a Fenske column (18 plates) under a nitrogen atmosphere. The distillation was discontinued when the temperature of the distilling liquid reached 95°. The residue was transferred to a smaller flask, hydroquinone added, and the liquid distilled *in vacuo* through the Nester spinning-band column. After removal of a small amount of solvent 37 fractions were collected which were combined to give the following: Forerun, 1.42 g., b.p. 64.0–68.1°/230 mm., n_D^{25} 1.4391; Liquid III, 33.04 g., 47% yield of diene, b.p. 68.1–68.5°/230 mm., n_D^{25} 1.4427–1.4443; Intermediate Fraction, 10.69 g., 15% yield of diene, b.p. 68.5–75.3°/230 mm., n_D^{25} 1.4448–1.4538; Liquid IV, 14.04 g., 20% yield of diene, b.p. 75.3–76.0°/230 mm., n_D^{25} 1.4543–1.4552. The total weight of distillate (59.19 g.) represented an 84.4% yield of diene.

Liquid III proved to be 1,3-heptadiene. The material had an infrared absorption nearly identical with that of Liquid I. In the ultraviolet this material had $\lambda_{max.}^{EtOH}$ 225.5 mμ, ε 23,600. Liquid III gave a maleic anhydride adduct of m.p. 68.7–69.2°, undepressed when mixed with the Liquid I adduct. The diene number (137.4) of Liquid III was 52% of the calculated value, which indicated this 1,3-diene to contain less of the *trans*-isomer than Liquid I.

Liquid IV was 2,4-heptadiene. Its infrared curve was almost identical with that of Liquid II. In the ultraviolet this 2,4-diene had $\lambda_{max.}^{EtOH}$ 229.5 mμ, ε 24,900. Liquid IV gave a maleic anhydride adduct of m.p. 68.8–69.2°, which gave no depression of melting point when mixed with the Liquid II adduct. Liquid IV had a diene number (60.6) which was 23% of the calculated value. This would indicate that Liquid IV contained much less of the *trans,trans*-isomer than did Liquid II.

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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, UNIVERSITIES OF NOTRE DAME AND PENNSYLVANIA]

Preparation and Properties of Ethyl Tetronate

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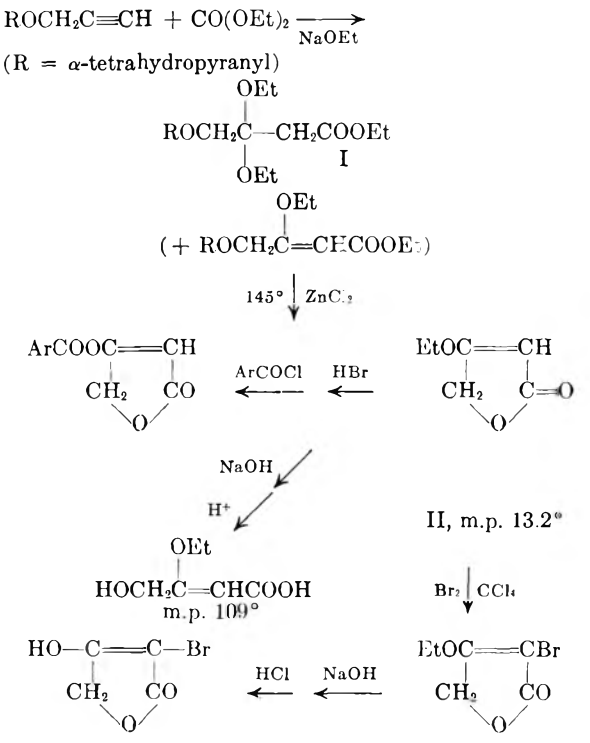
A three-step synthesis of ethyl tetronate (II) from propargyl alcohol has been developed. Its structure was proven by conversion to α-bromotetronic acid. II was found to be remarkably unreactive to a number of reagents.
Ethyl methoxytetrolate was also prepared and characterized.

It was hoped that alkyl or acyl derivatives of tetronic acid might prove useful starting materials for some projected syntheses. We therefore have developed a convenient preparation of these compounds, starting from propargyl alcohol. The latter is first converted to the 2-tetrahydropyranyl

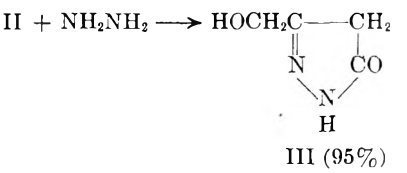


ether by reaction with dihydropyran.[2] Addition of diethyl carbonate to the triple bond[3] was successful but was accompanied by addition of ethanol as well, so that the product was principally ethyl β,β-diethoxy-γ-(2-tetrahydropyranyloxy)butyrate (I). Infrared data on the crude product indicated the presence of appreciable quantities of the β-ethoxycrotonate, but the only product which we were able to isolate in analytical purity by fractional distillation was I.

Treating the crude I with zinc chloride at 140–145° led to a smooth conversion to ethyl tetronate (II) in 55% overall yield from propargyl α-tetrahydropyranyl ether.

II proved to be resistant to reactions normally readily accomplished with vinyl ethers or α,β-unsaturated lactones. For example, attempted Michael addition of nitromethane and addition of aniline to the double bond failed. Cleavage of the vinyl ether group failed with hydrochloric acid but was accomplished by 48% hydrobromic acid.

On the other hand, reaction of the lactone ring appeared to be normal. Saponification led to the hydroxy acid and hydrazinolysis proceeded vigorously to produce a pyrazolone (III).



III (95%)

The double bond of II was also found to be unreactive in the Diels-Alder reaction and in free radical polymerization. In the latter regard, the unreactivity of the double bond resembles that of ethyl β-ethoxyacrylate.[4]

EXPERIMENTAL[5]

The reaction of 2-propargyloxytetrahydropyran with ethyl carbonate in the presence of sodium ethoxide. Powdered sodium ethoxide, prepared from 4.6 g. (0.2 g. atom) of clean sodium, and 295 g. (2.5 moles) of ethyl carbonate were stirred and heated to 80° and 140 g. (1 mole) of 2-propargyloxytetrahydropyran[2] was added over a 1-hr. period, the temperature being maintained at 75–80° by periodic cooling. After being heated for 7 hr. at 70–75°, the reaction mixture was cooled to room temperature and neutralized with 52 g. of 23% aqueous acetic acid. Extraction with ether, washing with water, drying over 20 g. of anhydrous potassium carbonate and distilling from 1 g. of anhydrous magnesium carbonate through a 6-inch column packed with 0.25 inch helices gave 190 g. of ethyl carbonate, 11 g. of 2-propargyloxytetrahydropyran, and 170.2 g. of product (A), b.p. 126–132° (1.2 mm.); n_D^{25} 1.4546.

By careful refractionation of a portion of this product (A) from anhydrous magnesium carbonate, a fairly pure sample of ethyl γ-(2-tetrahydropyranyloxy)-β,β-diethoxybutyrate was obtained, b.p. 110–110.5° (0.3 mm.), n_D^{25} 1.4504, d_{25}^{25} 1.056.

(1) Eli Lilly and Company Fellow, 1953–55.

(2) R. G. Jones and M. J. Mann, *J. Am. Chem. Soc.*, **75**, 4048 (1953).

(3) See W. J. Croxall and H. J. Schneider, *J. Am. Chem. Soc.*, **71**, 1257 (1949).

(4) C. C. Price and T. C. Schwan, *J. Polymer Sci.*, **16**, 577 (1955).

(5) Melting and boiling points are uncorrected. Analyses by Micro Tech. Laboratories, Skokie, Ill.

Anal. Calcd. for $C_{15}H_{28}O_6$: C, 59.19; H, 9.27; M_D 77.70. Found: C, 58.73; H, 8.97; M_D 77.54. Another sample, b.p. 118–119° (1.1 mm.), n_D^{25} 1.4530, was also analyzed. Found: C, 59.25; H, 9.11.

Preparation of ethyl tetronate. A 50 g. portion of the product (A) obtained from the reaction of 2-propargyloxytetrahydropyran with ethyl carbonate in the presence of sodium ethoxide was heated at 140–145° with 0.25 g. of anhydrous zinc chloride. Nitrogen was bubbled through the mixture until no further distillate was formed (about 1 hr.). The dark colored residue was submitted to vacuum distillation and 18.6 g. of ethyl tetronate was collected, b.p. 65–66° (0.08 mm.), m.p. 13–13.2°, n_D^{25} 1.4777, d_4^{25} 1.1609.

Anal. Calcd. for $C_6H_8O_3$: C, 56.24; H, 6.29; M_D 30.71; Sapon. Equiv. 128.1. Found: C, 56.33; H, 6.42; M_D 31.23; Sapon. Equiv. 129.1.

The overall yield of ethyl tetronate was 53.7% based on 2-propargyloxytetrahydropyran and 55.5% on the ethyl carbonate consumed. The ultraviolet spectrum of ethyl tetronate in 95% ethanol showed maxima at 219 and 270 mμ, log ε 4.02 and 3.64, respectively.

Preparation of γ-hydroxy-β-ethoxycrotonic acid. A 2 g. sample of ethyl tetronate was heated on a steam bath for 0.5 hr. with 15 ml. of 2*N* sodium hydroxide solution. The yellow-colored solution was cooled to 0° and acidified with 6*N* sulfuric acid. The white solid which separated was extracted with four 15-ml. portions of ether. After drying the combined ether extracts over 3 g. of anhydrous magnesium sulfate, the drying agent was separated and the ether evaporated. The crystals were filtered by suction and washed with 5 ml. of cold anhydrous ether. The resulting colorless crystals were dried in a vacuum desiccator; weight 1.94 g. (85.1%); m.p. 109–109.3°.

Anal. Calcd. for $C_6H_{10}O_4$: C, 49.31; H, 6.90; Neut. Equiv., 146.1. Found: C, 49.30; H, 6.91; Neut. Equiv., 146.6.

Acid hydrolysis of ethyl tetronate. A. *With hydrochloric acid.* Two drops of concentrated hydrochloric acid and 1.28 g. of ethyl tetronate in 2 ml. of water were warmed in a water bath until a homogeneous solution resulted. The solution was heated on a steam bath for 2 hr. and cooled in an ice bath, whereupon two phases separated. The organic layer was separated by extraction with four 10-ml. portions of ether and the combined ether extract dried over magnesium sulfate. Evaporation of the ether gave a residue, weight 0.85 g., having the same refractive index as ethyl tetronate. The aqueous layer when treated with *p*-nitrobenzoyl chloride under Schotten-Baumann conditions failed to give a precipitate.

In a second experiment, ethyl tetronate (1 g.) was refluxed with concentrated hydrochloric acid (5 drops) in 95% ethanol (3 ml.) for 1 hr. On evaporation and cooling, a small amount of white crystals separated, which were shown by mixed melting point to be γ-hydroxy-β-ethoxycrotonic acid. Ethyl tetronate was recovered in 80% yield.

B. *With hydrobromic acid.* A mixture of 3.6 g. (0.028 mole) of ethyl tetronate and 4.75 g. (0.03 mole) of 48% hydrobromic acid was allowed to stand overnight. The solution was then treated with 20 ml. of water and neutralized with 6*N* sodium hydroxide solution. After adding 6.0 g. (0.032 mole) of *p*-nitrobenzoyl chloride, the mixture was stirred at 40° with the occasional addition of sodium carbonate to keep the solution slightly basic to litmus. The solid which separated was filtered by suction, washed with two 10-ml. portions of water and dried in a vacuum desiccator, 4.65 g., m.p. 147.5–165°. The solid was dissolved in 125 ml. of boiling benzene, filtered, and allowed to crystallize. The *p*-nitrobenzoyltetronic acid crystallized as colorless rosettes. At the first sign of yellow needles, the mother liquor was decanted and the crystals washed, by decantation, with two 5-ml. portions of benzene and dried, weight 1.36 g., m.p. 167–170°.

A second crop of crude *p*-nitrobenzoyltetronic acid may be obtained by heating the mother liquor to boiling and adding 50 ml. of petroleum ether (b.p. 65–100°). Total yield 2.1 g. (30.1%). An analytical sample was prepared by recrystallization from benzene, m.p. 172.5–174°.

Anal. Calcd. for $C_{11}H_7O_6N$: C, 53.02; H, 2.83; N, 5.62. Found: C, 52.78; H, 3.07; N, 5.40.

A small sample of the yellow needles was separated manually and shown to be *p*-nitrobenzoic anhydride by mixed melting point with an authentic sample of *p*-nitrobenzoic anhydride and by comparison of infrared spectra of the known and unknown samples.

Attempted reaction of ethyl tetronate with nitromethane. A solution of 0.4 g (0.0174 mole) of metallic sodium in 100 ml. of absolute ethanol was cooled to room temperature and 5.5 g. (0.09 mole) of nitromethane in 125 ml. of absolute ethanol added over 15 min. A fine, white suspension was formed to which 7.7 g. (0.06 mole) of ethyl tetronate in 50 ml. of absolute ethanol was added and the mixture was stirred at room temperature for 60 hr. After neutralization with acetic acid (1.0 g.), the ethanol and unreacted nitromethane were removed to 40–45° under reduced pressure. The residue was filtered by suction and the filtrate distilled under reduced pressure to give 5.8 g. (75% recovery) of ethyl tetronate. The residue, weight 0.3 g., was a black, polymeric material.

Attempts to prepare Diels-Alder adducts of ethyl tetronate. A. *Anthracene.* To 2 g. (0.0156 mole) of ethyl tetronate in 5 g. of anhydrous xylene was added 2.78 g. (0.0156 mole) of anthracene. The anthracene dissolved when the mixture was heated to 120° and the resulting solution was refluxed for 1 hr. After the solution had cooled to room temperature, the crystals were filtered by suction, washed with 5 ml. of xylene and dried. The crystals were shown by mixed melting point to be pure anthracene, weight 2.65 g. (95.3% recovery).

B. *Cyclopentadiene.* A mixture of 2.5 g. (0.0195 mole) of ethyl tetronate, 5 g. of anhydrous benzene, 5 g. (0.076 mole) of freshly distilled cyclopentadiene, and a pinch of hydroquinone was refluxed overnight. The solvent and unreacted cyclopentadiene were removed under reduced pressure. The residue separated into two layers and, on cooling to room temperature, the upper layer solidified. The solid was shown by refractive index and melting point to be dicyclopentadiene. The lower layer was unchanged ethyl tetronate, quantitatively recovered.

C. *Butadiene.* A mixture of 1 g. of ethyl tetronate, 2.8 g. of butadiene, and a few crystals of hydroquinone was heated in a sealed tube at 100–102° for 2 days. The tube was cooled, opened, and the unreacted butadiene allowed to evaporate. Some jelly-like material adhered to the side of the tube; in the bottom of the tube was 0.8 g. of ethyl tetronate. The jelly-like material was heated for 1 hr. with 10 ml. of 2*N* sodium hydroxide solution, filtered, and the filtrate cooled. Acidification with 6*N* hydrochloric acid gave no precipitate.

The experiment was repeated, the tube being heated at 148–151° for 2 days; 90% of the ethyl tetronate was recovered.

D. *Furan.* A mixture of 1.5 g. (0.012 mole) of ethyl tetronate, 1.6 g. (0.024 mole) of furan, and a few crystals of hydroquinone was heated at 98–102° for 2 days in a sealed tube. The tube was cooled, opened, and weighed. The furan was evaporated on a water bath; loss in weight, 1.5 g. The residue had a refractive index at 25° of 1.4770; the refractive index of ethyl tetronate is 1.4777.

Reaction of ethyl tetronate with bromine. With stirring, 10.4 g. (0.065 mole) of bromine in 100 g. of carbon tetrachloride was added dropwise over a 1-hr. period to 7.7 g. (0.06 mole) of ethyl tetronate in 20 ml. of carbon tetrachloride at room temperature. Some hydrogen bromide was evolved during the addition. The mixture was slowly warmed to reflux temperature and maintained for 0.5 hr. The reflux condenser was turned downward and the carbon tetrachloride distilled off. The residue crystallized on cooling and was filtered by suction and washed with two 5-ml. portions of cold carbon tetrachloride; yield, 11.7 g. (94.2%), m.p. 93–97°. An ana-

TABLE I

INFRARED SPECTRA

Ethyl Methoxy-tetrolate[a]		Ethyl Tetronate[a]		γ-Hydroxy-β-ethoxy-crotonic Acid[b]		p-Nitro-benzoyl-tetronic Acid[c]		Ethyl α-Bromo-tetronate[c]		α-Bromo-tetronic Acid[c]	
λ	% Abs.	λ	% Abs.	λ	% Abs.	λ	% Abs.	λ	% Abs.	λ	% Abs.
3.4	29	3.2	15	2.9–	20–	3.4	80	3.45	72	3.2–	
4.45	22	3.35	18	3.6	30	5.65	81	5.68	95	4.2	—
5.85	80	5.65	68	5.96	71	5.72	84	6.15	95	3.45	68
6.8	30	5.72	72	6.25	88	6.16	79	6.88	59	5.65	43
7.28	37	6.15	83	6.78	weak	6.25	40	7.00	83	5.82	77
7.95	89	6.78	13	7.0	weak	6.56	80	7.16	74	6.1–	
8.38	35	6.90	18	7.16	weak	6.90	56	7.3	94	6.3	85
9.00	67	7.23	42	7.35	weak	7.28	weak	7.65	96	6.9–	
9.40	54	7.36	18	7.50	weak	7.40	74	8.20	88	7.2	75
9.9	27	7.57	68	7.68	weak	7.56	70	9.02	72	7.35	66
11.00	29	8.08	34	8.55	88	8.08	90	9.6	93	7.60	59
11.6	13	8.70	49	9.00	53	8.47	73	10.2	95	8.20	66
13.25	34	9.02	17	9.4–		8.62	70	11.75	88	9.47	76
		9.53	56	9.7	55	9.48	87	13.50	83	9.92	73
		9.8	40	10.35	38	9.65	75	13.95	83	10.05	60
		10.56	17			9.90	72			11.7	50
		11.3–				11.24	48			13.28	68
		11.5	28			11.62	66			13.65	75
		12.5	28								

[a] Pure liquid. [b] In chloroform. [c] Nujol mull.

lytical sample of ethyl α-bromotetronate was prepared by recrystallization from benzene, m.p. 96–98°.

Anal. Calcd. for $C_6H_7O_3Br$: C, 34.80; H, 3.41; Br, 38.60. Found: C, 34.93; H, 3.51; Br, 38.86.

Preparation of α-bromotetronic acid. A 3.0 g. sample of ethyl α-bromotetronate and 15 ml. of 2*N* sodium hydroxide were heated on a steam bath until solution was complete. After heating for a further 5 min., the solution was cooled in an ice-water bath, saturated with salt, and made strongly acid with concentrated hydrochloric acid. The precipitate was filtered by suction and the air-dried material recrystallized by dissolving it in a minimum of boiling ethyl acetate, treating with Norit, filtering, and allowing to crystallize in the refrigerator. The fine, white crystals of α-bromotetronic acid were collected on a filter and washed with a few drops of cold ethyl acetate. Yield of dried material, 0.53 g. (20.4%), m.p. 179° (dec.), corrected m.p. 182.8° (dec.), neut. equiv. 179.4, 179.6 (calcd. 179), pK_a 2.26. (Lit.[6] m.p. 183° (dec.), pK_a 2.23, Br, 44.2.)

Anal. Calcd. for $C_4H_3O_3Br$: C, 26.84; H, 1.69; Br, 44.65. Found: C, 27.24; H, 1.85; Br, 44.81.

Preparation of 3-hydroxymethyl-5-pyrazolone. A solution of 3.2 g. of ethyl tetronate in 5 ml. of methanol was cooled to 0° and was added, with stirring, to a solution of 5.0 g. of 85% hydrazine hydrate in 5 ml. of methanol, also at 0°. There was an exothermic reaction and the temperature rose to 40°. When the initial reaction had subsided, the solution was refluxed on a steam bath for 0.5 hr. The methanol and unreacted hydrazine were removed by heating to 120° at 20 mm. The residue crystallized to an orange-colored mass on cooling. When stirred with 15 ml. of cold acetone, the crystals crumbled and were then filtered by suction and washed with 5 ml. of cold acetone; yield 2.7 g. (95%), m.p. 144–152°.

Attempts to recrystallize the 3-hydroxymethyl-5-pyrazolone were unsuccessful. A portion was extracted by stirring with a small amount of phenylhydrazine, filtered, and the pale yellow crystals washed with ethyl acetate. The dried material melted at 152–156°.

(6) W. D. Kumler, *J. Am. Chem. Soc.*, **60**, 859 (1938).

Anal. Calcd. for $C_4H_6O_2N_2$: C, 42.1; H, 5.3; N, 24.6. Found: C, 41.6; H, 5.3; N, 25.6.

The *3,5-dinitrobenzoate* of 3-hydroxymethyl-5-pyrazolone was prepared and recrystallized from glacial acetic acid, m.p. 209° (dec.).

Anal. Calcd. for $C_{11}H_6O_7N_4$: C, 42.85; H, 2.61; N, 18.18. Found: C, 42.93; H, 2.82; N, 18.07.

Attempted reaction of ethyl tetronate with phenylhydrazine. A solution of 3.84 g. (0.03 mole) of ethyl tetronate in 5 ml. of methanol was cooled to 0° and added to a solution of 13.0 g. (0.12 mole) of phenylhydrazine in 10 ml. of methanol at 0°. No heat was evolved on mixing. The solution was refluxed for 0.5 hr. The methanol was distilled and the unreacted phenylhydrazine removed under reduced pressure. Vacuum distillation recovered 3.65 g. of ethyl tetronate. The residue, weight 0.3 g., failed to crystallize on cooling.

In a second experiment, a mixture of 2.56 g. (0.02 mole) of ethyl tetronate and 4.32 g. (0.04 mole) of phenylhydrazine was heated at 150° for 1 hr. Distillation gave 4.05 g. of phenylhydrazine and 2.2 g. of ethyl tetronate. The residue, a dark viscous oil, failed to crystallize on cooling to 0°.

Attempted reaction of ethyl tetronate with aniline. A solution of 3.84 g. (0.03 mole) of ethyl tetronate in 5 ml. of methanol was cooled to 0° and added to a solution of 11.16 g. (0.12 mole) of freshly distilled aniline in 10 ml. of methanol at 0°. There was no exothermic reaction on mixing. The solution was refluxed for 1 hr. and distilled to give 10.7 g. of aniline and 3.6 g. of ethyl tetronate.

In a second experiment, a mixture of 2.56 g. (0.02 mole) of ethyl tetronate and 7.47 g. (0.08 mole) of freshly distilled aniline was refluxed for 0.5 hr. Distillation under reduced pressure gave an almost quantitative recovery of aniline.

Attempted reaction of ethyl tetronate with 2-mercaptoethanol. A solution of 2.56 g. (0.02 mole) of ethyl tetronate and 1.56 g. (0.02 mole) of freshly distilled 2-mercaptoethanol [b.p. 55° (13 mm.), n_D^{25} 1.4980] was stirred by a magnetic stirrer for 24 hr. in the presence of ultraviolet light. The solution was distilled to give 1.50 g. of 2-mercaptoethanol, b.p. 53° (11 mm.), n_D^{25} 1.4977. The residue had a refractive index at

25° of 1.4780; pure ethyl tetronate has a refractive index of 1.4777.

Attempted copolymerization of ethyl tetronate with acrylonitrile. A mixture of 5.25 g. (0.041 mole) of ethyl tetronate, 2.19 g. (0.042 mole) of freshly distilled acrylonitrile, and 0.046 g. (0.0002 mole) of benzoyl peroxide was sealed under nitrogen, and placed in a constant temperature bath at 60 ± 0.1° for 1.5 hr. Some polymer separated from the monomer solution. The tube was cooled, opened, and the contents poured, with stirring, into 250 ml. of filtered methanol. After standing overnight in the refrigerator, the white, powdery precipitate was filtered on a sintered glass funnel, pressed, and dried to constant weight (1.25 g.) at room temperature and 0.06 mm. pressure. An infrared spectrum of this material failed to show any absorption in the carbonyl area, which would be expected had copolymerization taken place.

Ethyl methoxytetrolate. Methyl propargyl ether was prepared by reaction of the alcohol with methyl sulfate and alkali at 0–5°. The ether, obtained in 85% yield, b.p. 61–62°, n_D^{25} 1.3945, was treated with one equivalent of ethylmagnesium bromide in ether and then with an excess of diethyl carbonate. Extraction and distillation gave a 38% yield of ethyl methoxytetrolate, b.p. 63–64° (3 mm.), n_D^{25} 1.4397.

Anal. Calcd. for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.11; H, 7.00.

Infrared spectra of some of the compounds are summarized in Table I.

PHILADELPHIA 4, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Nitrogen Mustards Related to Chloroquine, Pamaquine, and Quinacrine[1]

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Procedures for the preparation of the nitrogen mustard analogs of the antimalarial drugs chloroquine, pamaquine, and quinacrine have been described.

Extensive investigations of the pharmacology of the quinoline antimalarial drugs[3] has indicated that they are selectively absorbed in certain tissues. For this reason we have undertaken a program involving the preparation and testing of a variety of derivatives of the antimalarial drugs in which the diethylamino group would be replaced by the bis(β-chloroethyl)amino group, the characteristic functional group of the nitrogen mustard gases. The quinoline nucleus and side chain might serve to carry the antimitotic activity of the nitrogen mustard function more selectively to certain areas of the organism, thus enhancing the chemotherapeutic value of the nitrogen mustards in the treatment of various types of cancer.

We here wish to report on the conversion of 4,7-dichloroquinoline to 7-chloro-4-[4-bis(β-chloroethyl)amino-1-methylbutylamino]quinoline (chloroquine mustard) and to 7-chloro-4-[6-bis(β-chloroethyl)aminohexylamino]quinoline (hexyl chloroquine mustard), of 2-methyl-4,7-dichloroquinoline to 2-methylchloroquine mustard, of 6-methoxy-8-(4-amino-1-methylbutylamino)quinoline (primaquine) to the 4-bis(β-chloroethyl) derivative (pamaquine mustard), and of 2-methoxy-6,9-dichloroacridine to 2-methoxy-6-chloro-9-[4-bis(β-chloroethyl)-amino-1-methylbutylamino]acridine (quinacrine mustard).

These mustards have been screened against several tumors in mice here and elsewhere[4] and chloroquine and quinacrine mustards have been given initial clinical testing.[2] The activity of these compounds against several ascites tumors in mice[4] is approximately equal to HN_2 [methyl bis(β-chloroethyl)amine] and the toxicity of some to mice is several-fold less. Details of the animal and clinical testing will be reported elsewhere.[4(b)]

EXPERIMENTAL[5]

5-Chloro-2-pentanone. This compound was prepared from α-acetyl-γ-butyrolactone,[6] essentially according to the procedure given in *Organic Syntheses*.[7]

5-bis(β-Hydroxyethyl)amino-2-pentanone. A mixture of 52.5 g. (0.5 mole) of diethanolamine and 30 g. (0.25 mole) of 5-chloro-2-pentanone in 125 ml. of absolute ethanol was gently refluxed for 48 hr. The volatile material was then removed by warming on a water bath under water pump suction. The residual mass was then cooled, treated with 40 ml. of water, and the solution was extracted repeatedly with chloroform. The combined chloroform extracts were dried

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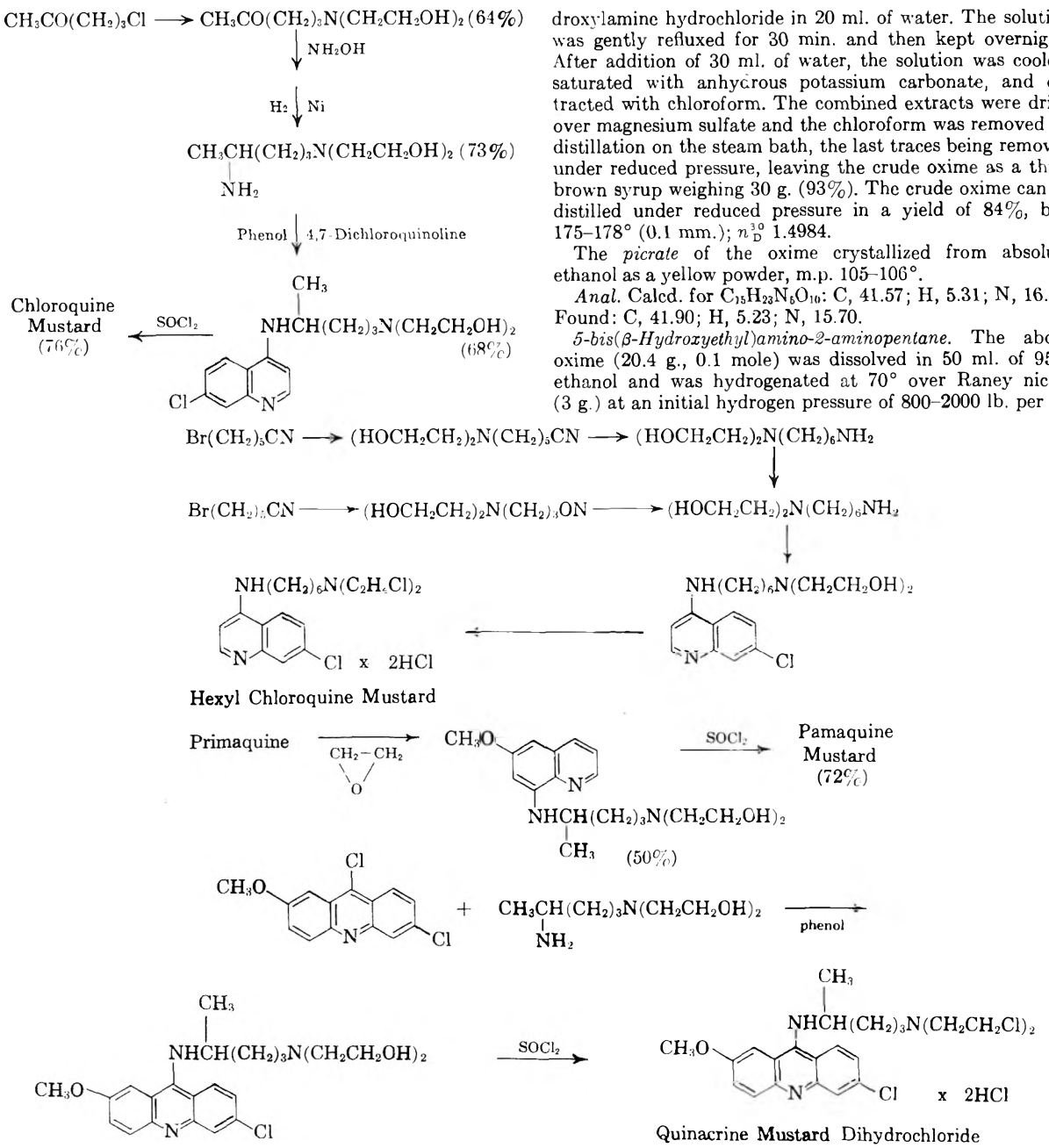
(3) L. H. Schmidt, *Survey of Antimalarial Drugs*, F. Y. Wiselogle, Ed., Edwards Bros., Ann Arbor, Mich., 1946, pp. 94, 106.

(4) (a) Hugh J. Creech, Lankenau Institute for Cancer Research, Fox Chase, Philadelphia 11, Pa.; (b) R. Jones, Jr., H. J. Creech, C. C. Price, A. K. Sen, R. M. Peck, R. F. Hankwitz, Jr., Ruth Rhines, Doris McKenzie, and W. F. Dunning, *Proc. Amer. Assoc. Cancer Research*, **2**, 132 (1956).

(5) All melting and boiling points are uncorrected. Microanalyses were carried out by Micro Tech Laboratories, Skokie, Ill. and Dr. Weiler and Dr. Strauss, Oxford, England.

(6) Obtained from Merck and Co., through the courtesy of Dr. Max Tishler.

(7) G. W. Cannon, R. C. Ellis, and J. R. Leal, *Org. Syntheses*, **31**, 74 (1951).



droxylamine hydrochloride in 20 ml. of water. The solution was gently refluxed for 30 min. and then kept overnight. After addition of 30 ml. of water, the solution was cooled, saturated with anhydrous potassium carbonate, and extracted with chloroform. The combined extracts were dried over magnesium sulfate and the chloroform was removed by distillation on the steam bath, the last traces being removed under reduced pressure, leaving the crude oxime as a thick brown syrup weighing 30 g. (93%). The crude oxime can be distilled under reduced pressure in a yield of 84%, b.p. 175–178° (0.1 mm.); n_D^{30} 1.4984.

The *picrate* of the oxime crystallized from absolute ethanol as a yellow powder, m.p. 105–106°.

Anal. Calcd. for $C_{15}H_{23}N_5O_{10}$: C, 41.57; H, 5.31; N, 16.16. Found: C, 41.90; H, 5.23; N, 15.70.

5-bis(β-Hydroxyethyl)amino-2-aminopentane. The above oxime (20.4 g., 0.1 mole) was dissolved in 50 ml. of 95% ethanol and was hydrogenated at 70° over Raney nickel (3 g.) at an initial hydrogen pressure of 800–2000 lb. per sq. in. The hydrogen consumption was completed in about 1–2 hours. The catalyst was filtered off, the ethanol removed, and the residue distilled under reduced pressure. The yield of 5-bis(β-hydroxyethyl)amino-2-aminopentane, b.p. 150° (0.5 mm.), was 15 g. (79%); n_D^{35} 1.4835.

Anal. Calcd. for $C_9H_{22}N_2O_2$: C, 56.80; H, 11.65. Found: C, 57.21; H, 11.61.

The *picrate* of the diamine, which separated from an ethanolic solution on seeding, was crystallized from a mixture of ethyl acetate and ethanol, m.p. 95–98°.

Anal. Calcd. for $C_{15}H_{25}N_5O_8$: C, 42.95; H, 6.01; N, 16.70. Found: C, 43.19; H, 5.98; N, 16.71.

7-Chloro-4-[4-bis(β-hydroxyethyl)amino-1-methylbutylamino)quinoline. A mixture of 9.4 g. (0.1 mole) of phenol, 9.5 g. (0.05 mole) of the above diamine and 9.9 g. (0.05 mole) of 4,7-dichloroquinoline[8] was stirred and heated at

over magnesium sulfate and the chloroform was removed on the steam bath, the last traces under reduced pressure. The residual crude amino ketone, which was obtained as a viscous oil, weighed 30.0 g. (63.5% based on chloropentanone). The crude amino ketone may be distilled under nitrogen in a short-path distillation apparatus and a moderate bath temperature (250–265°) to afford colorless oil, which darkens on standing, b.p. 148–150° (0.1 mm.), n_D^{29} 1.4739 and d_4^{20} 1.0592. The yield of the distilled ketone based on the crude ketone was 75–88%.

Anal. Calcd. for $C_9H_{19}O_3N$: C, 57.11; H, 10.12; N, 7.40. Found: C, 56.90; H, 10.07; N, 7.28.

The *2,4-dinitrophenylhydrazone* of the above ketone crystallized from ethanol as the hydrochloride in orange needles, m.p., 171–172°.

Anal. Calcd. for $C_{15}H_{24}N_5O_6Cl$: C, 44.39; H, 5.92; Cl, 8.75; N, 17.26. Found: C, 44.37; H, 6.60; Cl, 8.34; N, 16.90.

5-bis(β-Hydroxyethyl)amino-2-pentanone oxime. A 30-g. (0.158 mole) sample of the above amino ketone was added in portions to a chilled solution of 11.2 g. (0.16 mole) of hy-

(8) We are indebted to Sterling-Winthrop Research Institute for samples of 4,7-dichloroquinoline and primaquine diphosphate.

125° for 24 hr. The mixture was cooled to room temperature and a mixture of 10 ml. of acetic acid and 20 ml. of water was added. After stirring until complete solution was effected, the solution was cooled, made just alkaline with ammonia, and extracted with ether. The aqueous layer was then made strongly alkaline with ammonia and extracted with chloroform. The combined chloroform extracts were dried over potassium carbonate for 2 hr. and chloroform was removed as before. The residual oily 7-chloro-4-[4-bis(β-hydroxyethyl)amino-1-methylbutylamino]quinoline weighed 12 g. (68.3%).[9] The *picrate*, which separated from a mixture of ethyl acetate and ethanol, was crystallized from ethanol, m.p. 156–157°.

Anal. Calcd. for $C_{30}H_{32}ClN_9O_{16}$: C, 44.48; H, 3.98; N, 15.56. Found: C, 43.85; H, 4.09; N, 15.61.

7-Chloro-4-[4-bis(β-chloroethyl)amino-1-methylbutylamino]-quinoline dihydrochloride. A solution of 6.8 g. (0.057 mole) of thionyl chloride in 12 ml. of dry chloroform was added during 1 hr. to a solution of 10 g. (0.0284 mole) of 7-chloro-4-[4-bis(β-hydroxyethyl)amino-1-methylbutylamino]quinoline in 30 ml. of dry chloroform in a 200-ml. three-necked flask, kept immersed in an ice-salt bath and provided with a mercury-sealed stirrer, condenser, and dropping funnel. After the addition was over, the mixture was stirred at that temperature for 30 min. more and then 1 hr. on an oil bath at 70–75°. After cooling and adding 20 ml. of absolute ethanol, the mixture was stirred until solution was effected. The solution was diluted with 300 ml. of dry ether and kept overnight in the refrigerator. Supernatant liquid was decanted from the pasty mass, which, on trituration with fresh ether, transformed into a granular solid. This was filtered, washed with fresh dry ether, and dried in a vacuum desiccator. The dihydrochloride of the chloroquine mustard weighed 10 g. (76%). The compound decomposed above 60° but the point is not sharp and definite; λ_{max} (mμ), 222, 238, 251, 333, and 345; ε, 2.36×10^4, 1.43×10^4, 1.30×10^4, 1.23×10^4 and 1.20×10^4, respectively. For analysis the vacuum dessiccator dried sample was redried at 65° *in vacuo*, m.p. 110°, dec.

Anal. Calcd. for $C_{18}H_{24}Cl_3N_3 \cdot 2HCl$: C, 46.82; H, 5.68; N, 9.10; Cl, 38.40. Found: C, 45.15; H, 5.90; N, 8.60; Cl, 38.05.

Ionic chlorine, estimated conductimetrically by titrating with silver nitrate both before and after treatment with alkali, gave the following results:

Before alkali treatment, $C_{18}H_{24}Cl_3N_3 \cdot 2HCl$ requires: Cl, 15.38. Found: Cl, 15.00 to 15.57. After alkali treatment, $C_{18}H_{24}Cl_3N_3 \cdot 2HCl$ requires: Cl, 30.72. Found: Cl, 27.70 to 29.36.

The *dipicrylsulfonate*[10] of the quinoline mustard crystallized from acetone–petroleum ether to afford nearly colorless crystals, m.p. 150–153°, dec., but analysis of our best sample indicated less than two equivalents of picrylsulfonic acid in the salt.

Anal. Calcd. for $C_{30}H_{30}Cl_3N_9O_{18}S_2$: C, 36.99; H, 3.10; Cl, 10.91; N, 12.94; S, 6.58. Found: C, 38.26; H, 3.80; Cl, 10.86; N, 11.95; S, 5.68.

The *methylene bis(2-hydroxy-3-naphthoate)* was prepared by adding the calculated amount of chloroquine mustard dihydrochloride to a stirred solution of the bis-acid in an equivalent amount of aqueous sodium hydroxide. The precipitate, which could not be recrystallized, decomposed above 210°, with sintering. Although insoluble in water, this material is very difficult to dry completely.

Anal. Calcd. for $C_{41}H_{40}N_3O_6Cl_3$: C, 63.34; H, 5.19; N, 5.41; Cl, 13.69. Found: C, 63.37; H, 5.24; N, 5.22; Cl, 12.72.

6-Methoxy-8-[4-bis(β-hydroxyethyl)amino-1-methylbutylamino]quinoline. 6-Methoxy-8-(4-amino-1-methylbutylamino)quinoline was isolated from "Primaquine" phosphate[9] by suspending in water, adding excess ammonium hydroxide, and extracting with ether. A solution of 14 g. (0.32 mole) of ethylene oxide in 60 ml. of anhydrous methanol was added during 1 hr. to a solution of the primaquine base (30 g., 0.116 mole) in 180 ml. of anhydrous methanol, care being taken that the temperature did not rise above 10°. After the addition was over the mixture was left in the ice bath for an hour and then kept overnight at room temperature. The mixture was then gently refluxed for 4 hr. at a bath temperature of 65–70°, using acetone–dry ice in the condenser. A solution of 50 g. of picric acid in 250 ml. of ethanol was added to the above mixture. The dark oily material which separated gradually crystallized during 4 days' standing. This picrate was collected and recrystallized four times from 95% ethanol; yield, 46 g. (50%) m.p. 142–144°. A portion was twice more recrystallized for analysis, m.p. 145–147°.

Anal. Calcd. for $C_{31}H_{35}N_9O_{17}$: C, 46.21; H, 4.34; N, 15.65. Found: C, 46.37; H, 4.30; N, 15.70.

To generate the free base, the above picrate was decomposed with concentrated aqueous lithium hydroxide and extracted with ether. The combined ethereal extracts were dried over potassium carbonate for 2 hr. and the ether was removed, leaving 16 g. (40% based on primaquine base) of 6-methoxy-8-[4-bis(β-hydroxyethyl)amino-1-methylbutylamino]quinoline as a brown oil.

6-Methoxy-8-[4-bis(β-chloroethyl)amino-1-methylbutylamino]quinoline dihydrochloride. The method of preparation is the same as that described for the 7-chloro-4-amino analog. The compound, isolated in 72% yield, decomposed above 60°, and the point was also not sharp and definite. It was extremely hygroscopic and turned to a black tar in the presence of traces of moisture. By conductimetric titration of the chloride ion with standard silver nitrate solution, the equivalent weight was found to be 235.3, while that calculated for $C_{19}H_{27}Cl_2N_3O \cdot 2HCl$ is 228.5.

A portion was recrystallized from absolute ethanol–acetone mixture for analysis. The compound then melted with decomposition above 110°, with preliminary sintering.

Anal. Calcd. for $C_{19}H_{27}Cl_2N_3O \cdot 2HCl$: C, 49.89; H, 6.34; N, 9.19; Cl, 31.09. Found: C, 50.22, H, 6.47; N, 9.06; Cl, 28.23.

The *methylene bis(2-hydroxy-3-naphthoate)* was prepared by adding an absolute ethanolic solution of pamaquine mustard to an equivalent amount of a solution of the sodium salt of methylene bis(2-hydroxy-3-naphthoic acid) in absolute ethanol. After filtering off the insoluble material, the salt was precipitated by the addition of water. The sample was dried at 110° (1 mm.). It decomposed above 190°, with preliminary sintering.

Anal. Calcd. for $C_{42}H_{48}N_3O_7Cl_2$: C, 65.33; H, 5.61; N, 5.44; Cl, 9.18. Found: C, 65.46; H, 6.00; N, 5.33; Cl, 7.48.

7-Chloro-2-methyl-4-[4-bis(β-hydroxyethyl)amino-1-methylbutylamino]quinoline. The compound was prepared essentially according to the procedure described for the chloroquine analog, from 9.4 g. (0.10 mole) of phenol, 9.5 g. (0.05 mole) of the diamine and 10.6 g. (0.05 mole) of 2-methyl-4,7-dichloroquinoline, in a yield of 12.5–13 g. (70–75%). For crystallization the oil was dissolved in acetone (charcoal) and allowed to stand at room temperature when the diol crystallized out during slow evaporation of the solvent. For analysis the material was crystallized from ethyl acetate containing traces of ethanol, m.p. 140–141°.

Anal. Calcd. for $C_{19}H_{28}N_3ClO_2$: C, 62.36; H, 7.71; N, 11.50. Found: C, 61.86; H, 8.27; N, 11.02.

7-Chloro-2-methyl-4-[4-bis(β-chloroethyl)amino-1-methylbutylamino]quinoline dihydrochloride. The above crystallized diol was converted to the corresponding mustard derivative as the dihydrochloride in the same way as described for the chloroquine analog in a yield of 89%. A portion dried under 1 mm. pressure at 60° decomposed slowly over 130°.

Anal. Calcd. for $C_{19}H_{28}N_3Cl_5$: C, 47.96; H, 5.93; N, 8.83; Cl, 37.28. Found: C, 46.76; H, 5.99; N, 8.21; Cl, 37.87.

(9) Dr. B. F. Tullar, of Winthrop-Sterling Research Institute, succeeded in crystallizing the diol from ethyl acetate, m.p. 120–124° (Private communication).

(10) Prepared according to the procedure reported by C. Golumbic, J. S. Fruton, and M. Bergmann, *J. Org. Chem.*, 11, 518 (1946).

When a solution of this material in dry ethanol and acetone was kept at −10° for two weeks, crystals separated which decomposed slowly above 135°: λ_{max} (mμ), 341, 330, 250 and 223; ε (× 10^{-4}), 1.717, 1.654, 1.874 and 3.04, respectively.

Anal. Found: C, 47.20; H, 6.42; N, 8.87; Cl, 35.46.

2-Methoxy-6-chloro-9-[4-bis(β-hydroxyethyl)amino-1-methylbutylamino]acridine dihydrochloride. To a solution of 5.6 g. (0.02 mole) of 2-methoxy-6,9-dichloroacridine in 24 g. of phenol, 3.8 g. (0.02 mole) of the diamine was added and the mixture was heated with occasional shaking on a steam bath for 5 hr. The cooled solution was then poured into 150 ml. of cold 10% aqueous sodium hydroxide solution and the product extracted with chloroform. The organic layer was then extracted with dilute acetic acid. The acid solution was made alkaline with ammonia and again extracted with chloroform. The chloroform solution was dried with potassium carbonate for 2 hr. and chloroform removed, leaving 6.5 g. (76%) of residual highly viscous oil. The oil was dissolved in a minimum amount of boiling ethyl acetate and, on cooling, deposited yellow crystalline solid. The compound was recrystallized from acetone, m.p. 136–137°.

Anal. Calcd. for $C_{23}H_{30}N_3ClO_3$: C, 63.95; H, 7.00; N, 9.73. Found: C, 63.63; H, 7.32; N, 9.23.

To a solution of a portion of the oily base in absolute ethanol, concentrated hydrochloric acid was added until acidic to Congo Red when the compound crystallized out on cooling and scratching as the *dihydrochloride*. Ether was added to facilitate filtration and the material was collected and recrystallized from absolute ethanol, m.p. 217–218°.

Anal. Calcd. for $C_{23}H_{30}N_3ClO_3 \cdot 2HCl$: C, 54.71; H, 6.39; N, 8.32. Found: C, 54.20; H, 6.99; N, 8.31.

When the *dihydrochloride* was recrystallized from a mixture of 95% ethanol and ether, the compound melted at 209–210°. On analysis, a molecule of water was indicated.

Anal. Calcd. for $C_{23}H_{30}N_3ClO_3 \cdot 2HCl \cdot H_2O$: C, 52.82; H, 6.55; N, 8.03. Found: C, 52.55; H, 6.70; N, 7.94.

2-Methoxy-6-chloro-9-[4-bis(β-chloroethyl)amino-1-methylbutylamino]acridine dihydrochloride. The method of preparation was the same as that described for chloroquine mustard; yield, 97%. For crystallization, a portion was dissolved by stirring in absolute ethanol. Dry acetone was added to turbidity and, after keeping at −10° for a week, the yellow crystals were collected. On heating, these softened at 147–148°, with early shrinkage, and then slowly began to decompose: λ_{max} (mμ) 234, 283 and 345: log ε; 4.140, 4.692 and 3.758, respectively.

Anal. Calcd. for $C_{23}H_{30}N_3Cl_5O$: C, 50.99; H, 5.58; N, 7.75; Cl, 32.72. Found: C, 51.29; H, 5.78; N, 8.39; Cl, 32.45.

Conductimetric titration of chloride ion with silver nitrate solution, before and after alkali treatment, gave the following results. Before alkali treatment: Calcd. Cl, 13.11. Found: Cl, 12.98. After alkali treatment: Calcd. Cl, 26.22. Found: Cl, 26.39.

ε-Bis(β-hydroxyethyl)aminocapronitrile. A mixture of 44.0 g. (0.25 mole) of ε-bromocapronitrile[11] and 52.5 g. (0.5 mole) of diethanolamine in 100 ml. of absolute ethanol was heated under reflux for 48 hr. The solvent was then removed under reduced pressure, the residual mass was cooled, treated with 25 ml. of cold water, and the solution was extracted with 100-ml. and four 40-ml. portions of chloroform. The combined chloroform extracts were dried over magnesium sulfate. The solvent was removed and the residual oil was distilled under reduced pressure. The yield of ε-bis(β-hydroxyethyl)aminocapronitrile, b.p. 167–172° (0.1 mm.), was 25 g. (50% based on nitrile). On redistillation the product boiled at 162° (0.08 mm.); n_D^{30} 1.4744.

Anal. Calcd. for $C_{10}H_{20}N_2O_2$: C, 59.98; H, 10.06; N, 13.99. Found: C, 60.09; H, 9.94; N, 14.00.

6-bis(β-Hydroxyethyl)amino-1-aminohexane. A mixture of 20 g. (0.1 mole) of ε-bis(β-hydroxyethyl)aminocapronitrile and 3 g. of Raney nickel (W-2) in 50 ml. of absolute ethanol and 5 ml. of 10% alcoholic ammonia was shaken with hydrogen at 50 p.s.i. The theoretical amount of hydrogen was taken up in 5 hr. The catalyst was separated, solvent removed, and the residue distilled under reduced pressure. The yield of 6-bis(β-hydroxyethyl)aminohexyl amine, b.p. 155–157° (0.3 mm.), was 14.0 g. (75%). On redistillation, the product had a boiling point of 153° (0.2 mm.); n_D^{26} 1.4885.

Anal. Calcd. for $C_{10}H_{24}N_2O_2$: C, 58.79; H, 11.84; N, 13.72. Found: C, 58.86; H, 11.74; N, 13.78.

7-Chloro-4-[6-bis(β-hydroxyethyl)aminohexylamino]quinoline. The method of preparation was essentially the same as that described for chloroquine diol. For final extraction, two 100-ml. and six 60-ml. portions of chloroform were used as the present compound was not very soluble at ordinary temperatures. After removal of chloroform, the residue in the flask solidified *en masse* and was recrystallized from the same solvent; yield 60%, m.p. 128–130°.

Anal. Calcd. for $C_{19}H_{28}N_3ClO_2$: C, 62.36; H, 7.71; N, 11.48; Cl, 9.69. Found: C, 62.26; H, 8.01; N, 11.39; Cl, 9.96.

7-Chloro-4-[6-bis(β-chloroethyl)aminohexylamino]quinoline dihydrochloride. The above diol was converted to the mustard derivative exactly in the same way as described for chloroquine mustard. The crude compound, which was very hygroscopic and which decomposed slowly above 70°, was recrystallized from absolute ethanol–acetone mixture. The recrystallized product, which was not hygroscopic, melted at 175–176°.

Anal. Calcd. for $C_{19}H_{28}N_3Cl_5$: C, 47.96; H, 5.93; N, 8.83; Cl, 37.28. Found: C, 48.20; H, 6.09; N, 8.66; Cl, 35.98.

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(11) ε-Bromocapronitrile, b.p. 115–117°, (6 mm.) was prepared in several steps starting from cyclohexanone, essentially as described by D. S. Breslow and C. R. Hauser, *J. Am. Chem. Soc.*, **67**, 686 (1945).

[CONTRIBUTION FROM THE ROHM & HAAS COMPANY]

Base-Catalyzed Reaction of 2-Alkylaminoethanols with Acrylic and Methacrylic Esters[1]

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The reaction of 2-alkylaminoethanols with acrylic and methacrylic esters depends on the nature of the alkyl substituent. The 2-*t*-alkylaminoethanols give the corresponding *t*-alkylaminoethyl esters, but with less highly branched 2-alkylaminoethanols there is a predominance of amide-forming side-reactions which lead to high-boiling mixtures.

The base-catalyzed reaction of 2-dialkylaminoethanols with acrylic and methacrylic esters yields the corresponding 2-dialkylaminoethyl esters, by simple transesterification.[3] The secondary amino groups which are present in monoalkylaminoethanols should bring about a much more complicated reaction. The formation of the *N*-methyl-*N*-2-hydroxyethyl amide is reported in one case from the reaction of a carboxylic ester with 2-methylaminoethanol in the presence of sodium methoxide.[4] Amide formation can therefore be expected to be a major factor. Addition to the acrylic unsaturation may also occur. Addition of secondary amines to acrylic esters is particularly easy. This reaction is usually much slower with methacrylic esters. The base-catalyzed addition of hydroxyl groups to acrylic unsaturation can also occur.[5]

The reaction of several 2-alkylaminoethanols with methyl methacrylate in the presence of aluminum isopropoxide catalyst was studied using the customary transesterification procedures. The extent to which the possible reactions took place was controlled very largely by the nature of the *N*-alkyl substituent. This can best be seen by examining the reactions of three 2-alkylaminoethanols of increasing complexity (methyl, isopropyl and *t*-butyl) with methyl methacrylate. These are therefore given in detail in the experimental section.

The products obtained from 2-methyl- and 2-isopropylaminoethanol were high-boiling mixtures which had high neutralization equivalents, indicating a predominance of the amide-forming reaction. They were low in nitrogen content, indicating further transesterification of the hydroxy amide with another mole of the acrylic ester. All of the distilled fractions had low hydrogenation equivalents, showing little addition to the double bond. Large residues were always present. These may in part have resulted from vinyl polymerization, but condensation polymerization was probably involved. This would occur by addition of secondary amine or alcohol groups to the double bond, with accompanying transesterification and amide-forming reaction. A small fraction (b) was obtained from 2-isopropylaminoethanol which had the expected boiling point for the aminoethyl ester, but this could not be purified.

In contrast, a single distilled product, 2-*t*-butylaminoethyl methacrylate was obtained from 2-*t*-butylaminoethanol in good yield and purity. This structure was established by elementary analysis, neutralization equivalent, and determination of unsaturation by hydrogenation. The distillation residues obtained were relatively small. The small amount of high-boiling by-products and residue indicates that the addition of amine and the amide-forming reaction occurred to a negligible extent. By inference, since the hydroxyl group of the amino alcohol should behave independently of the nature of the *N*-substituent, the addition through the hydroxyl group can be accounted minor in all three reactions. The absence of large residues also shows that vinyl polymerization was probably well-controlled in all three reactions.

A consideration of the kinetic behavior of *t*-butylamine in the two interfering reactions (no data are available for 2-*t*-butylaminoethanol) explains the isolation of this ester in good yield. *t*-Butylamine reacts very poorly with esters;[6] its addition to methyl methacrylate is slow when compared with the addition of other primary amines.[7]

Base-catalyzed reactions of *t*-butylaminoethanol with acrylic esters and other methacrylic esters were equally successful. Examples of other effective catalysts were metallic sodium, sodium methoxide, and tetra-*n*-butyl titanate. The reaction was equally good with other 2-*t*-alkylaminoethanols of which 2-(1,1,3,3-tetramethylbutyl)aminoethanol is representative (Table I).

The hydrochlorides of a number of 2-alkylam-

(1) Given at the 130th Meeting of the American Chemical Society, Atlantic City, N. J., September, 1956.

(2) Present address: Department of Chemistry, Massachusetts Institute of Technology, Cambridge 39, Mass.

(3) (a) G. Graves, U.S. Patent **2,138,763**; *Chem. Abstr.*, **33**, 2147 (1939); (b) C. E. Rehberg and W. A. Faucette, *J. Am. Chem. Soc.*, **71**, 3164 (1949).

(4) R. F. Feldkamp and J. A. Faust, *J. Am. Chem. Soc.*, **71**, 4012 (1949).

(5) E. H. Riddle, *Monomeric Acrylic Esters*, Reinhold Publishing Co., New York, N. Y., 1954, pp. 146, 154.

(6) E. McC. Arnett, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, **72**, 5635 (1950).

(7) L. S. Luskin, M. J. Culver, G. E. Gantert, W E Craig, and R. S. Cook, *J. Am. Chem. Soc.*, **78**, 4044 (1956).

TABLE I

PREPARATION OF 2-*t*-ALKYLAMINOETHYL ESTERS, $CH_2{=}C(R^1)COOCH_2CH_2NHR^2$

R^1	R^2	Empirical Formula	Yield, %	B.P., °C.[a]	Mm.	n_D^{25}	d_4^{25}	Anal., % N Calcd.	Anal., % N Found	Equivalent Weight NE[b]	Equivalent Weight HE[b]
CH_3	$(CH_3)_3C$	$C_{10}H_{19}O_2N$	80[c]	100–105	12	1.4401	0.9165	7.6	7.6	185	192
CH_3	C_8H_{17}[d]	$C_{14}H_{27}O_2N$	63	135–138	12	1.4535	0.9130	5.8	5.8	241	254
H	$(CH_3)_3C$	$C_9H_{17}O_2N$	66	84–87	12	1.4396	0.9305	8.2	8.5	166	176
H	C_8H_{17}[d]	$C_{13}H_{25}O_2N$	43	129–131	12	1.4520	0.9175	6.2	6.3	224	228

[a] On redistilled samples. Yields are on basis of slightly less pure fractions, as determined by neutralization and hydrogenation equivalents. [b] NE is equivalent weight by titration with aqeuous HCl, HE is equivalent weight as determined by quantitative hydrogenation. Bromine number is also a satisfactory way to determine unsaturation. [c] Yield with sodium metal, 45%; with sodium methoxide, 61%; with tetra-*n*-butyl titanate, 79%. All yields in the table are given as obtained with aluminum isopropoxide catalyst. [d] 1,1,3,3-Tetramethylbutyl.

inoethyl esters have been prepared by the reaction of acid chlorides with 2-alkylaminoethanol hydrochlorides.[8] By neutralization and careful isolation, some of these have been obtained as the free amino esters, which have been distilled.[8b] However, they rearranged on standing, at a rate dependent on their structure, to the corresponding hydroxyethylamides.[8b,c]

A sample of 2-*t*-butylaminoethyl methacrylate which had been stored for six months in a refrigerator was redistilled and almost all of the compound was recovered. The residue appeared to be vinyl polymer. This ester appears to be considerably more stable than other reported 2-alkylaminoethyl esters.

These new monomers could be polymerized in solution or in bulk by heating with a small amount of azoisobutyronitrile initiator; 2-*t*-butylaminoethyl methacrylate, for example, yielded a hard, colorless, transparent polymer.

EXPERIMENTAL

Raw materials. The 2-alkylaminoethanols were prepared by the addition of ethylene oxide to the corresponding primary amines.[9] Other chemicals used were commercial materials.

Reaction of 2-alkylaminoethanols with methyl methacrylate. General procedure. A mixture of methyl methacrylate (100 g., 1 mole), 2-alkylaminoethanol (0.5 mole), di-β-naphthol inhibitor (6.7 g.), and aluminum isopropoxide (1 g.) was brought to reflux and carefully distilled through a 6-inch Vigreux column equipped with a total reflux-partial take-off stillhead. When the temperature at the stillhead reached 65°, the methanol-methyl methacrylate azeotrope was collected, using a reflux ratio such as to maintain the temperature of distillation below 70°. The elapsed time of distillation was approximately 24 hr. At the end, the temperature rose to the boiling point of methyl methacrylate. Determination of the saponification number of the distillates gave the per cent of methyl methacrylate. The rest of the material was assumed to be methanol. About 80% of the theoretical amount of methanol was recovered. The product was then distilled through a 12-inch packed column and fractions taken as noted. Data are given on the basis of grams per 100 grams of starting alkylaminoethanol. Analytical data obtained were NE (equivalent weight by acid titration), HE (equivalent weight by quantitative hydrogen absorption) and % N. *With methylaminoethanol*[9a] calcd. for $C_7H_{13}O_2N$,[10] mol. wt. 143, % N 9.8. Fraction (a) 10 g., b.p. 44–58° (1 mm.), NE, 257; HE, 359; % N 8.1. (b) 22 g., b.p. 58–123° (0.8 mm.), NE, 495; HE, 141; % N 7.7. (c) 15.9 g., b.p. 123° (0.8 mm.), NE, 1829; HE, 167; % N 7.3. (d) 20.7 g., b.p. 123–126° (1 mm.), NE, 1735; HE, 150; % N 7.1. (e) 16.0 g., b.p. 126–145° (1.5 mm.), NE, 831; HE, 135; % N 7.4. (f) residue 83 g. *With isopropylaminoethanol*[9b] calcd. for $C_9H_{17}O_2N$,[10] mol. wt. 171, % N, 8.2. Fraction (a) 13.8 g., b.p. 99–113° (28 mm.), % N, 11.2. (b) 19 g., b.p. 115° (28 mm.), NE, 221; HE, 285; % N, 9.0. (c) 3.5 g., b.p. 115–155° (28 mm.). (d) 30.2 g., b.p. 155–185° (28 mm.), NE, 821; HE, 257; % N, 6.6. (e) 10.0 g., b.p. 185° (28 mm.), % N, 6.4. (f) residue 70.5 g. *With t-butylaminoethanol*[9c] calcd. for $C_{10}H_{19}O_2N$,[10] mol. wt. 185; % N, 7.6. Fraction (a) 19.5 g., b.p. 105–116° (30 mm.), NE, 165; % N, 8.5. (b) 20.4 g., b.p. 117° (30 mm.), NE, 183; %N, 7.8. (c) 56 g., b.p. 120° (30 mm.), NE, 185; HE, 198; % N 7.5. (d) 6.0 g., b.p. 122° (30 mm.), NE, 190; HE, 181; % N, 7.5. (e) 11.0 g., b.p. 122–127° (30 mm.), NE, 242; HE, 155; % N, 5.6. (f) residue 19.0 g. The product fractions b, c, and d therefore distilled at 117–122° (30 mm.), and amounted to 82.4 g. from 100 g. *t*-butylaminoethanol (52%). Yields as high as 80% were obtained in later runs.

Reactions were carried out using sodium methoxide or tetra-*n*-butyl titanate in essentially the same manner. It was later found advantageous to dry the starting materials by refluxing the reaction mixture before adding the catalyst, and removing a small forerun. When metallic sodium was used as a catalyst, it was dissolved in the *t*-butylaminoethanol before the addition of the methyl methacrylate.

t-Butylaminoethyl acrylate. A mixture of *t*-butylaminoethanol[9c] (58.5 g., 0.5 mole), methyl acrylate (86 g., 1 mole), di-β-naphthol (7.2 g., 0.025 mole) and aluminum isopropoxide (1 g.) was distilled as described previously. After about 10 hr. distillation, there was obtained a fraction amounting to 29 g., b.p. 65–78°. The temperature of the distillate then was constant at 78°, the boiling point of methyl acrylate. Distillation was continued under reduced pressure. After removal of a small forerun, the product (56 g., 66%) was collected at 90–100° (13 mm.). On careful redistillation, the pure product, b.p. 84–87°/12 mm., was obtained.

2-(1,1,3,3-Tetramethylbutyl)aminoethyl acrylate. A mixture

(8) (a) J. S. Pierce, J. M. Salsbury, and J. M. Frederickson, *J. Am. Chem. Soc.*, **64**, 1691 (1942); (b) A. C. Cope and E. M. Hancock, *J. Am. Chem. Soc.*, **66**, 1448, 1738 (1944); (c) J. R. Reasenberg and S. D. Goldberg, *J. Am. Chem. Soc.*, **67**, 933 (1945).

(9) (a) L. Knorr and H. Matthes, *Ber.*, **31**, 1069 (1898); (b) H. Matthes, *Ann.*, **316**, 312 (1901); (c) N. Bortnick, L. S. Luskin, M. D. Hurwitz, W E Craig, L. J. Exner, and J. Mirza, *J. Am. Chem. Soc.*, **78**, 4040 (1956).

(10) The empirical formula corresponds to the sum of the atoms in the starting materials less a mole of methanol.

of 2-(1,1,3,3-tetramethylbutyl)aminoethanol[9c] (173 g., 1 mole), ethyl acrylate (200 g., 2 moles), di-β-naphthol (14 g.) and aluminum isopropoxide (2 g.) was distilled as before. There was collected 53 g., b.p. 74–80°, over a period of 21 hr. and then the temperature was allowed to rise and 74 g. of excess ethyl acrylate was collected, b.p. 80–95° over the next 6 hr. The product was then distilled and 135 g. (59%), b.p. 140–147° (25 mm.) was collected. A residue of 69 g. remained in the flask.

2-(1,1,3,3-Tetramethylbutyl)aminoethyl methacrylate. The procedure given above for the corresponding *t*-butylaminoethyl methacrylate was followed. On distillation of the product there was obtained a small forerun boiling 115–125° (9 mm.) which was apparently a mixture of the aminoethanol and the methacrylate. The product (63%) was collected at 125–132° (9 mm.).

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE UNION OIL COMPANY OF CALIFORNIA]

Synthesis of Unsymmetrical Trialkyl Phosphorotetrathioates

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Mercaptans react with phosphorus pentasulfide to give, among other products, alkyl phosphenotrithioates, dialkyl hydrogen phosphorotetrathioates, and trialkyl phosphorotetrathioates. This paper is concerned with the use of these reactions, as well as the addition of olefins to dialkyl hydrogen phosphorotetrathioates, to produce unsymmetrical trialkyl phosphorotetrathioates.

Infrared spectra of these compounds were helpful in their identification.

Trialkyl phosphorotetrathioates are organophosphorus compounds of the general structure $(RS)_3PS$. They are classified as symmetrical if all the R groups are identical; unsymmetrical if at least one R group is dissimilar.

A few compounds of this type are described in the literature. Schulze, Short, and Crouch prepared several tri-*t*-alkyl phosphorotetrathioates from phosphorus pentasulfide and *t*-alkyl mercaptans.[1] Triethyl phosphorotetrathioate, tri-*t*-amyl phosphorotetrathioate, tribenzyl phosphorotetrathioate, tri-*p*-tolyl phosphorotetrathioate, and triphenyl phosphorotetrathioate are described by Kosolapoff,[2] and tridodecyl phosphorotetrathioate is discussed by Salzberg and Werntz in a patent.[3] Methods of preparing these compounds include the reactions of mercaptans or sodium mercaptides with thiophosphoryl chloride, of mercaptans with alkyl phosphenotrithioates ($RSPS_2$), as well as of mercaptans with phosphorus pentasulfide.[4] Reference 2 is a general reference for all these reactions.

From the known reactivity of the alkyl phosphenates,[5] it appeared that if the corresponding alkyl phosphenotrithioates could be prepared easily they could become key intermediates in the synthesis of a wide variety of organophosphorus compounds. This paper, part of such a program, is concerned with unsymmetrical trialkyl phosphorotetrathioates prepared from methyl phosphenotrithioate as the intermediate.

The pertinent reactions in the preparation of unsymmetrical trialkyl phosphorotetrathioates are

$$2CH_3SH + P_2S_5 \longrightarrow 2CH_3SPS_2 + H_2S \qquad (1)$$

$$CH_3SPS_2 + RSH \longrightarrow \begin{matrix} CH_3S \\ | \\ P(S)SH \\ | \\ RS \end{matrix} \qquad (2)$$

$$\begin{matrix} CH_3S \\ RS \end{matrix}\!\!>\!P(S)SH + \text{olefin} \longrightarrow \begin{matrix} CH_3S \\ RS \end{matrix}\!\!>\!P(S)SR' \qquad (3)$$

Methyl mercaptan can react with phosphorus pentasulfide to yield a number of products. The simplest route to methyl phosphenotrithioate is shown in reaction (1), in which two moles of the mercaptan react with one mole of phosphorus pentasulfide. As the ratio of mercaptan to phosphorus pentasulfide increases, reactions (4) and (5) assume importance and eventually predominate.

$$4CH_3SH + P_2S_5 \longrightarrow 2(CH_3S)_2P(S)SH + H_2S \qquad (4)$$

$$6CH_3SH + P_2S_5 \longrightarrow 2(CH_3S)_3PS + 3H_2S \qquad (5)$$

The use of excess phosphorus pentasulfide results in a higher yield of methyl phosphenotrithioate

$$(CH_3S)_3PS + P_2S_5 \longrightarrow 3CH_3SPS_2 \qquad (6)$$

By using the proper amounts of reactants, and by carefully controlling the release of hydrogen sulfide, reaction (1) can provide at least 60 mole percent yields of methyl phosphenotrithioate. Control of hydrogen sulfide enhances the yield because of the possibility of reaction (7).

$$CH_3SPS_2 + H_2S \longrightarrow CH_3SP(S)(SH)_2 \qquad (7)$$

A simple way to achieve this control is to run reac-

(1) W. A. Schulze, G. H. Short, and W. W. Crouch, *Ind. Eng. Chem.*, **42**, 916 (1950).

(2) G. M. Kosolapoff, *Organophosphorus Compounds*, pp. 259, 260, 262, 346, John Wiley & Sons, Inc., New York, N. Y., 1950.

(3) P. L. Salzberg and J. H. Werntz (to E. I. du Pont de Nemours & Co.), U. S. Patent 2,063,639, Dec. 8, 1936.

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TABLE I

SYMMETRICAL TRIALKYL PHOSPHOROTETRATHIOATES

Phosphorotetrathioate	Mercaptan, Moles	P_2S_5, Moles	Reaction Temp., °C.	Reaction Pressure, P.S.I.G.	Reaction Time, Hours	Boiling Point of Product, °C./Mm.	Conversion Based on P_2S_5, Mole %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Phosphorus, % Calcd.	Phosphorus, % Found	Sulfur, % Calcd.	Sulfur, % Found
$(CH_3S)_3PS$	42	3.5	100	195	6	126–130/0.2	86	17.7	17.1	4.4	4.3	15.2	15.1	62.7	62.8
$(C_2H_5S)_3PS$	15	3	100	0	14	110/0.15	46	29.3	28.8	6.1	6.3	12.6	12.6	52.0	51.8
$(CH_3CH_2CH_2S)_3PS$	8.2	2	100	0	5	136–137/0.15	38	37.5	37.1	7.3	7.4	10.8	10.9	44.4	44.6
$\left(\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!CH\!-\!S\right)_3\!PS$	3	0.5	70	0	40	123–125/0.3	79	37.5	36.6	7.3	7.4	10.8	10.7	44.4	44.7

[a] Based on distilled product.

TABLE II

UNSYMMETRICAL TRIALKYL PHOSPHOROTETRATHIOATES

Phosphorotetrathioates	CH_3SPS_2, Moles	Mercaptan, Moles	Olefin, Moles	Reaction Temp., °C.[a,b]	Reaction Time, Hours[c]	Boiling Point of Product, °C./Mm.[d]	Conversion, Mole %[e]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Phosphorus, % Calcd.	Phosphorus, % Found	Sulfur, % Calcd.	Sulfur, % Found
$(CH_3S)_2P(S)\!-\!SC_2H_5$	0.62	CH_3SH 0.62	$CH_2{=}CH_2$ excess[f]	40 95	3 2	135–139/1.0	34	—	—	—	—	—	—	—	—
$CH_3S\!-\!P(S)(SC_2H_5)\!-\!S\!-\!CH(CH_3)_2$	0.37	C_2H_5SH 0.37	$CH_2{=}CHCH_3$ 1.0	25–28 100	66 16	105–115/0.2	15	29.2	26.9	6.1	5.9	12.6	12.8	52.1	53.2
$(CH_3S)_2P(S)\!-\!SCH(CH_3)_2$	0.5	CH_3SH 0.15	$CH_2{=}CHCH_3$ 1.0	40 80–110	21.5 2.5	125–130/0.8	22	25.8	26.0	5.6	5.7	13.4	13.7	55.2	55.2
$(CH_3S)_2P(S)\!-\!S\!-\!CH(CH_3)\!-\!C_4H_9$	0.5	CH_3SH 0.5	$CH_2{=}CHC_4H_9$ 1.0	40 100	16 16	Did not distill	100	35.0	33.4	6.9	6.1	11.3	12.2	46.8	47.8
$CH_3S\!-\!P(S)(SC_2H_5)_2$	0.37	C_2H_5SH 0.37	$CH_2{=}CH_2$ excess[f]	25–28 100–150	66 18	109–129/0.5	34	25.8	24.4	5.6	5.7	13.4	14.2	55.2	56.3
$CH_3SP(S)\left(S\!-\!CH\!<\!\begin{matrix}CH_3\\CH_3\end{matrix}\right)_2$	0.75	i-C_3H_7SH 0.75	$CH_2{=}CHCH_3$ 1.0	34 100	2 1.5	130–135/0.6	45	32.3	31.6	6.5	6.8	11.9	11.7	49.3	49.0

[a] First number is temperature of reaction of CH_3SPS_2 with RSH. Second number is temperature of addition of olefin. [b] Pressures were autogeneous. [c] First number is time of reaction of CH_3SPS_2 and RSH. Second number is time of addition of olefin. [d] All distillations were in a small Claisen flask equipped with Vigreux-type indentations. [e] Based on $CH_3S\!-\!P(S)(R)\!-\!SH$ and amount of distilled product. Some decomposition during distillation. [f] 300-ml. bomb at 500 p.s.i.g./25°, 3000 p.s.i.g./95°.

tion (1) in an inert solvent under conditions of pressure and temperature such that refluxing is continuous, yet hydrogen sulfide cannot liquefy in the condenser.

Reaction (2) is analogous to reaction (7) in that methyl phosphenotrithioate combines very readily with mercaptans to form methyl alkyl hydrogen phosphorotetrathioates. These compounds are moderately unstable and very reactive. They can be handled and stored in inert solvents for several weeks, but isolation for more than a few hours results in a slow decomposition, apparently back to the mercaptan and phosphenotrithioate. Exposure to air or moisture causes the rapid formation of an unidentified syrup, hydrogen sulfide, and possibly some methyl mercaptan.

In reaction (3) the olefins add according to Markownikoff's rule, *i.e.*, 1-olefins add in the 2-position. The additions of dialkyl hydrogen phosphorotetrathioates to olefins were so nearly quantitative that distillations usually were unnecessary. In most cases vacuum stripping to remove solvent gave a material indistinguishable from distilled product. This was fortunate because many of these compounds have poor thermal stability.

Trimethyl, triethyl, tri-*n*-propyl, and tri-*i*-propyl phosphorotetrathioates were prepared by the classical reaction of mercaptans and phosphorus pentasulfide. The infrared spectra of these known compounds, as well as the spectra of several mercaptans, dialkyl sulfides and dialkyl disulfides greatly assisted in the characterization of the unsymmetrical phosphorotetrathioates.[6]

EXPERIMENTAL

Preparation of methyl phosphenotrithioate. The apparatus consisted of a 1-gal. stainless steel autoclave fitted with stirrer, reflux condenser, and back-pressure controller. Dry phosphorus pentasulfide, 1110 g. (5 moles), was placed in the autoclave, followed by a solution of 432 g. (9 moles) of methyl mercaptan in 2000 ml. of toluene. The system was held at 100–110 p.s.i.g. and 125–150° for 20 hr. Hydrogen sulfide evolution was rapid during the first hour, but ceased almost entirely after 2 hr. Rapid draining of the autoclave, followed by filtration while the products were still hot, gave 140 g. (0.63 mole) of unreacted phosphorus pentasulfide. Crude methyl phosphenotrithioate crystallized from the toluene upon cooling to room temperature. Recrystallization from benzene gave 953 g. (67%) of large, yellow plates, m.p. 112° (uncorr.) with partial softening at 68° and 102°.

This reaction time was dictated by convenience only. The true reaction time appears to be less than 4 hr., but no serious attempts were made to define optimum conditions.

Anal. Calcd. for CH_3PS_3: C, 8.4; H, 2.1; P, 21.8; S, 6.7. Found: C, 8.4; H, 2.6; P, 21.6; S, 64.1. Considerable difficulties were encountered in analyzing all the samples in this work. The formation of glassy, fireproof masses tended to cause errors in the burning procedures.

Preparation of dimethyl hydrogen phosphorotetrathioate. The reaction vessel was a 500 ml. Parr hydrogenation bottle closed with a rubber stopper. Stirring was achieved by rotating the bottle end-over-end. Heat was supplied by a heat lamp. A mixture of 48 g. (1 mole) methyl mercaptan, 142 g. (1 mole) methyl phosphenotrithioate, and 200 ml. of inert solvent was tumbled in the bottle for 3 hr. or more at a temperature of 30–50°. The product was isolated by removing the solvent under vacuum.

When the solvent was carbon disulfide, ether, or an aromatic, a homogeneous solution was formed. When a paraffinic solvent was used, two liquid phases were formed. The lower phase was acid contaminated with solvent, and the upper phase was solvent contaminated with acid. Because of the instability of the acid, it was difficult to obtain in a pure form, thereby complicating elemental analyses.

Anal. Calcd. for $C_2H_7PS_4$: C, 12.6; H, 3.7; S, 67.4. Found: C, 14.2; H, 4.2; S, 61.3.

Preparation of methyl ethyl hydrogen phosphorotetrathioate. A mixture of 62 g. (1 mole) ethyl mercaptan, 142 g. (1 mole) methyl phosphenotrithioate, and 300 ml. of Skellysolve B was stirred at room temperature for 68 hr. Removal of the Skellysolve left a light yellow oil still containing traces of solvent.

Preparation of methyl i-propyl and methyl n-propyl hydrogen phosphorotetrathioates. Equimolar mixtures of methyl phosphenotrithioate and the appropriate mercaptan were refluxed for 2 hr. in an equal volume of ether. Removal of the ether *in vacuo* gave the crude acids.

Preparation of trimethyl phosphorotetrathioate. The apparatus was the same as for methyl phosphenotrithioate. Excess methyl mercaptan was used to suppress side reactions. Phosphorus pentasulfide, 778 g. (3.5 moles), was placed in the autoclave, nitrogen added to 100 p.s.i.g., and 2020 g. (42 moles) methyl mercaptan pumped in. With the back-pressure controller set at 195 p.s.i.g., refluxing began when the temperature in the autoclave reached 74° accompanied by a heavy evolution of hydrogen sulfide. The temperature in the autoclave was raised to 93° over a period of 2.5 hr. Gas evolution decreased steadily, but the excess mercaptan was kept at reflux throughout the entire run. After 3.5 hr. at 93° the excess mercaptan was removed by reducing the pressure to 1 atm. Distillation of the product through a 12 inch helix-packed column gave 1226 g. (86%), b.p. 126–130/0.2 mm. This product forms very large, waxy crystals at 20–25°.

Preparation of other symmetrical trialkyl phosphorotetrathioates. Data for triethyl, tri-*n*-propyl, and tri-*i*-propyl phosphorotetrathioates are summarized in Table I. They were prepared in essentially the same manner as trimethyl phosphorotetrathioate.

Addition of olefins to dialkyl hydrogen phosphorotetrathioates. The olefins were either refluxed with the acids at 1 atm. or rocked in a bomb under pressure. The data are summarized in Table II.

Trimethyl phosphorotrithioite. This material was prepared by the procedure of McLeod.[7]

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE UNION OIL COMPANY OF CALIFORNIA]

Identification of Alkylthio Groups by Infrared Spectroscopy

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Characteristic absorption bands have been found for CH_3S-, C_2H_5S-, n-C_3H_7S-, i-C_3H_7S-, and n-C_4H_9S- groups in a study of the infrared spectra of mercaptans, sulfides, disulfides, and alkyl phosphorothioate compounds. Spectra of several phosphorothioate compounds are shown.

Infrared spectra of a number of compounds containing sulfur were examined recently in an attempt to interpret the spectra of several phosphorothioate compounds. During this study it was found that individual alkylthio groups have specific identifying absorption bands. Although related spectral studies[1-8] have been made on many sulfur compounds, spectra-structure correlations for alkylthio groups have not been published.

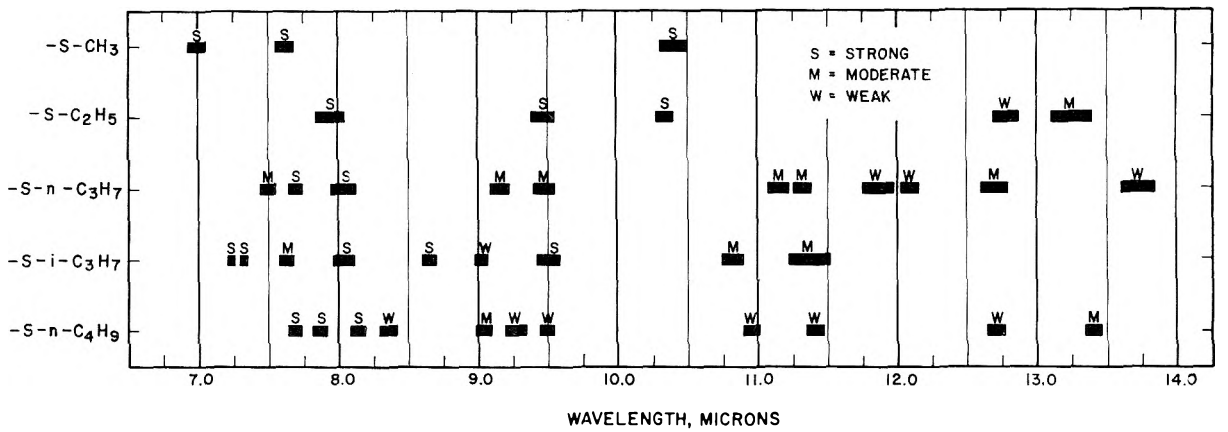

FIG. 1. SPECTRA-STRUCTURE CORRELATION CHART FOR ALKYLTHIO GROUPS

The spectra of four mercaptans, twenty-nine sulfides, fourteen disulfides, eight trialkyl phosphorotetrathioates, four dialkyl hydrogen phosphorotetrathioates, and one trialkyl phosphorotrithioite show that corresponding members of each series have absorption bands in the same spectral regions. This is true for symmetrical as well as unsymmetrical compounds. For example, the spectra of diethyl sulfide, diethyl disulfide, and triethyl phosphorotetrathioate are all quite similar. Likewise the spectra of ethyl i-propyl sulfide, ethyl i-propyl disulfide, and methyl ethyl i-propyl phosphorotetrathioate have a strong resemblance.

On the basis of these data we have assigned a number of identifying absorption bands to the following groups: methylthio, ethylthio, n-propylthio, i-propylthio, and n-butylthio. These correlations are listed in Figure 1, which shows the spectral range within which each characteristic absorption band occurs. This chart has proved very helpful as an aid in assigning structural formulas for trialkyl phosphorotetrathioates. The characteristic bands were used not only to identify specific alkylthio groups present, but also to distinguish between compounds of the type $(RS)(R'S)_2PS$ and $(RS)_2(R'S)PS$. This was done by comparing the intensities of bands related to one group with the intensities of bands related to the other group. Further study might yield average absorbance indices for different alkylthio groups, thereby making it possible to estimate the amount of these groups present in high molecular weight compounds or mixtures. Similar methods have been developed for alkyl groups not bonded to sulfur.[9,10] Work is being continued to evaluate these possibilities more completely.

The complexity of the molecules studied makes

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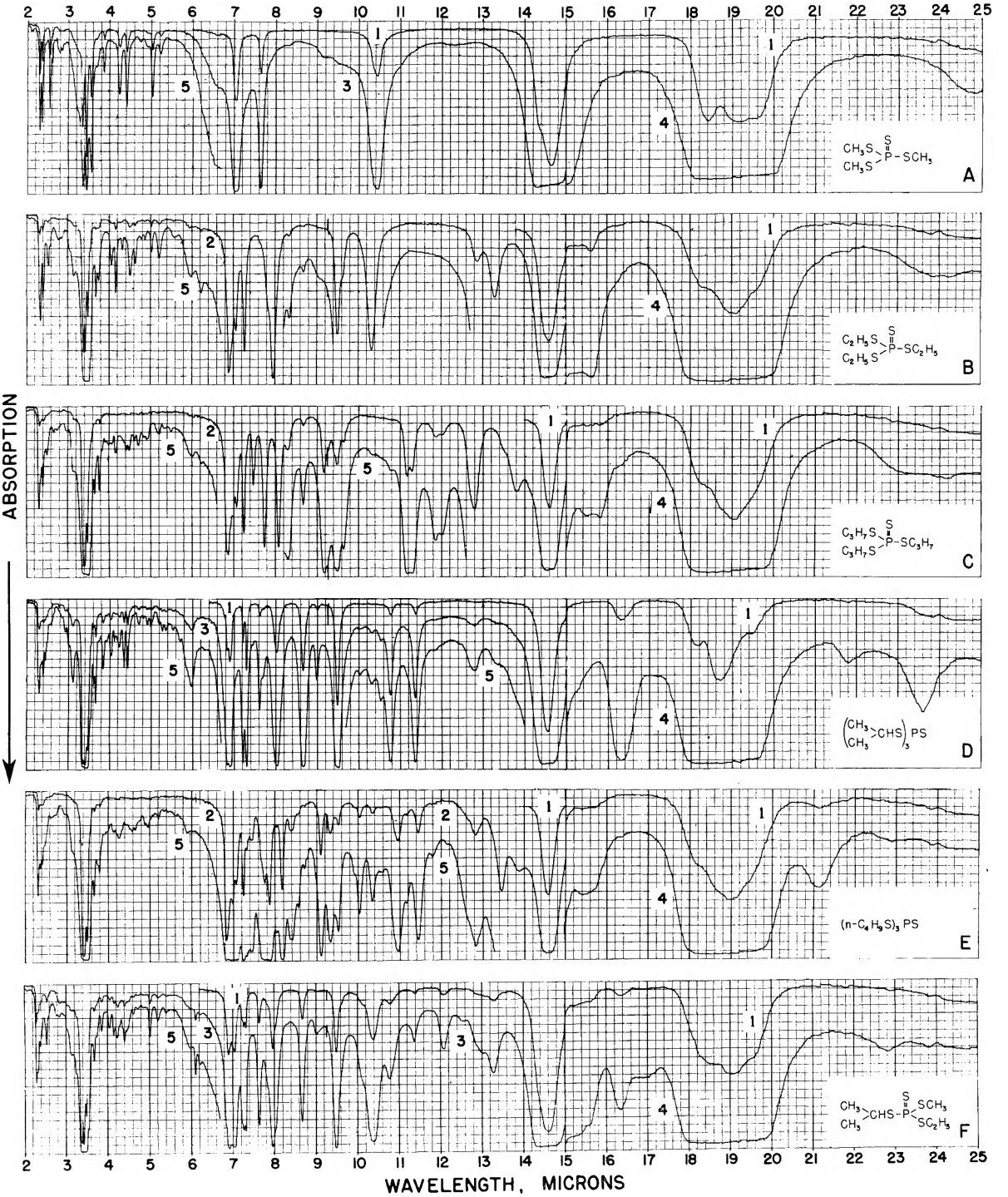

FIG. 2. INFRARED SPECTRA OF (a) trimethyl phosphorotetrathioate, (b) triethyl phosphorotetrathioate, (c) tri-*n*-propyl phosphorotetrathioate, (d) tri-*i*-propyl phosphorotetrathioate, (e) tri-*n*-butyl phosphorotetrathioate, and (f) methyl ethyl *i*-propyl phosphorotetrathioate. Cell lengths: (1) capillary, (2) 0.025 mm. (3) 0.054 mm. (4) 0.078 mm. and (5) 0.210 mm.

a unique assignment of the observed absorption bands to particular molecular vibrations extremely difficult. For this reason, we have not attempted to make definite frequency assignments to any specfic vibrations. We believe, however, that most of the characteristic bands listed in Figure 1 originate from C–H vibrations.[11,12,13] For example, the absorption band near 8 microns which is characteristic of ethylthio groups might be due to methylene wagging or twisting vibrations.[14] We have attributed absorption near 7.65 microns in the spectra of

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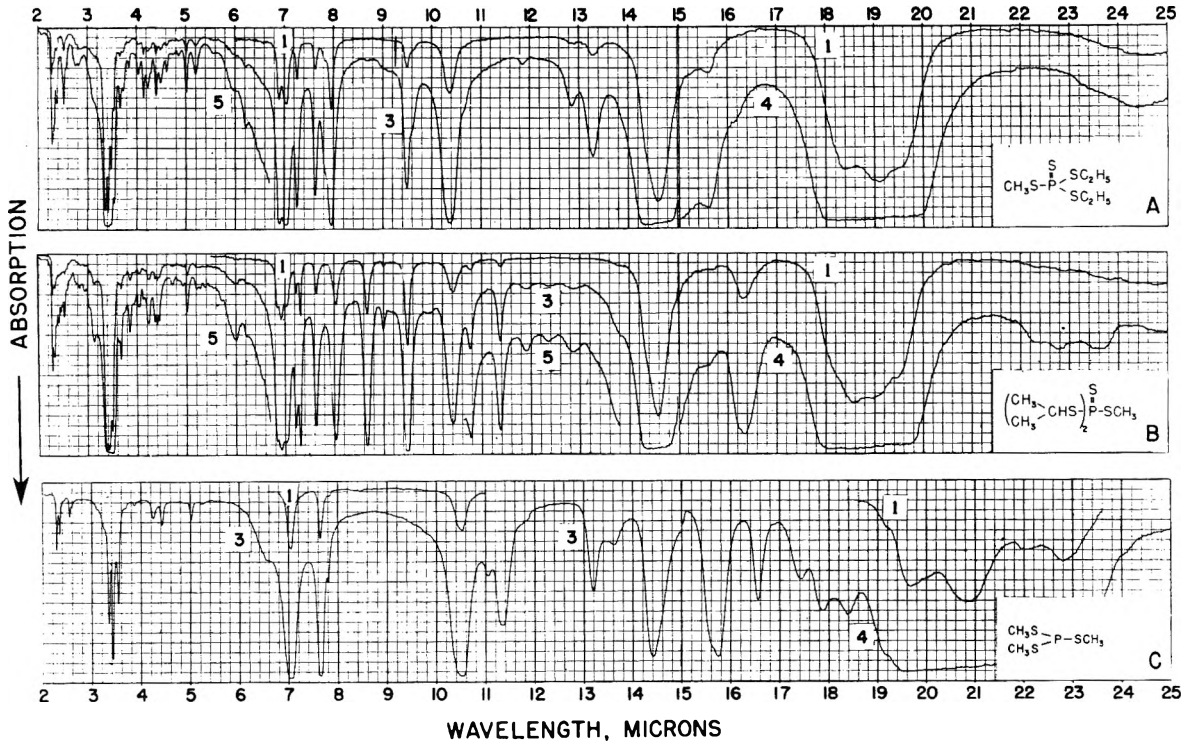

FIG. 3. INFRARED SPECTRA OF (a) methyl diethyl phosphorotetrathioate, (b) methyl di-*i*-propyl phosphorotetrathioate, and (c) trimethyl phosphorotetrathioate. Cell lengths: (1) capillary, (3) 0.054 mm, (4) 0.078 mm, and (5) 0.210 mm.

methylthio compounds to the symmetric methyl deformation vibration for reasons outlined in Sheppard's article on methyl group frequencies.[15] Absorption near 7.65 microns is attributed to the asymmetric deformation vibration of methyl groups attached to sulfur.

As an aid in interpreting spectra of the phosphorus compounds, approximation rules were used to estimate the spectral region in which certain absorption bands should occur. For example, Gordy's Rule,[16]

$$k = 1.67\,N\left[\frac{Xa \cdot Xb}{d^2}\right]^{3/4} + 0.30$$

where:

k = force constant $\times 10^{-5}$ dynes/cm.
N = bond order
Xa and Xb = electronegativities of atoms A and B
d = internuclear distances in Angstroms, Å

was used to estimate the wave length of the C—S stretching vibration in the methylthio group. Using a mass of 15 for the methyl group, a bond order of 1, a bond distance of 1.82 Å, electronegativity values of 2.55 for both carbon and sulfur and assuming simple harmonic oscillation, a wave length of 14.2 microns can be calculated for this vibration. Similarly, a wave length of 14.9 microns can be calculated for the P=S stretching vibration. Absorption bands are found near these wave lengths in the spectrum of trimethyl phosphorotetrathioate (Figure 2). We have attributed the intense band at about 14.6 microns to the P=S stretching vibration,[17] while the shoulder at about 14.4 microns on the side of this intense band is attributed to C—S stretching in the methylthio group. The 14.6-micron band associated with the P=S stretching vibration is present in the spectra of all phosphorotetrathioate compounds (see Figures 2 and 3). The spectrum of trimethyl phosphorotrithioite, which has no P=S group, shows absorption near 14.4 microns, but does not show the intense band near 14.6 microns.

Broad absorption bands near 19 microns in the spectra of phosphorotetrathioates are attributed to P—S— stretching vibrations. The spectrum of trimethyl phosphorortrithioite shows a similar broad band near 21 microns.

Other absorption bands near 15.6 microns and 16.4 microns are attributed to C—S stretching vibrations in ethylthio and *i*-propylthio groups, respectively.[4]

EXPERIMENTAL

Infrared spectra of mercaptans, sulfides, and disulfides published by American Petroleum Institute Research Projects 44 and 48 provided most of the data for this work. All

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organophosphorus compounds were synthesized in our laboratories.[18] Because of the possible toxic nature of the phosphorus compounds, they were handled with rubber gloves in a fume hood. Also, a small Plexiglas fume hood was placed over the sample space of the spectrophotometer to remove the strong odor characteristic of many of the samples. The spectra were recorded with a Perkin-Elmer Model 21 spectrophotometer equipped with interchangeable sodium chloride and potassium bromide optics.

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BREA, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF UTAH]

Porphyrins in Gilsonite

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A crystalline porphyrin, isolated from gilsonite, was identified to be deoxophyllerythroetioporphyrin or an isomer. The isolation creates the inference that it is the porphyrin originally present. It occurs in the form of the Ni(II) complex.

A knowledge of types of porphyrins in asphaltic materials can provide useful information in interpreting their origin and mode of formation. The presence of pyrroles[1] in the products of pyrolysis of gilsonite and the occurrence of nickel[2] in fractions of gilsonite soluble in organic solvents suggested the presence of porphyrin-nickel complexes in this asphaltite. Accordingly, a study was initiated to clarify this possibility.

A preliminary concentration procedure was found to be desirable to decrease the requirements for hydrogen bromide in acetic acid. An exhaustive extraction of gilsonite with ethyl acetate removed porphyrins into the soluble fraction, which constituted about one fourth of the total. A colorimetric method was used to follow the efficiency of the extraction procedure. A series of six extractions at room temperature removed the major portion of the desired compounds. The colorimetric analysis indicated the porphyrin content in gilsonite to be 0.03%.

The reaction of the porphyrin-metal complex in the concentrate with hydrogen bromide in acetic acid released the free porphyrins. The treatment with hydrogen bromide in acetic acid was assumed to have no effect on the porphyrin moiety of the metal complex. Using a sealed tube for this reaction, as described by Treibs,[3] was found to be unnecessary, when the reaction was repeated once. The modified approach permitted processing larger batches than would otherwise be possible. Basic porphyrin molecules were carried into the aqueous acid phase by this procedure. Accompanying neutral compounds were extracted partially with benzene. The porphyrin fraction was then placed in ether, and basic compounds removed by aqueous hydrochloric acid, leaving behind a further amount of contaminants.

Basic compounds, aside from porphyrins, in gilsonite[4] were contained in the main, in the crude fraction at this point. A procedure was devised to extract these compounds from the desired porphyrins by forming the porphyrin-nickel complex. The latter is not basic and is stable to mineral acids in general but cleaved by concentrated sulfuric acid.[5] Accordingly, the crude extract was treated with Ni(II) ion, and the resulting Ni(II) porphyrins in an ether solution were extracted with hydrochloric acid. The complex was cleaved with concentrated sulfuric acid, and the cycle was repeated to remove essentially all of the nonporphyrin bases.

Additional purification and separation of types of porphyrins were effected by applying a hydrochloric acid fractionation[6] and by chromatography. Using 2.5, 4, and 7% aqueous acid solutions, the porphyrins were separated into fractions, amounting approximately to 80%, 10%, and 10%, respectively. Final purification and separation were achieved by chromatography on calcium carbonate. Each of the fractions gave chromatograms with two red colored zones, moving away from small amounts of dark material adsorbed more tightly on the column. The major component from the 2.5% hydrochloric acid fraction amounted to about 73% of the total porphyrins.

Visible spectra were determined for the major and minor components in the 2.5% acid fraction

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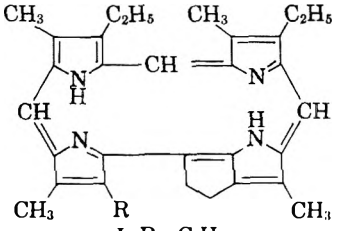
and the major components of the other two fractions. Essentially identical spectra were found in all instances with peaks at 618 (I), 566 (II), 534 (III), and 499 (IV) mμ and with relative intensities in the order IV, II, III, and I. These characteristics are suggestive of the phyllo-type of porphyrins,[7] and more specifically of deoxophyllerythroetioporphyrin (I). The presence of the two components in each hydrochloric acid fraction may be interpreted as reflecting the presence of a given porphyrin together with its precursor, a monocarboxylic acid. The spectra of deoxophyllerythroetioporphyrin (I) and deoxophylloerythrin (II) are reported[3] to be identical.



I, R = C_2H_5
II, R = $CH_2CH_2CO_2H$

A sufficient amount of only the principal component of the 2.5% hydrochloric acid fraction was available for added characterization studies. The porphyrin was crystallized from chloroform and methanol in the form of reddish-brown needles. Additional recrystallizations from this solvent and from pyridine and methanol provided a sample, whose ultimate analyses for carbon and hydrogen agreed with the calculated values for deoxophyllerythroetioporphyrin. Its infrared spectrum contained a peak at 3.06 μ, characteristic of an NH stretching frequency displaced to a higher wave length because of hydrogen bonding. Absorption characteristic of a carbonyl group was missing, indicating the absence of a carboxyl group.

As an added contribution to the identification of the major porphyrin, deoxophyllerythroetioporphyrin was synthesized for comparison purposes. This extended synthesis was carried out, as detailed in the experimental section, by procedures described in the literature with a few modifications. Separation of the porphyrins from unreacted pyrromethenes was readily accomplished by using the same procedure as was applied in separating nonporphyrin bases from the crude extract. Unfortunately the yield of the synthetic compound was so limited that a visible spectrum determination only was possible. When this spectrum was compared to that of the major gilsonite porphyrin, determined on the same instrument, by adjusting the peaks at 499 mμ to the same heights, the positions and the heights of the other three peaks were found to be identical. This and the additional data described strongly suggest that the major porphyrin isolated is deoxophyllerythroetioporphyrin. However, isomeric compounds with different sequences of side-chains cannot be discounted as possibilities, although, to our knowledge, the natural occurrence of such porphyrins has not been demonstrated.

Studies directed toward the identification of the cation associated with the gilsonite porphyrins have been made. The concentrate, obtained by ethyl acetate extraction of the bitumen, was chromatographed three times on alumina and twice on silica gel to obtain a chromatographically homogeneous fraction. A visible spectrum of this porphyrin-metal complex exhibited peaks at 552 and 514 mμ. This spectrum was found to be identical with that of the nickel complex formed by reaction of Ni(II) acetate with the porphyrin fraction prior to hydrochloric acid fractionation. Complexes formed from Cu(II) and Co(II) ions were found to possess distinctly different spectra. A flame spectrum of the isolated complex showed peaks at 349.2 and 353.5 mμ, in agreement with those for nickel.[8] An arc spectrum showed a dominant nickel line together with indications of traces of cations, which might be expected to be derived from the adsorbents used in the chromatographic purification. The absence of the vanadium line in the arc spectrum and the absence of any absorption at 570 mμ in the visible spectrum of the complex provide strong evidence for the absence of vanadium, commonly found as the cation in metal complexes of porphyrins of asphaltic materials.

The findings in this study permit several speculations. Gilsonite appears to have been derived largely, if not entirely, from plants. The predominance of decarboxylated porphyrins indicates that the temperature range involved in the formation of this bitumen was, at one time, not less than 250° to 350°, since such temperatures are normally required to decarboxylate porphyrins containing propionic acid side chains.[9] However, temperatures appreciably in excess of 400° could not have been involved, since porphyrins undergo degradation at such temperatures.

EXPERIMENTAL[10]

Isolation of total porphyrins. Bonanza gilsonite[11] (200 g.) was placed in a 1-quart Waring Blendor with 500 ml. of ethyl acetate and agitated for 1 min. The suspension was allowed to settle, and the liquid was decanted. A second 500-ml. portion of the solvent was added, and the agitation and decantation repeated. After eight extractions, removal of ethyl acetate-soluble compounds was essentially complete. Combination of the extracts and distillation of the solvent left 53.4 g. (26.7% of the gilsonite) of a black, tarry mass.

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(10) All melting points are uncorrected. Analyses were made by G. Weiler and F. B. Strauss, Oxford, England.

(11) Gilsonite mined from the Bonanza vein.

The latter (269 g.) was dissolved in a minimum volume (1 l.) of benzene, an equal volume of 15% hydrogen bromide in acetic acid was added, and the resulting solution was allowed to stand for 1 hr. at room temperature. The reaction mixture was then poured over cracked ice, and the resulting red acid layer was removed. Concentrated hydrochloric acid, used instead of hydrogen bromide in acetic acid, failed to extract any red color, indicating absence of free porphyrins and failure to cleave porphyrin-metal complexes. The benzene solution was retreated with hydrogen bromide in acetic acid in the same manner. The organic layer was finally extracted with one half its volume of 7% hydrochloric acid and discarded. The combined acid solutions (about 2 l.) were washed three times with 300-ml. portions of benzene to remove accompanying neutral compounds. The porphyrin fraction was extracted by ether (1 l.) by reducing the acidity of the aqueous solution with sodium acetate. The red color was transferred from the aqueous to the organic phase. The ether solution was extracted with 200 ml. of 7% hydrochloric acid, and the resulting red acid solution was extracted three times with 50-ml. portions of chloroform. The chloroform solution was washed with aqueous sodium bicarbonate and with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue (about 1 g.) was dissolved in 100 ml. of acetic acid, and the resulting solution was treated with 1 g. of nickel(II) acetate and refluxed for 15 min. The reaction mixture was poured onto ice and water, and a sufficient volume of ether (500 ml.) was added to dissolve the nickel(II) porphyrins. When the ether solution was repeatedly washed with water, a solid (B) (120 mg.) separated at the ether-water interface. The ether solution was washed three times with 50-ml. portions of concentrated hydrochloric acid to remove accompanying basic contaminants. The ether solution was then washed with aqueous sodium bicarbonate and with water, dried over anhydrous sodium sulfate, and evaporated to leave a solid (A) (140 mg.). The latter was dissolved in 50 ml. of concentrated sulfuric acid to cleave the complex, and the resulting solution was poured on ice and water. Any unchanged complex was removed by extraction of the aqueous solution with ether.

The solid B was dissolved in 500 ml. of chloroform. This solution was treated as described in the above to remove accompanying basic contaminants to yield 120 mg. of the nickel complex, which was cleaved in concentrated sulfuric acid.

Each of the sulfuric acid solutions resulting from A and B was extracted with 100-ml. portions of chloroform (total volume, 500 ml.) until all red color was removed from the acid phase. The chloroform solution was washed with aqueous sodium bicarbonate and with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was dissolved in acetic acid and treated with nickel(II) acetate as previously described, and the cycle was repeated. Fractions derived from both A and B yielded a red solid at the ether-water interface during the washing operation, but not at the chloroform-water interface. The combined free porphyrins from A and B yielded 220 mg. of red solid.

An ether solution of the porphyrin fraction was extracted with 10% sodium hydroxide. A separation of insoluble porphyrin salts was not observed.

A solution of 70 mg. of porphyrins in 500 ml. of ether was fractionated with 100-ml. portions of 2.5, 4, and 7% hydrochloric acid. The completeness of removal of porphyrins was followed by use of ultraviolet light. When no fluorescence was evident in a given acid extract, the next higher concentration of acid was applied. Each acid fraction was extracted with 50-ml. portions of chloroform until removal of red color from the aqueous acid solutions was complete. Three extractions were usually required. The chloroform solutions were washed with aqueous sodium bicarbonate and with water, dried over anhydrous sodium sulfate, and evaporated to dryness, leaving 55 mg., 7 mg., and 7 mg., respectively, from the 2.5, 4, and 7% hydrochloric acid fractions.

Chromatography of porphyrins. The porphyrins (50 mg.) from the 2.5% hydrochloric acid fraction were dissolved in 100 ml. of chloroform and placed on a chromatographic column, packed with calcium carbonate (180 × 53 mm. diam.).[12] Development was effected with a mixture of benzene–petroleum ether (60–70°) (4 : 1, by vol.). The major portion of the sample moved rapidly down the column as a discrete band. A sufficient volume of the developer was introduced to move the leading zone near the bottom of the column. A second, red zone appeared near the top of the chromatogram. The adsorbent bed was extruded, and the two red-colored portions sectioned. Each of these was eluted with acetone, and solvent was evaporated from the resulting solutions. Each of the two fractions was dissolved in 100 ml. of chloroform and rechromatographed on calcium carbonate in the same fashion. The chromatogram containing the more tightly adsorbed fraction was developed by the same solvent as used initially, but with 1% (by vol.) of *t*-butyl alcohol added. The rapidly moving fraction contained 35 mg. of deoxyphyllerythroetioporphyrin, and the second fraction about 3 mg. of material. Crystallization of deoxophyllerythroetioporphyrin from chloroform and methanol provided reddish-brown needles, which did not melt when heated to 350°, although decomposition began at about 300°. The analytical sample was recrystallized twice from chloroform and methanol, once from pyridine and methanol, and once again from chloroform and methanol.

Anal. Calcd. for $C_{32}H_{36}N_4$: C, 80.63; H, 7.61. Found: C, 80.49; H, 7.64.

Chromatography of the porphyrins from the 4 and 7% hydrochloric acid fractions showed essentially the same chromatograms, with rapidly moving zones containing the major portions of the samples. Total weight of porphyrins isolated from 70 mg. of the porphyrin fraction was about 48 mg.

Spectra. Visible spectra determinations were made on a Beckman DK-2 spectrometer. Deoxophyllerythroetioporphyrin from gilsonite, dissolved in chloroform, gave a spectrum[13] with maxima at 618 (I), 566 (II), 534 (III), and 499 (IV) mμ and with relative intensities in the order IV, II, III, and I. The second portion from the 2.5% hydrochloric acid fraction and the principal portions from the 4 and 7% hydrochloric acid fractions gave essentially the same spectra with maxima appearing at the same wave lengths. Relative intensities varied very slightly, possibly because the small amounts of materials did not permit exhaustive recrystallizations.

Extinction coefficients of deoxophyllerythroetioporphyrin from gilsonite were determined with a Beckman DU spectrophotometer at a concentration of 0.0165 mg. per milliliter of chloroform. Molar extinction coefficients at 618, 566, 534, and 499 mμ were found to be 3530, 5220, 5100, and 11200, respectively.

The infrared spectrum of deoxophyllerythroetioporphyrin from gilsonite was run on a Perkin-Elmer, Model 21, spectrophotometer with a sodium chloride prism at a concentration of 6 mg. per ml. of carbon disulfide. A small NH peak at 3.06 μ and the absence of a carbonyl absorption at 5.8 μ were noted.

Deoxophyllerythroetioporphyrin. 2,4-Dimethyl-3-ethylpyrrole was prepared using the procedure of Treibs and Schmidt.[14] 2,3-Dimethyl-4-ethylpyrrole was synthesized as described by Fischer and Klarer,[15] except that a Huang-Minlon modification was used in place of the standard Wolff-Kishner reduction. 4-(β-Bromovinyl)-5-formyl-3-methyl-2-pyrrolecarboxylic acid was prepared by a slight modifica-

(12) Dimensions of the adsorbent.

(13) This and other spectral curves are given in the Ph.D. dissertation of L. R. McGee, University of Utah, 1956.

(14) A. Treibs and R. Schmidt, *Ann.*, 577, 105 (1952).

(15) H. Fischer and J. Klarer, *Ann.*, 450, 181 (1926).

tion of the method of Fischer and Süs,[16] since their procedure in our hands yielded only polymeric products. 5-Carbethoxy-2,4-dimethyl-3-pyrrole-α,β-dibromopropionic acid[16] (16 g.) was dissolved in 50 ml. of ethanol and 150 ml. of water added. The resulting solution was heated over a boiling water bath until carbon dioxide ceased to be evolved. The product, which separated, was filtered and dissolved in 200 ml. of ether. The ether solution was washed with 2% aqueous sodium carbonate and with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was crystallized from ethanol to yield 5.5 g. (39%) of light brown crystals of ethyl 4-(α,β-dibromoethyl)-3,5-dimethyl-2-pyrrolecarboxylate, m.p. 132–133,° reported[17] for compound prepared by bromination of ethyl 4-vinyl-3,5-dimethyl-2-pyrrolecarboxylate, 133°. A solution of 5.5 g. of ethyl 4-(α,β-dibromoethyl)-3,5-dimethyl-2-pyrrolecarboxylate in 150 ml. of absolute ether was cooled in an ice bath, and while stirring, a solution of 5.5 g. of sulfuryl chloride in 20 ml. of absolute ether was added slowly. After addition was complete, stirring was continued for 1 hr., and then the reaction mixture was allowed to stand overnight. The ether was removed at room temperature under reduced pressure. The residue was dissolved in 10 ml. of ethanol, 50 ml. of water was added, and the mixture was heated on a boiling water bath for 30 min. Ethyl 4-(β-bromovinyl)-5-formyl-3-methyl-2-pyrrolecarboxylate separated first as an oil, which crystallized upon cooling. Recrystallization from ethanol gave 2.3 g. (52%) of light brown crystals, m.p. 138–140°; reported,[16] 140°. The latter compound was then processed as described[17] to form 4-(β-bromovinyl)-5-formyl-3-methyl-2-pyrrolecarboxylic acid.

5-Bromo-5′-bromomethyl-3,4′-dimethyl-3′,4-diethylpyrromethene hydrobromide[15] and 3-(β-bromovinyl)-5-carboxy-3′-ethyl-4,4′,5′-trimethylpyrromethene hydrobromide[18] were prepared by the methods described. Condensation of the two (500 mg. each) was effected in 10 ml. of 90% formic acid (instead of succinic acid[18]) by refluxing at 110° for 8 hrs. Isolation of the desired porphyrin was effected by a modified procedure. Chloroform (200 ml.) was added to the reaction mixture. The resulting chloroform solution was washed thoroughly with water, dried over anhydrous sodium sulfate, and evaporated. The residue was dissolved in 100 ml. of glacial acetic acid containing 1 g. of nickel(II) acetate, and the mixture was refluxed for 15 min. The solution was then poured onto ice, and sufficient ether (500 ml.) was added to dissolve all the precipitated solid material. The ether solution was extracted four times with 100-ml. portions of concentrated hydrochloric acid to remove unreacted pyrromethenes, washed well with aqueous sodium bicarbonate and with water, dried over anhydrous sodium sulfate, and evaporated. The residue was dissolved in 50 ml. of concentrated sulfuric acid to cleave the nickel complex. The acid solution was poured onto ice and water. Ether (200 ml.) was added and sufficient sodium acetate was introduced to reduce acidity and permit extraction of the porphyrins into the organic phase. The ether solution was extracted four times with 50-ml. portions of 2% hydrochloric acid, the red color going to the acid phase. The latter was extracted four times with 50-ml. portions of chloroform. The chloroform solution was washed with sodium bicarbonate and with water, dried over anhydrous sodium sulfate, and concentrated to a volume of about 25 ml. The latter was placed on a chromatographic column, packed with talc (180 × 53 mm., diam.).[12] Development of the chromatogram was effected with benzene: *t*-butyl alcohol (1000:1, by vol.). The major product, etioporphyrin I, moved more rapidly down the column. The column was extruded and sectioned. The colored segments were eluted with acetone. The solvent was evaporated from the eluates, the solids obtained were redissolved in chloroform, and each of the resulting solutions was rechromatographed on talc. Deoxophyllerythroetioporphyrin was obtained in an amount of about 0.3 mg. as determined spectrophotometrically.

The visible spectrum of deoxophyllerythroetioporphyrin showed maxima at the same wave lengths as the spectrum of the major gilsonite porphyrin. When the absorbancies of the maxima at 499 mμ of the two curves were adjusted to coincide, the heights of the other three maxima were found to be identical. The major synthetic product, etioporphyrin I, possessed a distinctly different visible spectrum with maxima at 619, 566, 533, and 497 mμ with relative intensities in the order IV, III, II, and I.

Isolation and identification of the metal-porphyrin complex. A solution containing 4 g. of the ethyl acetate extract in 10 ml. of benzene was placed on a chromatographic column packed with alumina (150 × 35 mm., diam.)[12]. The chromatogram was developed with 200 ml. of benzene: *t*-butyl alcohol (1000:1, by vol.). The column was extruded and divided into two parts. The lower half of the column, orange-red in color, containing the porphyrin-metal complex in almost its entirety, was eluted with acetone. Two additional chromatograms on alumina and two on a mixture of silica gel-Celite[19] (3:1, by wt.) provided chromatographically-homogeneous material, in an amount of about 0.8 mg.

An arc spectrum of the sample showed a dominant line for nickel together with indications of trace amounts of cations contained in the adsorbents used in the chromatographic purification. A flame spectrum of the sample determined on a Beckman DK-2 spectrophotometer with a flame attachment showed peaks at 349.2 and 353.5 mμ, in agreement with those for nickel.[3]

Portions of the porphyrin fraction purified by converting into the nickel complex two times, were dissolved in acetic acid and reacted with nickel(II), copper(II), and cobalt(II) acetates. The complexes were purified by chromatography on silica gel. Visible spectra were determined, and the maxima for the nickel, copper, and cobalt complexes were found to be 552 and 514 mμ, 562 and 528 mμ, 558 and 517 mμ, respectively. The spectrum of the porphyrin-metal complex isolated possessed maxima at 552 and 514 mμ.

Colorimetric determination of porphyrins as the nickel complex. Chromatographically-homogeneous porphyrin-nickel complex, prepared as described in the previous section, was dissolved in benzene to form solutions of varying concentrations. Using a Klett-Summerson photoelectric colorimeter with a green filter, 480–550 mμ, readings were made on solutions containing from 1 to 25 parts per million of the nickel porphyrins. A plot demonstrated that Beer's Law applied over this concentration range.

The porphyrin content in any given crude fraction was approximated by this colorimetric method. In each instance samples were processed through the same purification procedure as described for the reference sample. The efficiency of the ethyl acetate extraction procedure was followed by this technique. After the sixth extraction, percentage of porphyrins in the residue dropped markedly. Based upon this colorimetric method, gilsonite was found to contain 0.03% porphyrins.

Acknowledgment. We are very grateful to the American Gilsonite Co. for a generous research grant which made this investigation possible.

SALT LAKE CITY, UTAH.

(16) H. Fischer and O. Süs, *Ann.*, 484, 113 (1930).

(17) H. Fischer and K. Zeile, *Ann.*, 462, 210 (1928).

(18) H. Fischer and H. J. Hofmann, *Ann.*, 517, 274 (1935).

(19) A diatomaceous earth, Johns-Manville Co., New York, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OKLAHOMA AGRICULTURAL AND MECHANICAL COLLEGE]

A New Series of Anticonvulsant Drugs: Branched-Chain α-Aminoacetamides

SIDNEY D. UPHAM[1] AND OTIS C. DERMER

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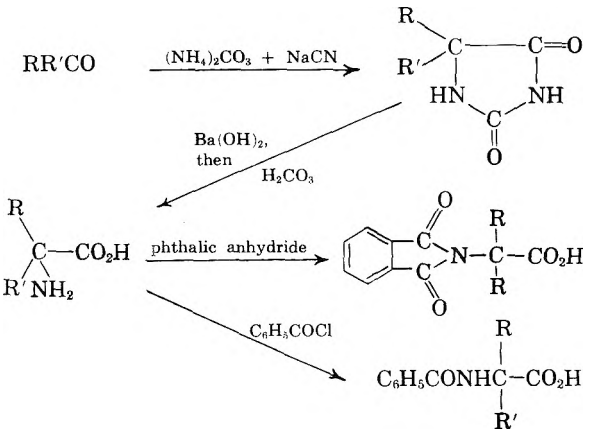
A number of α,α-dialkyl-α-phthalimidoacetamides and α,α-dialkyl-α-benzamidoacetamides have been synthesized from ketones by way successively of the hydantoins, aminoacetic acids, acylaminoacetic acids, and acylaminoacetyl chlorides. The most serious difficulties in this scheme were the resistance of some hydantoins to hydrolysis and of some aminoacetic acids to phthaloylation. Both types of acetamides proved to be highly active anticonvulsants.

The search for new hypnotics, sedatives, and anticonvulsants has led to the production of a number of acid amides and ureides now in medical use. The di- and trisubstituted acetamides and acetylureas in particular have been shown to have value as therapeutic agents. A literature search in this field revealed that while halogen, alkyl, and aryl groups had been used as α-substituents, very little was known about the effect of an amino group in this position. Billman and Hidy[2] postulated that α,α-diphenyl-α-aminoacetamide is a product in the hydrolysis of 5,5-diphenylhydantoin. They accordingly prepared this amide and a number of derivatives and found that some of these compounds possess anticonvulsant and antispasmodic activity. This work was substantiated and extended by R. Duschinsky.[3]

Since the trisubstituted acetamides, as a group, are low in activity when compared to the barbiturates, it was deemed advisable to synthesize a series of α,α-disubstituted-α-aminocetamides in which the amino group is acylated. It was hoped that in such compounds, which contain two or more amide groups, the pharmacological activity would be enhanced. Benzoyl chloride and phthalic anhydride were chosen as acylating agents with the thought that the acyl groups might confer more resistance to elimination by the body and thus produce a longer-acting drug.

The scheme of synthesis used is outlined in Chart I. It was chosen because of the ready availability of the ketones required, as well as the excellence of yields of amino acids. While phthaloylation of natural amino acids by fusion with phthalic anhydride[4] proceeds smoothly and in high yields, such is not the case with the α,α-disubstituted amino acids. Unexpected resistance to reaction and susceptibility to side reaction contributed to the low yields; moreover, much difficulty was met in crystallizing the phthaloylated acids and amides. The considerable effect of the α-benzamido and α-phthalimido groups on the reactivity of the acids and their derivatives was evident when attempts were made to synthesize the ureides. Methods which were successful with α,α-dialkylacetic acids[5] failed to give any ureides when the acylamino acid chlorides were used.

Both the α-benzamido- and α-phthalimidoacetamides proved to be highly active as anticonvulsants when tested by the supramaximal electrocorneal shock test described by Swinyard.[6] Members of the α-phthalimido series were the more active. For 94 rats, the ED_{50} (effective oral dose[6]) for α,α-diethyl-α-phthalimidoacetamide was 13.2 (95% confidence interval estimate, 10.3–16.9) mg./kg., whereas Dilantin showed ED_{50} of 26.5 (16.6–42.3) mg./kg. Tables 3 and 5 show the relative activities of the amides prepared when tested by the above method.



EXPERIMENTAL

Preparation of hydantoins and amino acids. The hydantoins were prepared by the method of Henze and Holder[7] (Table I). Hydrolysis of the hydantoins was carried out in a manner like that of Nadeau and Gaudry.[8] Barium hydroxide (1.5 moles) was dissolved in 1200 ml. of hot water and the hydantoin (0.5 mole) was added and dissolved by stirring. The solution was autoclaved in steam at 50 to 60 lbs/sq.

(1) American Cyanamid Co., Fine Chemicals Division, Princeton, N. J.

(2) J. H. Billman and P. H. Hidy, *J. Am. Chem. Soc.*, **65**, 760 (1943).

(3) R. Duschinsky, U. S. Patent 2,642,433 (June 16, 1953).

(4) J. C. Sheehan and V. S. Frank, *J. Am. Chem. Soc.*, **71**, 1856 (1949).

(5) R. W. Stoughton, H. L. Dickison, and O. G. Fitzhugh, *J. Am. Chem. Soc.* **61**, 408 (1939).

(6) E. A. Swinyard, *J. Am. Pharm. Assoc.*, **38**, 201 (1949)

(7) H. R. Henze and C. B. Holder, *J. Am. Chem. Soc.*, **63**, 1943 (1941).

(8) G. Nadeau and R. Gaudry, *Can. J. Research*, **27B**, 421 (1949).

TABLE I

PREPARATION OF 5,5-DISUBSTITUTED HYDANTOINS

Substituents	Me, Et	Et, Et	Me, *iso*-Bu	Me, *n*-C_5H_{11}	Et, Bu	Me, Ph	Et, Ph	Pentamethylene	*iso*-Pr, *iso*-Pr	*iso*-Bu, *iso*-Bu
Yield, %	55	64	64	54	60	52	38	90	20	12
M.p., °C.	144–5	163	145	101	122–3	194–5	198	215	205	147–8
Lit. m.p., °C.	145–6[a]	165[b]	148[c]	102[c]	[d]	197[e]	199[f]	215[g]	207[c]	[h]

[a] H. T. Bucherer and W. Steiner, ref. 10. [b] G. Errera, *Gazz. chim. ital.*, 26, I, 197 (1896). [c] H. R. Henze and R. J. Speer, *J. Am. Chem. Soc.*, 64, 522 (1942). [d] H. R. Henze, Document No. 1603, American Documentation Institute, Washington, D. C. [e] K. Abe, *Science Repts. Tokyo Bunrika Daigaku*, Sec A, 2, 1 (1934). [f] W. T. Read, *J. Am. Chem. Soc.*, 44, 1746 (1922). [g] H. T. Bucherer and V. A. Libe, *J. prakt. Chem.*, 141, 5 (1934). [h] A. Lumiére and F. Perrin, *Bull. soc. chim. France*, 35, 1022 (1924).

in. for 1 to 2 hr. or at 15 to 20 lbs/sq. in. for 15 hr. The mixture was then filtered hot to remove the precipitated barium carbonate and treated with carbon dioxide until a pH of about 7 was reached. The additional barium carbonate thus formed was removed by filtration and the amino acid isolated by vacuum evaporation of the clear filtrate. The amino acids thus obtained were crystalline compounds which were characterized as the phthalimido or benzamido derivatives. Table II lists the amino acids prepared.

TABLE II

PREPARATION OF SUBSTITUTED AMINOACETIC ACIDS

Substituents in Alpha Position	Pressure to Hydrolyze Hydantoin, Lb./Sq. In.	Time, Hr.	Yield, %
Dimethyl[a]	50–60	1	80
Methyl ethyl[a]	50–60	1	70
Diethyl[b]	15	10	67
Methyl isobutyl[c]	15	15	93
Methyl *n*-pentyl[d]	50–60	1	51
Methyl phenyl[a]	50–60	1	74
Ethyl phenyl[a]	50–60	1	50
Pentamethylene[a,e]	50–60	2	55
Diisopropyl	50–60	1	0
Diisobutyl[b]	50–60	1	11

[a] H. T. Bucherer and W. Steiner, ref. 10. [b] H. Felkin, *Compt. rend.*, 227, 510 (1948). [c] H. Adkins and H. R. Billica, *J. Am. Chem. Soc.*, 70, 3121 (1948). [d] New compound, but used as intermediate without analysis. [e] From cyclohexanone; better named 1,3-diazaspiro[4.5]decane-2,4-dione.

5,5-Diphenylhydantoin could not readily be prepared from benzophenone and was obtained by the method of Sikdar and Ghosh.[9] This hydantoin could not be hydrolyzed by the above method but was finally hydrolyzed with 60% sulfuric acid according to the method of Bucherer and Steiner.[10]

Because of difficulty in effecting hydrolysis of 5,5-diisopropyl- and 5,5-diisobutylhydantoin, no further work was done on these compounds.

Phthaloylation of amino acids. This reaction was tried by various methods, including that of Kidd and King.[11] These authors used pyridine as a solvent in which to convert the amino acid and phthalic anhydride to the phthalamic acid, which in turn was cyclized to the phthalimido acid with acetic anhydride. This method gave poor results with the α,α-dialkylated amino acids. Likewise glacial acetic acid as a solvent and Carbitol and toluene as a suspending agent proved useless. The process used finally was that described by Sheehan,[4] who fused phthalic anhydride and natural amino acids together at 175–180° for 15 min. The nature of the alkyl groups on the amino acid affected the ease of phthaloylation greatly, the yields varying between 0 and 70%. Unlike the phthaloylated natural amino acids, the substituted acids gave great difficulty in crystallization, showing a strong tendency to oil out of solution and remain as oils or gums.

The general procedure is given in the following description of the preparation of α,α-diethyl-α-phthalimidoacetic acid. α,α-Diethyl-α-aminoacetic acid (13.3 g., 0.1 mole) was thoroughly stirred into 14.8 g. (0.1 mole) of molten phthalic anhydride. The temperature was then quickly raised to 180° and kept there for 20 min., during which time frothing occurred and water was given off. Clear melts were not obtained although the reaction mixture became fluid. The mixture was then cooled to 100° and treated with 500 ml. of water. The oily suspension was stirred and boiled for 5 min. During this time or on cooling the oil usually set to a solid which was removed by filtration. The solid was then recrystallized from 50% aqueous methanol. Results of various preparations are given in Table III.

TABLE III

PREPARATION AND PROPERTIES OF PHTHALIMIDOACETIC ACIDS

α,α-Dialkyl-α-Aminoacetic Acid, Phthaloylated	Yield, %	Neut. Equiv. Calcd.	Neut. Equiv. Found	M.P., °C.
Dimethyl	76	233	230	152–153[a]
Methyl ethyl	54	247	253	137–138[b]
Diethyl	57	261	258	163–164[c]
Methyl isobutyl	70	275	278	133–135
Methyl phenyl	47	299	304	186–187

[a] S. Gabriel, *Ber.*, 44, 57 (1911) obtained the value 153–154°, and J. H. Billman and W. F. Harting, *J. Am. Chem. Soc.*, 70, 1473 (1948) gave 152–153°. [b] P. Freytag, *Ber.*, 48, 648 (1915) found 141.5–143°, and Billman and Harting 139–140°. [c] Freytag found 161–162°.

No phthaloylated acid was formed from α-ethyl-α-phenyl-α-aminoacetic acid but an almost quantitative yield of the diketopiperazine was obtained instead. This result was duplicated repeatedly. The 3,6-diphenyl-3,6-diethyl-2,5-piperazinedione was recrystallized from glacial acetic acid.

(9) J. Sikdar and T. N. Ghosh, *J. Indian Chem. Soc.*, 25, 109 (1948).

(10) H. T. Bucherer and W. Steiner, *J. prakt. Chem.*, 141, 5 (1934).

(11) D. A. A. Kidd and F. E. King, *Nature*, 162, 776 (1948); F. E. King and D. A. A. Kidd, *J. Chem. Soc.*, 3315 (1949).

TABLE IV

PROPERTIES OF α,α-DIALKYL-α-PHTHALIMIDOACETAMIDES

Alkyl Groups Present	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	M.P., °C.	Oral Dose, Mg./Kg.	Protection Against Maximal Electroshock Seizure[a]
Dimethyl	62.06	62.43	5.17	5.28	12.07	11.91	258–260	50	3+
Methyl ethyl	63.41	63.27	5.69	5.76	11.30	11.35	208	40	4+
Diethyl	64.61	64.63	6.15	6.26	10.76	10.88	190–191	30	4+
Methyl isobutyl	65.69	65.64	6.57	6.98	10.21	10.59	170	200	2+

[a] E. A. Swinyard, ref. 6.

TABLE V

PREPARATION AND PROPERTIES OF BENZAMIDOACETIC ACIDS

α,α-Dialkyl-α-aminoacetic Acid Benzoylated	Yield, %	Neut. Equiv. Calcd.	Neut. Equiv. Found	M.P., °C
Dimethyl	72	207	203	196[a]
Methyl ethyl	54	221	227	204–205[b]
Diethyl	72	235	232	211[c]
Methyl isobutyl	53	249	246	179–180
Methyl *n*-pentyl	57	264	261	131
Methyl phenyl	44	269	263	145–146[d]
Ethyl phenyl	85	283	280	180–181
Pentamethylene	13.5	247	244	190–191[e]

[a] The literature values vary: 198°, E. Mohr and T. Geis, *Ber.*, 41, 798 (1908) and *J. prakt. Chem.*, (2) 81, 56 (1910); 199°, G. Heller and H. Lauth, *Ber.*, 52, 2302 (1919); 193–198°, J. H. Billman and E. E. Parker, *J. Am. Chem. Soc.*, 66, 538 (1944); 202°. R. E. Steiger, ref. 13; 196–197°, E. Shaw and J. McDowell, *J. Am. Chem. Soc.*, 71, 1691 (1949). [b] M. D. Slimmer, *Ber.*, 35, 400 (1902) gave the value 198–199° and A. Kjaer, *Acta Chem. Scand.*, 7, 889 (1953), 196°. [c] Kjaer found 210°. [d] Kjaer found 146–147°. [e] H. T. Bucherer and W. Steiner, ref. 10, found 190°.

tallized from 1-butanol and then aqueous methanol, m.p. 220° (lit.,[12] 225°).

Anal. Calcd. for $C_{21}H_{15}NO_2$: C, 80.51; H, 4.49; N, 4.86. Found: C, 79.85; H, 5.07; N, 4.69.

Although phthaloylation of α-methyl-α-*n*-pentyl-α-aminoacetic acid seemed to take place, the product could not be crystallized. Attempts were made to form the amide from the oil.

α,α-Dialkylated-α-phthalimidoacetamides. The acid chlorides of the substituted acetic acids were prepared by suspending the acids in benzene with an equivalent weight of PCl_5 and refluxing for 0.5 hr. The benzene was removed by vacuum distillation and enough dry dioxane added to the residue to dissolve the acid chloride. This solution was then dipped into concentrated aqueous ammonia at 0° with stirring to form the amide. The oily α-methyl-α-*n*-pentyl-α-phthalimidoacetic acid treated by the standard procedure gave a gummy reaction mixture which could not be crystallized. Yields varied considerably and difficulty was again encountered in crystallization. Amides formed are listed in Table IV.

α,α-Dialkyl-α-benzamidoacetic acids and their amides. These acids were prepared by the excellent method of Steiger.[13] No difficulty nor abnormality was encountered except with α,α-diphenyl-α-aminoacetic acid, the sodium salt of which was so insoluble that reaction with benzoyl chloride would not take place. Acids prepared are listed in Table V.

TABLE VI

PROPERTIES OF α,α-DIALKYL-α-BENZAMIDOACETAMIDES

Alkyl Groups Present	N, % Calcd.	N, % Found	M.P., °C	Oral Dose, Mg./Kg.	Protection Against Maximal Electroshock Seizure[a]
Dimethyl	13.60	13.58	199[b]	50	3+
Methyl ethyl	12.72	12.44	158[c]	44	1+
Diethyl	11.96	12.21	211–212[d]	500	3+
Methyl isobutyl	11.28	11.03	145–148	44	1+
Methyl *n*-pentyl	10.68	10.35	125	500	4+
Methyl phenyl	10.44	9.90	127[e]		
Ethyl phenyl	9.92	9.54	99	250	2+
Pentamethylene	11.38	11.12	187	200	4+

[a] E. A. Swinyard, ref. 6. [b] E. Mohr and T. Geis, *Ber.*, 41, 798 (1908) gave 201°. [c] Kjaer, *Acta Chem. Scand.*, 7, 889 (1953) gave 161–162°. [d] Kjaer gave 198–200°. [e] Kjaer gave 129–130°.

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.50; H, 6.84; N, 8.70. Found: C, 74.13; H, 7.05; N, 8.54.

α,α-Pentamethylene-α-aminoacetic acid was recovered unchanged from the phthaloylation mixture. α,α-Diphenyl-α-aminoacetic acid underwent decarboxylation as well as phthaloylation, giving *N*-benzohydrylphthalimide, recrys-

The acid chlorides and amides of the benzamido compounds were prepared in the manner described for the

(12) G. Vanags, *Acta Univ. Latviensis Kim. Fakultat.*, Ser. 4, No. 8, 405 (1939); *Chem. Abstr.*, 34, 1982 (1940).

(13) R. E. Steiger, *J. Org. Chem.*, 9, 396 (1944).

phthalimido amides. Crystalline amides prepared are listed in Table VI.

Acknowledgment. The authors gratefully acknowledge the kind assistance of Dr. Raymond Cunningham, Mr. Frank Smith, and Mr. Charles Rauh of the Pharmacology Department of Lederle Laboratories Division of American Cyanamid Company, who performed the pharmacological tests. The authors are also indebted to Mr. Louis Branconne who performed the analysis. Finally they wish to thank the Lederle Laboratories Division of American Cyanamid Company for financial support of the work in the form of a research fellowship.

STILLWATER, OKLA.

[CONTRIBUTION FROM THE "LABORATORIO DE QUÍMICA BIOLÓGICA," FACULTAD DE CIENCIAS MÉDICAS AND THE "LABORATORIO DE QUÍMICA ORGÁNICA," FACULTAD DE CIENCIAS EXACTAS Y NATURALES]

Reaction of Ammonia with Some Acetylated and Benzoylated Monosaccharides. IV. Derivatives of L-Rhamnose

JORGE C. DEFERRARI AND VENANCIO DEULOFEU

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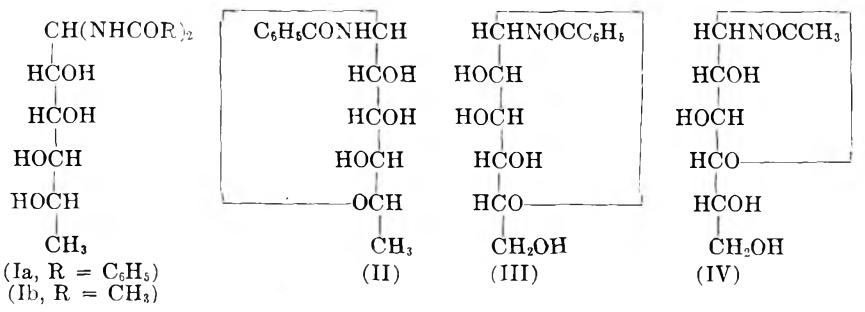
Tetrabenzoyl-L-rhamnose, on treatment with ammonia in methanol gave two products, *N,N'*-dibenzoyl-L-rhamnosylidenediamine and *N*-benzoyl-L-rhamnopyranosylamine. The products are analogous to those obtained previously from pentabenzoyl-D-mannose. Both tetraacetyl-L-rhamnose and pentaacetyl-7-desoxy-1-*glycero*-L-*gala*-heptononitrile, on treatment with ammonia in methanol, gave *N,N'*-diacetyl-L-rhamnosylidenediamine.

The formation of *N,N'*-diacetyl- and *N,N'*-dibenzoylhexosylidenediamines as the principal products, by the action of alcoholic ammonia on pentaacetyl- and pentabenzoylhexoses, is a general reaction which has been applied with success to derivatives of D-glucose,[1] D-mannose,[2] and D-galactose.[3] It has now been applied to tetraacetyl- and tetrabenzoyl-L-rhamnose, which is interesting for various reasons. In L-rhamnose, according to the mechanism of this reaction[4] only three acyl groups can participate in the intramolecular displacement and supply the elements for the formation of the amide molecules. Furthermore, benzoyl derivatives of this hexose, pentabenzoyl-D-mannose and hexabenzoyl-D-*glycero*-D-*gala*-heptononitrile, have a particular place in this reaction because they produce, at variance with the other hexoses, not only *N,N'*-dibenzoyl-D-mannosylidenediamine but also a cyclic monobenzamide compound, *N*-benzoyl-D-mannopyranosylamine.[2,5] Similar products were obtained when tetrabenzoyl-L-rhamnose was submitted to the ammonolysis. The principal one was *N,N'*-dibenzoyl-L-rhamnosylidenediamine (Ia) accompanied by *N*-benzoyl-L-rhamnopyranosylamine (II) in smaller amounts. L-Rhamnose was also present.



L-rhamnose has the same steric relationship in the asymmetric carbon atoms as D-mannose. The

That the *N*-benzoyl-L-rhamnosylamine and the *N*-benzoyl-D-mannosylamine (III) have a pyranose structure was determined by periodate oxidation. Each consumed two moles of periodate with production of one mole of formic acid; no formaldehyde was detected. For comparison purposes we studied the oxidation of *N*-acetyl-D-glucoforanosylamine (IV), to which a furanose structure was

(1) V. Deulofeu and J. O. Deferrari, *J. Org. Chem.*, **17**, 1087 (1952).

(2) J. O. Deferrari and V. Deulofeu, *J. Org. Chem.*, **17**, 1093 (1952).

(3) J. O. Deferrari and V. Deulofeu, *J. Org. Chem.*, **17**, 1097 (1952).

(4) H. S. Isbell and H. L. Frush, *J. Am. Chem. Soc.*, **71**, 1579 (1949); V. Deulofeu and J. O. Deferrari, *Anales. Asoc. Quim. Argentina*, **38**, 241 (1950); R. C. Hockett, V. Deulofeu, and J. O. Deferrari, *J. Am. Chem. Soc.*, **82**, 1840 (1950).

(5) P. Brigl, H. Mühlschlegel, and R. Schinle, *Ber.*, **64**, 2921 (1931).

assigned by Hockett and Chandler,[6] on the basis of its oxidation with lead tetraacetate. Niemann and Hays[7] found that its periodate oxidation was anomalous, consuming no less than five moles of oxidant.

In experiments carried at 35°, we have found that one mole of periodate is consumed very fast, with production of one mole of formaldehyde and no formic acid. The oxidation is produced between carbon atoms 5 and 6 in agreement with structure (IV). The rapid reaction is accompanied by slow reactions that lead to the production of nearly 3 moles of formic acid. This is explained by the formation and subsequent oxidation of tartronic aldehyde.[8]

By ammonolysis in methanol of tetraacetyl-L-rhamnopyranose, only *N,N'*-diacetyl-L-rhamnosylidenediamine (Ib) was obtained, with 38.6% yield. The same compound was produced by Wohl's degradation of the pentaacetyl-7-deoxy-L-*glycero*-L-*gala*-heptononitrile, with almost the same yield (40.5%). The results are indentical with those obtained with pentaacetyl-D-mannose.

Our pentaacetyl-7-deoxy-L-*glycero*-L-*gala*-heptononitrile was prepared by acetylation of the 7-deoxy-L-*glycero*-L-*gala*-heptononitrile and by dehydration of the pentaacetyl-7-deoxy-L-*glycero*-L-*gala*-heptonoamide. The products were identical in the two cases, but their physical constants do not agree with those of the similar compound described by Mikšic.[9]

The 7-desoxy-L-*glycero*-L-*gala*-heptononitrile has a higher melting point when recrystallized from acetic acid than when recrystallized from methanol, as was observed by Zemplen[10] with D-gluconononitrile.

The higher melting form exhibits a stable specific rotation when dissolved in water, while the lower melting form presents mutarotation of a complex nature, a difference which has also been described by Papadakis and coworkers[11] for the two similar forms of the D-gluconononitrile. Wolfrom, Thompson, and Hooper[12] found the same type of mutarotation with *N*-methyl glucosaminonitrile, prepared in alcoholic solution.

The existence of two forms of each nitrile, differing in melting point and stability of rotation, seems to be a general property of these substances as we have found that it is also the case with D-*glycero*-D-*gala*-heptononitrile.

(6) R. C. Hockett and L. R. Chandler, *J. Am. Chem. Soc.*, 66, 957 (1944).

(7) C. Niemann and J. T. Hays, *J. Am. Chem. Soc.*, 67, 1302 (1945).

(8) P. Fleury, *Bull. soc. chim. France*, 1126 (1956).

(9) J. Mikšic, *Vestnik Králov. Ceské. Společnosti. Nauk.*, Cl. II, 18 pp. (1926); *Chem. Abstr.* 23, 2941 (1926).

(10) G. Zemplen, *Ber.*, 60, 171 (1927).

(11) P. E. Papadakis and H. J. Cohen, *J. Am. Chem. Soc.*, 60, 765 (1939); P. E. Papadakis, *J. Am. Chem. Soc.*, 64, 1950 (1942).

(12) M. L. Wolfrom, A. Thompson, and I. R. Hooper, *J. Am. Chem. Soc.*, 68, 2343 (1946).

EXPERIMENTAL

*N,N'-Dibenzoyl-*L*-rhamnosylidenediamine* (Ia). Thirteen grams of tetrabenzoyl-α-L-rhamnopyranose[13] were dissolved, by shaking at room temperature, in 330 ml. methanolic ammonia, and the solution left standing for 24 hrs. It was then evaporated to dryness in vacuum at low temperature. The syrup obtained was dissolved in 40 ml. of ethanol and allowed to stand at 5° to deposit fine needles. The crystals were separated and well washed with ethanol. Yield: 0.95 g., m.p. 221–222.5°. The mother liquors were evaporated again to dryness in vacuum, and the residue dried in a desiccator. It was then extracted four times with 40 ml. of ethyl acetate to eliminate the benzamide. The ethyl acetate insoluble material was dissolved in the minimum amount of boiling water. By cooling, crystals appeared which were separated and found identical with the former product. Yield: 700 mg. m.p. 219° (total yield: 1.65 g.; 19%). For analysis the material was recrystallized once from ethanol and three times from water. Fine needles melting 222–223°. $[\alpha]_D^{26}$ + 14.4° (c, 0.693, pyridine).

Anal. Calcd. for $C_{20}H_{24}N_2O_6$: C, 61.84; H, 6.18; N, 7.21. Found: C, 61.25; H, 6.32; N, 6.29.

*N-Benzoyl-*L*-rhamnopyranosylamine*, (II). The aqueous mother liquors from the preparation of the second batch of crystals of *N,N'*-dibenzoyl-L-rhamnosylidenediamine were evaporated again to dryness and a crystalline residue obtained. This residue was suspended in a small amount of cold water, filtered, dried and treated first with boiling ethyl acetate and then with 2 ml. of warm ethanol. Rectangular prisms, melting at 237–238°, were obtained (yield: 110 mg.). Recrystallized five times from ethanol the material melted at 240–241°. $[\alpha]_D^{17}$ + 10.6 (c, 0.564, pyridine).

Anal. Calcd for $C_{13}H_{17}NO_6$: C, 58.42; H, 6.36. Found: C, 58.70; H, 6.15.

O-Tetrabenzoyl-N,N'-dibenzoylrhamnosylidenediamine. One gram of *N,N'*-dibenzoyl-L-rhamnosylidenediamine was dissolved in 12.5 ml. of pyridine, 3 ml. of benzoyl chloride was added, and the mixture was heated to 60–70° for 15 min. After 24 hr. standing at room temperature, it was poured into 200 ml. of ice water and extracted with chloroform. The chloroform solution was washed with cold 3*N* sulfuric acid, saturated sodium hydrogen carbonate solution and with water, and dried with sodium sulfate. By evaporation, a crystalline residue was obtained, that was recrystallized from 50 ml. of ethanol. Prisms melting 211–212°. Yield: 1.62 g. Recrystallized four times from ethanol, melted 213–213.5°. $[\alpha]_D^{14}$ −32.1° (c, 0.88, chloroform).

Anal. Calcd. for $C_{48}H_{40}N_2O_{10}$: C, 71.59; H, 4.97. Found: 71.40; H, 4.75.

Eight hundred milligrams of *O*-tetrabenzoyl-*N,N'*-dibenzoylrhamnosylidenediamine were dissolved with 20 ml. of methanolic ammonia and the solution, after standing 24 hr. at room temperature, was evaporated to dryness. The residue, by crystallization from ethanol yielded 380 mg. of material melting at 213–214°, and a second crop of 28 mg. Recrystallization of the material from water gave 320 mg. (83%) of *N,N'*-dibenzoyl-L-rhamnosylidenediamine, m.p. 222–223°. No *N*-benzoyl-L-rhamnopyranosylamine could be detected.

*O-Triacetyl-N-benzoyl-*L*-rhamnopyranosylamine.* The *N*-benzoyl-L-rhamnopyranosylamine (65 mg.) was boiled to dissolution, with 1.9 ml. of a mixture (1:1) of acetic anhydride and pyridine. After standing overnight, the solution was evaporated in a desiccator and 105 mg. of crystals melting at 205–220° were obtained. After four crystallizations from ethanol, m.p. 208° $[\alpha]_D^{20}$ + 25.1° (c, 0.596, chloroform).

Anal. Calcd. for $C_{19}H_{23}NO_8$: C, 58.00; H, 5.85; N, 3.56. Found: C, 58.40; H, 5.81; N, 3.40.

L-*Rhamnose.* The water mother liquors and washings from the preparation of *N*-benzoyl-L-rhamnopyranosylamine were

(13) R. K. Ness, H. G. Fletcher, and C. S. Hudson, *J. Am. Chem. Soc.*, 73, 296 (1951).

evaporated again to dryness. The residue after purification weighed 300 mg. and melted at 92–95°. In water solution it exhibited mutarotation with an equilibrium $[\alpha]_D^{20}$ + 8.7°, in substantial agreement with $[\alpha]_D^{20}$ + 8.9° reported by Hudson and Yanovsky.[14] Identification was confirmed by preparation of the previously known[15] L-rhamnose-*p*-phenylhydrazone, m.p. 191°.

Pentaacetyl-7-deoxy-L-glycero-L-gala-heptonoamide. Twelve grams of 7-deoxy-L-*glycero*-L-*gala*-heptonoamide[16] was suspended in 150 ml. of a mixture of pyridine and acetic anhydride (1:1) and stirred at 65–70°. The amide dissolved in 1.5 hr. and heating was continued for 15 min. The solution was cooled and poured into 300 ml. of ice water. The acetylated amide was separated, washed with ice water, and dried. Yield: 22.8 g. (94%) of crude crystalline product that melted at 130–131°. Dried at 100° in vacuum it melted at 146°.

For analysis, a sample was recrystallized three times from ethanol, m.p. 146–147° (dried in vacuum 100°), $[\alpha]_D^{22}$ −20.1° (c, 1.48, chloroform).

Anal. Calcd. for $C_{17}H_{25}NO_{11}$: C, 48.68; H, 5.99. Found: C, 47.86; H, 6.13.

Pentaacetyl-7-deoxy-L-glycero-L-gala-heptononitrile. Five grams of pentaacetyl-7-deoxy-L-*glycero*-L-*gala*-heptonoamide, was heated to 80–85° for 30 min., with 15 ml. of phosphorus oxychloride. The excess of the phosphorus oxychloride was eliminated by distillation in vacuum, and the residue dissolved in a mixture of 50 ml. of ice water and 150 ml. of chloroform. The chloroform solution was washed with water, a saturated solution of sodium hydrogen carbonate, water again, dried with sodium sulfate, and evaporated in vacuum. The oily residue crystallized from a small amount of warm ethanol, 1.8 g. (37.6%) of prisms melting at 124–125°. Recrystallized from ethanol, it melted at 127–218° $[\alpha]_D^{25}$ −33.9°, (c, 1.16, chloroform). Mikšic[9] gives m.p. 85–86° $[\alpha]_D^{20}$ −76.4°.

Anal. Calcd. for $C_{17}H_{25}NO_{10}$: C, 50.37; H, 5.53; CN, 6.48. Found: C, 50.76; H, 5.80; CN, 6.56.

One gram of the nitrile was shaken with 4 ml. of a mixture (1:1) of acetic acid and acetic acid saturated with hydrogen bromide. After 2 hr., when the material had dissolved, the solution was left 5 hr. at room temperature and then poured into ice water. The solid that precipitated was separated and recrystallized from ethanol. The product, pentaacetyl-7-desoxy-L-*glycero*-L-*gala*-heptonamide, was identical with that already described.

7-Desoxy-L-glycero-L-gala-heptononitrile. Two grams of L-rhamnose hydrate was dissolved in 1.05 ml. of warm water. The solution was cooled to 0°, two drops of 12% ammonia in water added and then 0.5 ml. of anhydrous hydrogen cyanide. Crystallization was induced by scratching with a glass rod. After allowing crystallization to continue for 30 min., 1 ml. of hydrogen cyanide was added. After another 30 min. the suspension was diluted with 10 ml. ethanol, kept for 30 min. at 0°, filtered, washed with cold ethanol, and dried in a desiccator. Yield: 600 mg., m.p. 112–115°. Recrystallized from acetic acid (3.3 ml. acid per g. of nitrile), prisms melting at 139–141° were obtained $[\alpha]_D^{25}$ −10.0° (c, 2.08, water); when these crystals were recrystallized from absolute ethanol (10 ml. ethanol per g. of nitrile) prisms melting at 115–116° were obtained. $[\alpha]_D^{20}$ −9.9° (initial) → +10.8° (75 min.) → 0.7° (final) 150 min. (H_2O, c, 1.45).

Pentaacetyl-7-desoxy-L-glycero-L-gala-heptononitrile by acetylation of 7-desoxy-L-glycero-L-gala-heptononitrile. Two hundred and fifty milligrams of the free nitrile, m.p. 115–116°, was dissolved at room temperature in a mixture of 3 ml. of pyridine and 3 ml. of acetic anhydride. After 24 hr. the solution was poured into 25 ml. of ice water. The acetylated nitrile that separated in crystalline form was collected on a filter, washed and dried; m.p. 127–128°, unchanged by recrystallization from ethanol.

Twenty mg. of the free nitrile, m.p. 139–141°, was acetylated exactly as described for the low melting form. The acetylated nitrile recrystallized from ethanol melted at 126–127°. Both preparations gave no depression when mixed with a sample of pentaacetyl-7-desoxy-L-*glycero*-L-*gala*-heptononitrile melting at 127–128°.

N,N'-Diacetylrhamnosylidenediamine. (Ib) (a) *From pentaacetyl-7-desoxy-L-glycero-L-gala-heptononitrile.* Three grams of the acetylated nitrile was dissolved at room temperature in 180 ml. of methanolic ammonia (16%). After 48 hr., the solution was evaporated to dryness in vacuum at low temperature. The well-dried residue was mixed with 18 ml. of absolute ethanol and the insoluble solid filtered. A yield of 800 mg. (40.5%) of crystals, m.p. 230–231°, was collected. Recrystallized from 70% ethanol, long needles, melting at 239–240° were obtained; $[\alpha]_D^{22}$ + 23.1° (c, 0.497, H_2O).

Anal. Calcd. for $C_{10}H_{20}N_2O_6$: C, 45.45; H, 7.57; N, 10.60. Found: C, 44.67; H, 7.58; N, 10.62.

(b) *From tetraacetyl-L-rhamnose.* Three grams of a mixture of α- and β-tetraacetyl-L-rhamnose prepared by the method of Fisher, Bergmann, and Rabe,[17] were dissolved in 60 ml. of methanolic ammonia. After 24 hr. at room temperature, the solution was evaporated in vacuum and the crystalline residue suspended in 8 ml. of cold ethanol and filtered. After washing with methanol, 920 mg. (38.6%) of fine needles melting at 238–239° were obtained. A mixed melting point determination showed the material to be the same as the *N,N'*-diacetylrhamnosylidenediamine, prepared from pentaacetyl-7-desoxy-L-*glycero*-L-*gala*-heptononitrile.

D-*Glycero*-D-*gala-heptononitrile.* It was prepared according to Brigl, Mühlschlegel, and Schinle.[5] Recrystallization from acetic acid yielded crystals melting at 149°, $[\alpha]_D^{20}$ + 19.9° (H_2O, c, 1.25). From ethanol m.p. 122–123°, $[\alpha]_D^{20}$ + 21.4 (initial) → + 2.7° (55 min.) → + 13.1° (final, 165 min.) (H_2O, c, 1.25). Mikšic[9] gives m.p. 121–122° $[\alpha]_D$ + 31.4.

Oxidation of N-benzoyl-L-rhamnopyranosylamine and N-benzoyl-D-mannopyranosylamine with periodate. *N*-benzoyl-L-rhamnopyranosylamine (13.55 mg., 5 × 10^{-5} moles) was dissolved in 40 ml. of water, 5.0 ml. of 0.1*M* solution of sodium periodate added (5.0 × 10^{-4} moles) and then water to 50 ml. After 18 hr. at room temperature, 1.83 moles of periodate per mole of substance were consumed and 1.0 mole of formic acid was titrated. Formaldehyde could not be detected with dimethyldihydroresorcinol. After 23 hr., results were substantially the same.

Under the same conditions, 28.30 mg. (1 × 10^{-4} moles) of *N*-benzoyl-D-mannopyranosylamine consumed after 24 hr., 2.0 moles of sodium periodate and produced 1.0 mole of formic acid per mole. Formaldehyde could not be detected.

Oxidation of N-acetyl-D-glucofuranosylamine with periodate. *N*-Acetyl-D-glucofuranosylamine (88.4 mg.) was dissolved in water, 25 ml. of 0.1*M* solution of sodium periodate

TABLE I

OXIDATION OF *N*-ACETYL-D-GLUCOFURANOSYLAMINE WITH PERIODATE (35°) IN MOLES PER MOLE OF SUBSTANCE

Time, Min.	$NaIO_4$ Consumed	Formic Acid	Formaldehyde
15	1.19	0.00	1.00
75	1.49	0.10	—
135	2.16	0.32	0.958
205	2.56	0.84	—
275	3.01	1.13	—
1195	4.21	2.11	—
1690	5.23	2.76	0.998

(14) C. S. Hudson and E. Yanovsky, *J. Am. Chem. Soc.*, 39, 1032 (1917).

(15) A. W. van der Haar, *Anleitung zum Nachweiss, zur Trennung und Bestimmung der Monosaccharide und Aldehydsäuren*, Geb. Borntraeger, Berlin, 1920, page. 184.

(16) E. L. Jackson and C. S. Hudson, *J. Am. Chem. Soc.*, 56, 2455 (1934).

(17) E. Fischer, M. Bergmann, and A. Rabe, *Ber.*, 53 2362 (1920).

added, the volume completed to 200 ml., and the resulting solution maintained at 35°. Samples were taken at intervals, the periodate consumed and the formic acid produced were titrated in the usual way. Formaldehyde was determined according to Reeves.[18] Results are given in the table below.

(18) R. E. Reeves, *J. Am. Chem. Soc.*, 63, 1476 (1941).

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BUENOS AIRES, ARGENTINA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITÉ DE MONTRÉAL]

Preparation of L-Cystinyl and L-Cysteinyl Peptides Through Catalytic Hydrogenation of Intermediates

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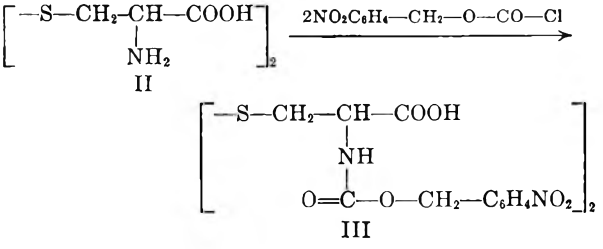
The preparation of peptides containing cystine or cysteine by the general method of catalytic hydrogenolysis of intermediates becomes possible if the classical carbobenzoxyl group is replaced by the more labile *p*-nitrocarbobenzoxyl radical to cover uncondensed α-amino groups. The hydrogenation procedure can be arrested at the cystine stage or allowed to proceed to cysteine. Likewise, if the *p*-nitrobenzyl radical is used to cover the thio group of cysteine, it can be removed by catalytic hydrogenation, whereas *S*-benzylcysteine intermediates are only cleaved by sodium in liquid ammonia. The preparation of L-cystinyldiglycine, L-cystinyldi-L-phenylalanine, and of L-cysteinyl-L-phenylalanine are proposed as typical examples.

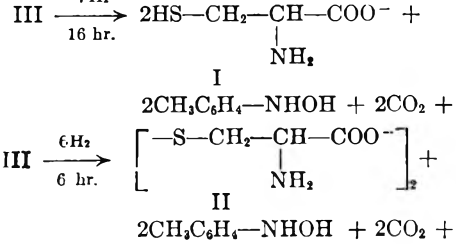
Cystine has been reduced to cysteine by catalytic hydrogenation with palladium.[1,2] However, in attempting to hydrogenate dicarbobenzoxycystine according to the general Bergmann and Zervas procedure,[3] White[4] found that no reduction took place. It has indeed frequently been observed and it is now accepted that the efficiency of palladium or of platinum as a catalyst is sharply reduced whenever sulfur is present in the form of a dithio linkage as in cystine, of a thiol group as in cysteine, or of a thioether as in *S*-benzylcysteine. The exact limits of this incompatibility have not, however, been explored since Siffered and du Vigneaud's alternate method[5] of reduction of *N*-carbobenzoxyl and *S*-benzyl derivatives of cystine or of cysteine with sodium in liquid ammonia was adopted at an early period for the introduction of these two amino acids in synthetic peptides.

The authors have previously shown[6] that α-*p*-nitrocarbobenzoxy-L-arginyl derivatives are easily reduced to L-arginyl peptides by hydrogen at atmospheric pressure in the presence of palladium on carbon. In view of the increased ease of removal of the *p*-nitrocarbobenzoxyl radical which was noted as a result of labilization by the strong inductive effect of the nitro group, the authors were brought to use this radical to cover the basic amino groups of cystine and to investigate the possibility of its removal by catalytic hydrogenation under conditions where the carbobenzoxyl group is stable.

Di(*p*-nitrocarbobenzoxy)-L-cystine III was prepared by condensing *p*-nitrocarbobenzoxyl chlorocarbonate with L-cystine II in tetrahydrofuran or dioxane. The disubstituted cystine was submitted

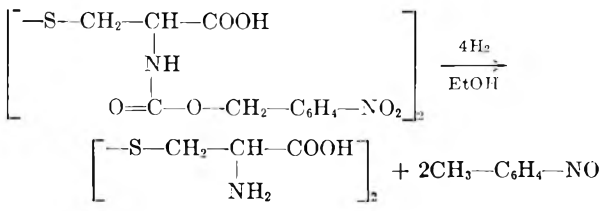


to catalytic hydrogenation at room temperature under atmospheric pressure in the presence of palladium black on carbon. In aqueous medium, when the disubstituted cystine was dissolved as the sodium salt, absorption of hydrogen proceeded rapidly at first, and continued until an equivalent of seven moles were consumed in about 16 hr. The products of reduction consisted of L-cysteine I and *p*-tolylhydroxylamine. If the hydrogenation process was arrested when 6 moles of hydrogen had been absorbed (about 6 hr.), L-cystine II and *p*-tolylhydroxylamine were obtained.

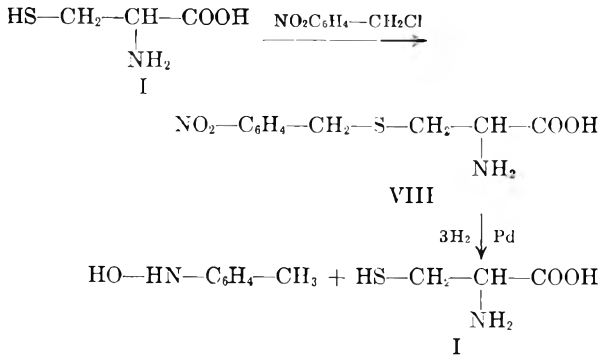


(1) M. Bergmann and G. Michalis, *Ber.*, 63B, 987 (1930).
(2) E. Kavanagh Kevin, *J. Am. Chem. Soc.*, 65, 2721 (1942).
(3) M. Bergmann and L. Zervas, *Ber.*, 65, 1192 (1932).
(4) J. White, *J. Biol. Chem.*, 106, 141 (1934).
(5) H. Sifferd and V. du Vigneaud, *J. Biol. Chem.*, 108, 753 (1953).
(6) C. Berse and L. Piché, *J. Org. Chem.*, 21, 808 (1956).

When the disubstituted cystine was hydrogenated in ethanol, four moles of hydrogen only were absorbed. Cystine was afforded in quantitative yield (96%) while *p*-nitroso-toluene was also probably formed. Reduction to cysteine was not then possible, cystine precipitating out of solution as it is formed.



The authors have found that *S*-*p*-nitrobenzylcysteine is similarly reduced by catalytic hydrogenation, whereas *S*-benzylcysteine is cleaved only by reduction with sodium in liquid ammonia.[4] *S*-*p*-nitrobenzyl-L-cysteine VIII was prepared by condensing L-cysteine I with *p*-nitrobenzyl chloride; it was suspended in 1*N* HCl or dissolved in alcohol and hydrogenated at room temperature, under atmospheric pressure over 10% palladium on carbon. Three moles of hydrogen were absorbed and cysteine was obtained.



L-cysteinyl dipeptides or symmetrical L-cystinyl tripeptides were accordingly prepared by first condensing di(*p*-nitrocarbobenzoxy)-L-cystine III with the ethyl ethers of glycine and of phenylalanine by the mixed anhydride method.[7]

The resulting covered ester of a symmetrical tripeptide IV was saponified with a slight excess of sodium hydroxide in the cold; the dithio linkage and the peptide bond remain untouched, and the resulting dicarboxylic structure V is hydrogenated as indicated for III. Partial hydrogenation, arrested when four moles of hydrogen have been absorbed, yields the L-cystinyl symmetrical tripeptides VI. Or V can be fully hydrogenated to provide the L-cysteinyl dipeptides VII. Oxidation of VII with air in alkaline aqueous solution affords a return to VI; cystinyl derivatives thus obtained were found to be identical to those prepared directly by partial reduction.

The labilization of the classical carbobenzoxyl and benzyl groups produced by the introduction of a *p*-nitro radical affords the possibility of reducing peptide intermediates containing cystinyl or cysteinyl residues, in which part of the structure is not amenable to reduction with sodium in liquid ammonia.

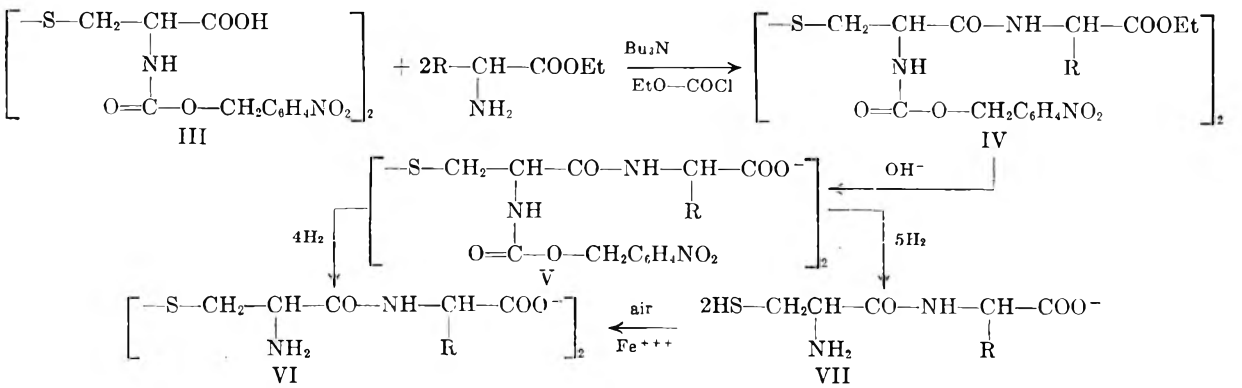
EXPERIMENTAL

Melting points, unless otherwise indicated, have been determined in semicapillary tubes and are uncorrected. In some cases where the materials decomposed, instantaneous melting points have been determined on the Maquenne block.

Di-p-nitrocarbobenzoxy-L-cystine. L-cystine (12 g., 0.05 mole) was dissolved in 50 ml. of 2*N* NaOH and 20 ml. of purified dioxane was added. The solution was stirred vigorously and cooled to 0°; *p*-nitrocarbobenzoxyl chloride (33 g., 0.15 mole) dissolved in 150 ml. of dioxane with 100 ml. of 2*N* NaOH was added in 5 portions (30 min.). Stirring was continued for 0.5 hr. after the addition of all reactants. The mixture was allowed to come to room temperature and 300 ml. of water was added. The resulting alkaline solution was washed twice with ethyl acetate and acidified to Congo Red with 1*N* HCl. The product was extracted 4 times with 100-ml. portions of ethyl acetate. After evaporation of the ethyl acetate, the crude product, an oil, was crystallized from nitromethane. Yield: 22.2 g. (74%); m.p. 110–111°; $[\alpha]_D^{25}$ − 126.4 (c, 2.0 in ethanol).

Anal. Calcd. for $C_{22}H_{22}N_4O_{12}S_2$: C, 44.16, H, 3.70; N, 9.36. Found: C, 44.16; H, 3.73; N, 9.28.

Hydrogenation of di-p-nitrocarbobenzoxy-L-cystine. (a) *In aqueous solution.* Di-*p*-nitrocarbobenzoxy-L-cystine (0.599 g.,



R = H (glycine)
R = CH_2-C_6H_5 (L-phenylalanine)

(7) R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951).

1mmole) was dissolved in .05*N* NaOH (40 ml.) and was hydrogenated at room temperature and at atmospheric pressure over 10% palladium on carbon (250 mg.). After approximately 6 hr., 6 moles of hydrogen were absorbed. The catalyst and *p*-tolylhydroxylamine were separated by filtration and the solution was acidified to *p*H 5 with HCl. By concentration, L-cystine crystallized in practically quantitative yield.

When hydrogenation was allowed to continue, an extra mole of hydrogen was absorbed in the course of 10 hr. After filtration, the solution was neutralized with HCl, concentrated to a low bulk under reduced pressure, and the residue was dissolved in warm 5*N* HCl. On cooling, the hydrochloride of L-cysteine crystallized. Yield, 284 mg. (90%).

p-Tolylhydroxylamine was extracted with ether from the mother liquors and recrystallized from a mixture of benzene and petroleum ether. It melted at 93–94°.

(b) *In alcohol.* Di-*p*-nitrocarbobenzoxy-L-cystine (0.599 g., 1 mmole) was dissolved in 95% ethanol (40 ml.) and was hydrogenated as above. After approximately 6 hr., 4 moles of hydrogen were absorbed, and the reaction ceased. It was found that cystine precipitated out of solution as it was formed. Filtration separated the catalyst and cystine; cystine was extracted with 20 ml. of *N* NaOH. After filtration, the solution was acidified with HCl to *p*H 5. By concentration, L-cystine crystallized. Yield, 230 mg. (96%).

The mother liquor contained a yellow, unstable product which was considered to be *p*-nitrosotoluene; no formal characterization was attempted.

Ethyl di-p-nitrocarbobenzoxy-L-cystinyl diglycinate. Di-*p*-nitrocarbobenzoxy-L-cystine (4.8 g., 0.008 mole) was dissolved in tetrahydrofuran, (30 ml.) previously dried over sodium, and tri-*n*-butylamine (3.8 ml., 0.016 mole) was added. The mixture was cooled with ice-salt mixture and ethyl choroformate (1.5 ml., 0.016 mole) was added. The mixture was stirred for 15 min. After this time, a solution of glycine ethyl ester hydrochloride (2.23 g., 0.016 mole) and tri-*n*-butylamine (3.8 ml., 0.016 mole) in chloroform (20 ml.) was added. The mixture was stirred for 1 hr. at room temperature and the solvent was evaporated *in vacuo* at 50–60°. The residue, a thick oil, was dissolved in chloroform (100 ml.) and this solution was washed with 1*N* HCl, water, 5% aqueous bicarbonate and water, and then dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the residue was recrystallized from nitromethane. Yield, 4.4 g., (75%); m.p. 160–161, $[\alpha]_D^{25}$ − 76.6 (*c*, 1.1, in acetone).

Anal. Calcd. for $C_{30}H_{36}N_6O_{14}S_2$: C, 46.87; H, 4.72; N, 10.82. Found: C, 46.84; H, 4.68; N, 10.94.

Ethyl di-p-nitrocarbobenzoxy-L-cystinyl-di-L-phenylalanate. This compound was prepared from di-*p*-nitrocarbobenzoxy-L-cystine (2.4 g.) and phenylalanine ethyl ester hydrochloride (1.83 g.) as above, and recrystallized from nitromethane; yield, 3.1 g. (81%); m.p. 173–174°; $[\alpha]_D^{25}$ − 37.8 (*c*, 0.6 in acetone).

Anal. Calcd. for $C_{44}H_{48}N_6O_{14}S_2$: C, 55.68; H, 5.09; N, 8.85. Found: C, 55.65; H, 5.09; N, 8.80.

Di-p-nitrocarbobenzoxy-L-cystinyldiglycine. Ethyl di-*p*-nitrocarbobenzoxy-L-cystinyldiglycinate (2 g.) was dissolved in dioxane (75 ml.) and NaOH 0.1*N* (70 ml.) was added in two portions during the course of 1 hr. The mixture was stireed at 0–5° for the first hour and at room temperature for 0.5 hr. Four hundred ml. of water was added to the solution. The solution was extracted with ethyl acetate, and the aqueous layer was acidified to Congo Red with concentrated hydrochloric acid. The resulting crystalline product was collected, and was recrystallized from nitromethane. Yield, 1.75 g., (95%); m.p. 111–113°; $[\alpha]_D^{25}$ − 79.8 (*c*, 1.3 in acetone).

Anal. Calcd. for $C_{26}H_{28}N_6O_{14}S_2 \cdot H_2O$: C, 43.01; H, 4.14; N, 11.50. Found. C, 43.02; H, 4.29; N, 11.32.

Di-p-nitrocarbobenzoxy-L-cystinyl-di-L-phenylalanine. Ethyl di-*p*-nitrocarbobenzoxy-L-cystinyldiphenylalanate (2 g.) was dissolved in dioxane (70 ml.) and 0.2*N* NaOH (23 ml.) was added in two portions during the course of 1 hr. The mixture was stirred at 0–5° for the first hour and at the room temperature for 0.5 hr. The solution was acidified to Congo Red and extracted with ether. The ether layer was dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the residue was recrystallized from dioxane (minimum)-ether. Yield, 1.6 g., (85%); m.p. 118–120°; $[\alpha]_D^{25}$ − 49.1 (*c*, 2.5 in acetone).

Anal. Calcd. for $C_{40}H_{40}O_{14}N_6S_2$. C, 53.80; H, 4.51; N, 9.41. Found: C, 53.91; H, 4.85; N, 9.20.

L-Cystinyldiglycine. Di-*p*-nitrocarbobenzoxy-L-cystinyldiglycine (7.30 g.) was dissolved in 95% ethanol (25 ml.). The compound was hydrogenated for 8 hr. at room temperature and at atmospheric pressure over 10% palladium on carbon (250 mg.). Filtration separated the catalyst and L-cystinyl diglycine; L-cystinyl-diglycine was extracted with 20 ml. of *N* NaOH. The solution was neutralized to litmus with HI (15%). After filtration, the solvent was concentrated *in vacuo* at 40–50°; the product then was precipitated with ethanol. The peptide was recrystallized from water-ethanol. Yield: 0.320 g. (90%), m.p. 210° dec. (literature[8] m.p. 210° dec.) $[\alpha]_D^{25}$ − 84.2 (c, 0.5 in 1*N* HCl).

Anal. Calcd. for $C_{10}H_{18}N_4O_6S_2$. C, 33.89; H, 5.12; N, 15.79. Found. C, 34.39; H, 5.27; N, 15.40.

L-Cystinyl-di-L-phenylalanine (2 HCl). Di-*p*-nitrocarbobenzoxy-L-cystinyldi-L-phenylalanine (0.893 g., 1 mmole) was hydrogenated in 95% ethanol (30 ml.) in the manner described above; L-cystinyldi-L-phenylalanine was extracted with 20 ml. of *N* NaOH. The solution was neutralized to litmus with HI (15%). After filtration, the solvent was evaporated *in vacuo* at 40–50° and the residue was washed with ethanol in order to remove sodium iodide. The solution of the peptide in *N*-hydrochloric acid at about 5% concentration slowly deposited crystals; addition of an equal volume of concentrated hydrochloric acid and chilling gave the hydrochloride. Yield: 0.530 g. (87%), m.p. 256° dec. $[\alpha]_D^{25}$ − 57.3 (*c*, 0.8 in 1*N* HCl).

Anal. Calcd. for $C_{24}H_{32}N_4O_6Cl_2S_2$: C, 47.43; H, 5.31; N, 9.22. Found: C, 47.45; H, 5.38; N, 9.23.

L-Cysteinyl-L-phenylalanine. L-cystinyldi-L-phenylalanine hydrochloride (0.608 g., 1 mmole) was dissolved in 1*N* NaOH (40 ml.). The compound was hydrogenated for 12 hr. at room temperature and atmospheric pressure over 10% palladium on carbon (250 mg.). The catalyst was then removed by filtration and the filtrate was concentrated and adjusted to about *p*H 4.8 by addition of concentrated HCl. Crystals were obtained by adding ethanol cautiously to a small portion of the solution, and on inoculation of the main bulk, crystallization rapidly set in. After keeping overnight, the precipitate was collected and dried. Yield: 0.485 g., (91%), m.p. > 300° (dec.) $[\alpha]_D^{25}$ − 8.9 (*c*, 2, 1*N* HCl).

Anal. Calcd. for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.67; H, 5.99; N, 10.40.

S-p-Nitrobenzyl-L-cysteine. L-cysteine hydrochloride (3.14 g., 20 mmoles) was dissolved in 1*N* NaOH (60 ml., 60 mmoles). The solution was stirred vigorously and *p*-nitrobenzyl chloride (1.71 g., 20 mmoles) dissolved in dioxane (30 ml.) was added at 0° during 30 min., in five approximately equal portions. The reaction mixture was then stirred at room temperature for 30 min. The resulting alkaline solution was washed twice with ether, acidified to litmus with concentrated HCl and the organic solvent was evaporated *in vacuo*. *S-p*-nitrobenzyl-L-cystine hydrate precipitated within a few hours and was recrystallized from hot water. Yield: 3.2 g. (60%); m.p. 233–234°. For analysis the product was dried for 18 hr. *in vacuo* over P_2O_5 at 78°.

Anal. Calcd. for $C_{10}H_{12}N_2O_4S \cdot H_2O$: C, 43.78; H, 5.14; N, 10.21. Found: C, 43.73; H, 5.09; N, 10.22.

Ethyl ester, m.p. 172–173°. $[\alpha]_D^{25}$ + 27.3 (*c*, 1.06 in ethanol 95%).

Anal. Calcd. for $C_{12}H_{16}O_4N_2S \cdot HCl$: C, 44.93; H, 5.02; N, 8.73. Found. C, 44.80; H, 5.31; N, 8.69.

(8) H. S. Loring and V. du Vigneaud, *J. Biol. Chem.*, **111**, 385 (1935).

Catalytic reduction of S-p-nitrobenzyl-L-cysteine. S-p-nitrobenzyl-L-cysteine H_2O (0.548 g.) was dissolved in ethanol (40 ml.) and 1*N* HCl (20 ml.). The compound was hydrogenated for 3 hr. at room temperature and atmospheric pressure over 10% palladium on carbon (138 mg.). The catalyst was separated by filtration. The filtate gave the positive nitroprusside test for sulfhydryl. The product was precipitated as mercaptide with Hopkin's reagent. After 24 hr., the mercaptide was filtered and washed with cold water. The product was suspended in water (20 ml.) then stirred and saturated with H_2S, and the mercury sulfide was separated by filtration. The filtrate was made alkaline with sodium hydroxide and a small crystal of copper sulfate was added. Air was bubbled through the solution until the violet color disappeared (2 hr.). The solution was decolorized with charcoal, filtered, and neutralized with HCl. Crystallization soon began. After standing for 2 hr. at room temperature, the product was filtered, washed with cold water, alcohol and ether. For recrystallization the product was dissolved in 1*N* NaOH, then neutralized with 1*N* HCl. Yield: 96 mg. (40%), m.p. 255–260° (dec.) $[\alpha]_D^{25}$ − 225° (*c*, 1.04 in 1*N* HCl).

Acknowledgment. The authors wish to express their thanks for the aid of Rougier Frères Ltée who supported their research.

MONTREAL, QUE.
CANADA

Isolation of Vitamin Dm and Vitamin D_3 from the Irradiation Products Obtained from Sterols of the Mussel, *Modiolus Demissus*, Dillwyn[1]

HAROLD G. PETERING[2]

Received November 3, 1954

A new vitamin D named vitamin Dm has been isolated from the irradiation products of the sterols derived from the ribbed mussel, *modiolus demissus*, Dillwyn. It has been characterized by the physical and chemical properties of the crystalline dinitrobenzoate. Its biological efficacy has been shown to be about 30,000,000 U.S.P. or A.O.A.C. units per g. of resin, and to be equal for rats and chicks.

The new compound is distinct from the known purified and crystalline vitamins D. It exists side by side in the ultraviolet irradiation products of the mussel sterols with vitamin D_3. A method for separating these two compounds as the dinitrobenzoates is described.

According to available reports only three compounds having vitamin D activity have been obtained in crystalline form or as crystalline derivatives. Calciferol, or vitamin D_2, was first obtained by Askew *et al.*,[3] and later also by Windaus and coworkers.[4] Vitamin D_3 was first isolated by Brockmann[5,6] from fish liver oils as the crystalline dinitrobenzoate, from which Brockmann and Busse[7,8] prepared the crystalline vitamin. Later the same compound was obtained by Windaus, Schenck, and von Werder[9] and by Schenck[10] from the irradiation products of 7-dehydrocholesterol both as crystalline esters and as the free alcohol. Finally, vitamin D_4 was obtained in pure form as the free alcohol and as an ester by Windaus and Trautmann[11] from the irradiation products of 22,23-dihydroergosterol.

The biological efficacy of these three vitamins D are established with reasonable accuracy because of the availability of the pure compounds. The existence of other vitamins D from time to time has been reported, but in every instance the evidence rests on comparative biological assay and little actually is known of the structure of these compounds or of their real efficacy and physiological function.

This report deals with the isolation of a fourth vitamin D, vitamin Dm, from the irradiation products of the sterols obtained from the mussel, *modiolus demissus*, Dillwyn, and also describes the separation of this compound from vitamin D_3 which is also found in the irradiation products of the mussel sterols.

Petering and Waddell[12] recently described the isolation and characterization of a new provitamin Dm which was isolated from the same ribbed mussel, *modiolus demissus*, Dillwyn, and which appears to be a C_{29} sterol. In the early stages of that investigation of the sterols of the ribbed mussel, it did not seen likely that a sufficient sample of the purified provitamin Dm would be available to permit a careful study of its properties and also allow for the irradiation of a portion for the isolation of the corresponding vitamin D. Therefore, it was de-

(1) This work was carried out in the Biological Laboratory of the E. I. du Pont de Nemours & Co., Inc.

(2) Present Address: The Upjohn Co., Kalamazoo, Mich.

(3) F. A. Askew, R. B. Bourdillon, H. M. Bruce, R. K. Callow, J. S. L. Philpot, and T. A. Webster, *Proc. Royal Soc.* (*Lond.*), 109B, 488 (1932).

(4) A. Windaus, A. Luttringhaus, and M. Deppe, *Ann.*, 489, 252 (1931); A. Windaus, and A. Luttringhaus, *Z. Physiol. Chem.*, 203 70 (1931).

(5) H. Brockmann, *Z. Physiol. Chem.*, 241, 104 (1936).

(6) H. Brockmann, *Z. Physiol. Chem.*, 245, 96 (1936).

(7) H. Brockmann, and A. Busse, *Z. Physiol. Chem.*, 249, 176 (1937).

(8) H. Brockmann, and A. Busse, *Naturwissenschaften*, 26, 122 (1938).

(9) A. Windaus, F. Schenck, and F. v. Werder, *Z. Physiol. Chem.*, 241, 100 (1936).

(10) F. Schenck, *Naturwissenschaften*, 25, 159 (1937).

(11) A. Windaus, and G. Trautmann, *Z. Physiol. Chem.*, 247, 185 (1937).

(12) H. G. Petering, and J. Waddell, *J. Biol. Chem.*, 191, 765 (1951).

cided to attempt the isolation and separation of the vitamins D produced commercially by the irradiation of the crude mussel sterols, a sufficient quantity of which had been made available to me, even though it was realized that such a study might be complicated by the presence of a multiplicity of active compounds.

This investigation resulted in the separation of the total vitamin D fraction from the other irradiation products and unchanged sterols as crude dinitrobenzoates, and the subsequent purification of this fraction and its separation into two distinct compounds, one being vitamin D_3 dinitrobenzoate and the other a new compound named vitamin Dm dinitrobenzoate. There was no evidence for the existence of vitamin D_2 in the crude vitamin fraction, and other unpublished work shows that the vitamin fraction contained no compounds having low chick-activity.

The data presented here indicate that vitamin Dm constitutes a large portion of the vitamin D formed by the irradiation of mussel sterols, and that it has a biological efficacy of about 30,000,000 U.S.P. and A.O.A.C. units per gram. A gram of the crystalline dinitrobenzoate contains about 20,000,000 U.S.P. and A.O.A.C. units of vitamin D activity. These values indicate that vitamin Dm is definitely of the D_3-type in its biological action, but is only about two-thirds as active as vitamin D_3.

Vitamin Dm dinitrobenzoate crystallizes readily from acetone in light yellow needles which tend to form rosettes, and is hardly distinguished from the high melting form of vitamin D_3 dinitrobenzoate obtained from the same solvent. No evidence of polymorphism of vitamin Dm dinitrobenzoate was obtained during this investigation.

The physical properties, like the biological activity, of vitamin Dm are distinctly different from those of any other known vitamin D. The absorption spectra of vitamin Dm and vitamin D_3 dinitrobenzoates are qualitatively similar, but the specific absorption of the former ester is considerably less than is that of the latter. At 2650 Å the ratio of the specific constants of vitamin Dm and vitamin D_3 dinitrobenzoates is 1.07, and the ratio of specific rotation constants is also 1.07, which probably reflect the larger molecular weight of the vitamin Dm moiety rather than any peculiar difference in structure. The mixed melting point of the dinitrobenzoates of vitamins Dm and D_3 is lower than that of either, and has a wide range as well as a clearing point not observed with either compound alone. These facts together with the isolation of vitamin D_3 dinitrobenzoate from the same crude irradiation fraction indicate the distinctiveness of vitamin Dm.

The vitamin D_3 dinitrobenzoate obtained from crude mussel vitamin D esters has been characterized by its physical and chemical properties, all of which are identical with those reported in the literature[14,15] and which are identical with similar compounds prepared from the irradiation products of 7-dehydrochholesterol. The mixed melting point of the isolated ester and an authentic sample of vitamin D_3 dinitrobenzoate shows no lowering of the value which identifies the latter compound and no lack of sharpness. As further evidence of the identity of the compound obtained from the mussel vitamin fraction, the dinitrobenzoate has been obtained in two crystalline forms, the melting points of which correspond with those of vitamin D_3 dinitrobenzoate.

The fact that vitamin D_3 dinitrobenzoate has been obtained in good yield from the crude irradiation products of mussel sterols indicates that 7-dehydrocholesterol must constitute an appreciable portion of the provitamins D present in *modiolus demissus*, Dillwyn.

EXPERIMENTAL

Isolation of vitamin Dm dinitrobenzoate (I). Two hundred milliliters of ethanolic solution of the activation products of crude sterols obtained from *modiolus demissus*, Dillwyn by the method of Rosenberg and Waddell[13] and containing about 25 g. of transformed provitamin D was used as the starting product. The bulk of the sterols had been previously removed by crystallization at 5°. The alcohol was removed by distillation under nitrogen at reduced pressure. The residual resin was dissolved in 200 ml. of benzene and the solution was again concentrated under nitrogen at reduced pressure to 60 ml. to remove alcohol and traces of water. Sixty milliliters of dry pyridine were added to the benzene solution and this was followed with the slow addition under constant agitation of 33 g. of 3,5-dinitrobenzoyl chloride in 80 ml. of dry benzene. The mixture, which had warmed to 60° during the addition of the acid chloride, was allowed to stand at room temperature for 16 hr., after which the pyridinium chloride was removed by filtration and washed with benzene.

The filtrate and benzene washings were transferred to a separatory funnel and washed successively with several volumes of 10% acetic acid, 5% sodium carbonate solution, and finally water to remove the excesses of pyridine and acid chloride which remained. The benzene layer was dried over anhydrous sodium sulfate and passed through a large chromatographic column containing 225 g. of 60–80 mesh adsorptive grade alumina. The vitamins D dinitrobenzoates were washed through the column with benzene, the washing being continued until the filtrates were clear, leaving a brown impurity remaining on the column.

The benzene filtrate was concentrated under nitrogen at reduced pressure and at 65° bath temperature until the resin containing only a trace of benzene was obtained. The resin, which weighed 36 g., was dissolved in 35 ml. of acetone. This solution deposited a crystal crop of 3.4 g. on standing 24 hr. at 5°; the crystals were high-melting mixed sterol esters and were discarded. The filtrate from this crop and the acetone washings were combined and methanol was added until a permanent turbidity remained at room temperature. The mixture was allowed to stand at 5° until two layers separated. The upper methanolic layer was removed

(13) H. R. Rosenberg, and J. Waddell, *J. Biol. Chem.*, 191, 757 (1951).

(14) W. Huber, G. W. Ewing, and J. Kriger, *J. Am. Chem. Soc.*, 67, 609 (1945).

(15) W. Huber, and O. W. Barlow, *J. Biol. Chem.*, 149, 125 (1943).

and an amount of acetone equal to the remaining lower layer was added. Ethanol was added dropwise until a slight turbidity appeared and then acetone was added dropwise until this turbidity just disappeared. This solution was set aside at 5° for 24 hr., after which a crop of crystals (A) weighing 5.1 g. was removed and washed with cold acetone.

The mother liquor and washings were concentrated by distillation under nitrogen and at reduced pressure until a thick resin remained. The resin was taken up in an amount of acetone equal to its volume, ethanol was added until a slight turbidity resulted, and the mixture was cleared with acetone. Crystallization was again allowed to proceed at 5°, with the formation of 1.7 g. of crop B. Repetition of this procedure produced a C crop of 2.8 g.

The A and B crops (6.8 g.) were combined and dissolved in 60 ml. of boiling acetone. The hot solution was filtered, and after cooling to room temperature the solution was allowed to stand at 5° for several days. The first crop of light yellow crystals consisting of rosettes of needles was filtered and carefully washed with cold acetone. It amounted to 5.0 g. and had a melting point of 127–128°, and an $[\alpha]^{25}_{5461}$ + 100 (1.14% in $CHCl_3$). A second crop of crystals amounting to 0.70 g. and having a m.p. of 124–125° was obtained from the mother liquor.

The dinitrobenzoate having a m.p. of 127–128° (4.7 g.) was recrystallized from 35 ml. of acetone at room temperature to give 3.5 g. of vitamin Dm dinitrobenzoate (I) having a m.p. of 128.0–128.5°, and $[\alpha]^{25}_{D}$ + 90.8 (1.60% in $CHCl_3$) and $[\alpha]^{25}_{5461}$ + 106.0 (1.16% in $CHCl_3$).

The mother liquor from this recrystallization step as well as the C-crop and second crystal crops described above were worked up to yield 2.6 g. of a similar preparation of vitamin Dm dinitrobenzoate with a m.p. of 128–129° and $[\alpha]^{25}_{D}$ +90.8 (1.6% in $CHCl_3$). Thus a total of 6.1 g. of vitamin Dm dinitrobenzoate of highest purity was obtained from the starting material, which represents about 40% of the estimated amount of vitamin D available.

Further attempts to raise the purity of these preparations by crystallization from acetone and other solvents such as methyl ethyl ketone or by a combination of these with chromatographic methods failed to change the physical constants given above. $E^{1\%}_{1\ cm.}$ (2650 Å) = 38.0 ± 0.5 (solvent 1% $CHCl_3$- 99% ethanol). This value is significantly lower than that of vitamin D_3 dinitrobenzoate found to be 40.6 ± 0.5.

Anal. Found: C, 71.25, 71.52; H, 8.24, 8.30; N, 5.50, 5.22.

Isolation of vitamin D_3 dinitrobenzoate (II) *from the irradiation products of mussel sterols.* During the course of the work described above it was observed that a small amount of a vitamin D ester could be obtained from one of the crops of crude dinitrobenzoate by crystallization from methyl ethyl ketone, which on purification appeared to be vitamin D_3 dinitrobenzoate. The amount obtained was too small for extensive analyses, and therefore an attempt was made to fractionate a larger amount of crude vitamins D dinitrobenzoates obtained from the irradiation products of ribbed mussel sterols. Esterification and separation of the vitamins D dinitrobenzoates from unchanged sterol esters and impurities was accomplished as described for (I) above.

Thirty-eight grams of purified crude esters, labeled Fraction I, were dissolved in 150 ml. of warm methyl ethyl ketone, and the solution allowed to stand at room temperature for deposition of crystals. Fraction IA, amounting to 18.8 g., had $[\alpha]^{25}_{D}$ +93.4 (1.00% in $CHCl_3$). A second crop of crystals, Fraction IB, was obtained from the mother liquor by adding an equal volume of methanol and allowing the crystallization to go on at 5°. Fraction IB amounted to 13.1 g. and had an $[\alpha]^{25}_{D}$ +85.4 (1.00% in $CHCl_3$). A small third crop of crystals with low specific rotation constant and the mother liquor were discarded.

In a similar manner 32 g. of Fraction II was dissolved in 200 ml. of warm methyl ethyl ketone and allowed to deposit crystals at 5°. When no crystals formed, an equal volume of methanol was added and the mixture was allowed to stand overnight at room temperature. Fraction IIA crystals (13.1 g.) were removed from this mixture. Fraction IIA had $[\alpha]^{25}_{D}$ +92.5 (1.00% in $CHCl_3$). The addition of 150 ml. of methanol to the mother liquor and washings permitted the deposition of 13.6 g. of Fraction IIB crystals at 5°. This fraction had an $[\alpha]^{25}_{D}$ +73.2 (1.00% in $CHCl_3$).

Fraction IA and IIA were combined to give 31.8 g. of composite I and IIA, which was recrystallized at room temperature from 180 ml. of methyl ethyl ketone. Fraction IIIA amounted to 4.6 g. and had an $[\alpha]^{25}_{D}$ +96.3 (1.00% in $CHCl_3$). Fraction IIIB was obtained by adding an equal volume of methanol to the mother liquor and crystallizing at 5°. It amounted to 17.8 g., and had $[\alpha]^{25}_{D}$ +96.2 (1.00% in $CHCl_3$). A third crop of crystals having $[\alpha]^{25}_{D}$ +78.6 (1.00% in $CHCl_3$) and amounted to 5.8 g. It was not used in subsequent fractionations.

A second composite I and IIB, from fractions IB and IIB, amounting to 26.7 g. was recrystallized from 130 ml. of methyl ethyl ketone at 5°. The crystals (0.8 g.) which formed were discarded, and the filtrate was mixed with an equal volume of methanol and allowed to stand at room temperature overnight. Fraction IVA (15.5 g.) had $[\alpha]^{25}_{D}$ +86.7 (1.00% in $CHCl_3$). A third crop of crystals, amounting to 5.2 g., and having $[\alpha]^{25}_{D}$ +69.7 was discarded.

Fractions IIIA and IIIB, amounting to 22.2 g., and having nearly identical specific rotations were combined and allowed to deposit crystals from 130 ml. of methyl ethyl ketone at 5°. Fraction VA, weighing 9.9 g., was obtained. It melted at 134.2–135.2° and had $[\alpha]^{25}_{D}$ +96.2 (1.00% in $CHCl_3$). This compound showed no depression of the melting point when mixed with an authentic sample of vitamin D_3 dinitrobenzoate. It is considered to be the high-melting form of vitamin D_3 dinitrobenzoate, which crystallizes in lemon yellow needles which form rosettes. Its extinction coefficient is given in Table I.

Anal. Found: N, 4.96, 5.02; Theory: N, 4.85.

TABLE I

Preparation	M.P.[a]	$[\alpha]^{25}_{D}$ (in $CHCl_3$)	$E^{1\%}_{1\ cm.}$ (2650Å.) (in Ethanol Containing 1% $CHCl_3$)
Vitamin Dm dinitrobenzoate (I)	128–128.5	+90.8	38.0
Vitamin D_3 dinitrobenzoate (II)[b]	134.5–135.5	+96, +98	40.6
(II) from mussels Fraction V-A	134.2–135.2	+96.2	40.7
(II) from mussels Fraction V-B	127.5–128.5	+98.8	40.0
(I) from mussels Fraction VI-A	128–129	+91.2	37.5

[a] All melting points determined on an electrically heated microscopic stage, rate of heating being 1° per min. Sample placed on stage about 15° below the melting point. [b] Data reported are the author's. Some variation in these constants has been reported by Huber *et al.*[14,15]

A second crop of (II) of the low-melting form was obtained from the mother liquor of Fraction VA by adding an equal volume of methanol and allowing crystallization to proceed

at 5°. Fraction VB (8.2 g.) had m.p. 127.5–128.5° and $[\alpha]_D^{25}$ +98.8 (1.00% in $CHCl_3$). The crystals of this fraction were long orange colored needles which did not tend to form rosettes. They were indistinguishable from vitamin D_3 dinitrobenzoate crystals obtained from crystallization from benzene-methanol. The extinction coefficient of Fraction VB was identical with that of Fraction VA (cf. Table I).

Fraction IVA (15.5 g.) was dissolved in 80 ml. of methyl ethyl ketone and allowed to stand overnight at 5°. The small crop of crystals which formed was discarded, and an equal volume of methanol was added. Crystallization at 5° yielded 14.7 g. of vitamin Dm dinitrobenzoate (I) as Fraction VIA. This fraction had m.p. 128.5–129° and $[\alpha]_D^{25}$ (+91.2 1.00% in $CHCl_3$). Mixed melting point with authentic vitamin D_3 dinitrobenzoate showed a marked lowering, a wide range of melting and a high clearing point, it being 127–131–137°. The extinction coefficient given in Table I for this fraction is identical with that described above for (I).

Anal. Found: N, 5.00, 4.87.

Biological efficacy of vitamin Dm. Since vitamin Dm (III) has not yet been obtained in crystalline form as the free alcohol, the biological efficacy of the vitamin was determined by using a resin obtained from highly purified dinitrobenzoate (I), or by using the vitamin in solution obtained from a given amount of highly purified ester and calculating the efficacy on the basis of the ester.

The dinitrobenzoate I (0.600 g.) was saponified according to the procedure of Petering and Waddell[12] with the exception of the use of hexane instead of benzene. The hexane solution, containing the free vitamin Dm, was concentrated under nitrogen and reduced pressure until a resin resulted. The resin was then subjected to alternate periods of dry ice bath temperature and warming to 25° while being evacuated under high vacuum. In the end a brittle resin free of all solvent, which could be weighed readily, was obtained.

This resin (0.1000 g.) was dissolved in hexane (250 ml.) and an aliquot of 2.50 ml. was transferred to 100.0 g. of corn oil. The corn oil mixture was evacuated under nitrogen at 50° to remove the hexane. This sample was then used for biological assays.

The corn oil solution, containing 10.00 γ of vitamin Dm resin per g., was tested against Standard U.S.P. Reference Cod Liver Oil in the accepted U.S.P. assay for rat activity and A.O.A.C. test for chick vitamin D activity. It was found that the oil contained 335 U.S.P. units per g. and 300 A.O.A.C. units per g. These data indicate that the resin itself then has a biological efficacy of 33,000,000 U.S.P. units per g. and 30,000,000 A.O.A.C. units per g. This indicates a rat-chick ratio of activity of about 1.0, which identifies the vitamin as of the D_3-type.

In another experiment in which the resin was not isolated, it was found that the ester (I) contains 22,500,000 U.S.P. units per g. and 19,500,000 A.O.A.C. units per g., which agrees well with the above data. If one assumes a molecular weight of 425 for the free vitamin Dm, which is indicated by the spectroscopic and specific rotation data, then the values obtained above for free resin and (I) are self-consistent.

On the other hand, although vitamin Dm is of the D_3-type insofar as its physiological function is concerned, yet a comparison of the efficacy of vitamin D_3, which has an activity of about 45,000,000 USP or AOAC units per gram, with vitamin Dm, which contains about 30,000,000 units per gram, indicates that the latter is a less active compound. The lower efficacy of vitamin Dm over that of vitamin D_3 cannot be explained on the basis of the higher molecular weight of the former compound. These facts indicate the need for careful work with purified compounds rather than the reliance only on comparative biological assay for the determination of structural relationships in the area of the vitamins D.

Acknowledgment. It is a pleasure to thank J. Waddell for helpful advice, and E. L. Rohdenberg, G. H. Kennedy, and J. P. Marvel for assistance in obtaining the biological assays used in this report. A. Bratcher gave me valuable aid in obtaining the physical data reported here.

KALAMAZOO, MICH.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

On the Color of Diaminopyromellitic Esters and Related Compounds*

LEE IRVIN SMITH AND ROGER L. ABLER[1]

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The tetramethyl and tetraethyl esters of diaminopyromellitic acid (I, II) are inherently colored compounds, and the colors do not arise from the presence of diimino compounds or from molecular compounds (quinhydrones) formed from diimino and diamino compounds. Several other diaminobenzenecarboxylic acids and their derivatives have been reported in the literature as being colored, and the color of these substances is discussed in terms of resonance among the functional groups present. The principal frequencies in the ultraviolet, visible, and infrared spectra of compounds I, II, XII, XIII and XIV are given in tabular form.

Many years ago, it was reported by Nef that tetramethyl diaminopyromellitate (I) and the corresponding ethyl ester (II) were colored orange-red and red, respectively.[1–3] These are not the only diaminobenzenepolycarboxylic acids that show color of themselves or in their derivatives. 3,6-Diaminophthalic acid (III) forms brown needles which become black when heated above 200°;[4] 4,6-diaminoisophthalic acid (IV) and its ethyl ester (V) are colored pink and yellow, respectively;[5] diethyl 2,5-diaminoterephthalate (VI) is

(*) Abstracted from a thesis by Roger L. Abler, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the M.S. degree, April 1956.

(1) J. U. Nef, *Ann.*, **258**, 261 (1890).

(2) J. U. Nef, *Ann.*, **237**, 1 (1887).

(3) J. U. Nef, *J. Chem. Soc.*, **53**, 428 (1888).

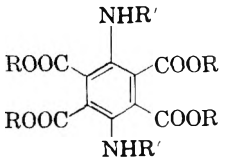
(4) V. Merz and W. Weith, *Ber.*, **15**, 2708 (1882).

(5) M. T. Bogert and A. H. Kropft, *J. Am. Chem. Soc.*, **31**, 841 (1909).

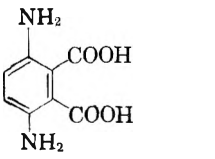
orange-red whereas the acid (VII) is yellowish-green. Often the ester VI forms light yellow crystals which, upon recrystallization, are transformed into the orange-red form.[6] Dimethyl 2,6-diaminoterephthalate (VIII) is yellow.[7] The only definitely characterized diaminobenzenepolycarboxylic acid (or derivative) which is not colored is 3,5-diaminophthalic acid (IX).[4] 2,6-Diaminobenzoic acid (X) is not known, but 6-acetylaminoanthranilic acid (XI) forms brown crystals which do not melt below 300°.[8] Nef[9] reported that the diamino ester II was converted into the orange-yellow quinone diimide (XII) by the action of bromine in chloroform, and that XII was converted back to II by action of zinc dust and acetic acid.

The color of these compounds is difficult to explain on the basis of the structures assigned to them. On the other hand, if the diamino esters (I, II) were really the diimino esters (XII, XIV) or a quinhydrone of the diamino- and diimino-compounds, the color would be expected, and such changes would cause but slight differences in the analytical values. Nef's preparation of the quinone imide (XII) could well have led to a quinhydrone, and aside from Nef's work, only Smith and Byrkit[10] have prepared II and no work was done by these authors to investigate the structure of II or to explain its color. Moreover, at the time of this work the modern physical tools for investigating structure of organic compounds were unknown. It appeared worthwhile, therefore, to repeat Nef's preparation of I and II and in larger quantities, to purify these compounds carefully, to obtain accurate analytical values, to determine their absorption curves in the infrared and ultraviolet, and to determine whether or not a quinhydrone type of compound could be formed from I and XII.

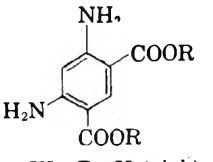
Dinitropyromellitic acid was prepared from 5-acetopseudocumene[11] via durylic acid,[12] and dinitrodurylic acid,[2,3] which was purified according to Gissman.[13] Oxidation of this produced dinitropyromellitic acid,[2,3] which was converted into the tetramethyl and tetraethyl esters by action of diazomethane and diazoethane, respectively. These esters required several recrystallizations to remove the yellow polymers of the diazohydrocarbons, particularly of diazomethane. Reduction of the tetramethyl and tetraethyl esters by action of zinc dust and acetic acid led to the diamino esters I and II, respectively.



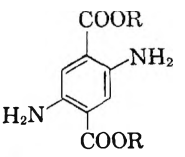
I, R = CH_3; R′ = H (orange-red)
II, R = C_2H_5; R′ = H (red)
XIII, R = CH_3; R′ = COC_6H_5



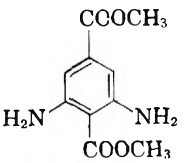
III, (brown → black) 200°)



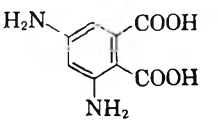
IV, R = H (pink)
V, R = C_2H_5 (yellow)



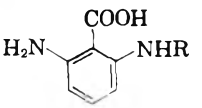
VI, R = C_2H_5 (orange-red / dimorphic yellow)
VII, R = H (yellowish-green)



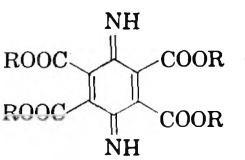
VIII, (yellow)



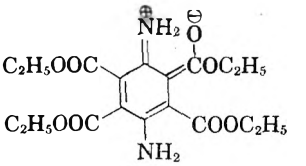
IX, (colorless)



X, R = H (not known)
XI, R = Ac (brown, m.p. 300°)



XII, R = CH_3
XIV, R = C_2H_5



XV

imide (XII) could well have led to a quinhydrone, and aside from Nef's work, only Smith and Byrkit[10] have prepared II and no work was done by these authors to investigate the structure of II or

The tetramethyl ester I, crystallized several times from methanol, formed orange needles melting at 149.4–151° which gave excellent analytical values in agreement with formula I. This material was chromatographed from chloroform onto alumina, and the column was developed and eluted with petroleum ether (C)-chloroform mixtures. Three eluates were taken: from the first, I

(6) M. T. Bogert and A. W. Dox, *J. Am. Chem. Soc.*, **27**, 1127 (1905).
(7) H. Kaufmann and L. Weisel, *Ann.*, **393**, 1 (1912).
(8) T. S. Moore, M. T. Marrack, and A. K. Proud, *J. Chem. Soc.*, 119, 1786 (1921).
(9) J. U. Nef, *Am. Chem. J.*, **11**, 1 (1889).
(10) L. I. Smith and G. D. Byrkit, *J. Am. Chem. Soc.*, **55**, 4305 (1933).
(11) R. Wegler, *J. prakt. Chem.*, **148**, 135 (1937).
(12) W. H. Mills, *J. Chem. Soc.*, **101**, 2191 (1912).
(13) R. Gissman, *Ann.*, **216**, 200 (1883).

was recovered as orange needles melting at 149.6–150.6°. From the second and third eluates I was recovered as orange needles, but mixed with these was a very small amount of brick-red needles. The two types of crystals were separated mechanically; the red material, at 120–130°, became orange and then melted at 149–150°. The orange needles melted, after crystallization from methanol, at 150–151°. No other material was recovered from the column, and it can be concluded that the red and orange forms of I are polymorphs. The significant bands in the infrared spectrum of I are shown in Table II. The ultraviolet and visible spectra of I are given in Table I.

TABLE I

ABSORPTION SPECTRA IN ULTRAVIOLET AND VISIBLE LIGHT (IN 95% ETHANOL)

	Ultraviolet		Visible	
Compound	λ_{max} mμ	$\epsilon_{max} \times 10^{-4}$	λ_{max} mμ	$\epsilon_{max} \times 10^{-4}$
I	215	1.34	445	0.503
	252	0.975		
II	217	2.83	440	0.582
	252	0.985		
XII	245	1.56	375	1.92
	376	2.16	450	0.902
XIV	246	1.19	376	1.75
	375	1.70	453	0.855
XIII	232	3.82		
	272	1.67		

TABLE II

INFRARED FREQUENCIES

Compound	Phase[a]	ν(cm.$^{-1}$)
I	A	NH: 3450, 3420 (doublet); 3380, 3340 (doublet); 1613. C=O: 1726
	B	NH: 3480, 3380, 1590. C=O: 1713
	C	NH: 3450, 3360. C=O: 1715
II	A	NH: 3490, 3400, 1600. C=O: 1721
	B	NH: 3490, 3390, 1589. C=O: 1706
Monobenzoyl I	A	NH: 3430, 3320, 1599, 1542. C=O: 1741, 1702, 1667
XIII	A	NH: 3400, 1520. C=O: 1727, 1700, 1684
XII	A	NH: 3480, 3360, 1595 (NH?). C=O: 1752, 1730, 1718, 1696
	B	NH: 3440, 3340, 1592 (NH?) C=O: 1713
XIV	A	NH: 3490, 3450 (doublet); 3390, 3350 (doublet), 1588. C=O: 1729, 1704
	B	NH: 3470, 3360, 1591 (NH,?) C=O: 1709

[a] A = Nujol mull; B = solution in chloroform; C = solution in carbon tetrachloride.

The ester I was converted into a white hydrochloride when dry hydrogen chloride was passed through the chloroform solution of I. This white salt decomposed in air with regeneration of I. The ester I was converted into a monobenzoyl derivative (yellow, melting at 194.5–195.5°) and a dibenzoyl derivative (XIII) melting at 264–266° which was only slightly yellow. Several attempts were made to oxidize XIII to a dibenzoylquinone imide by action of lead tetraacetate, but the reagent was essentially without action and unchanged XIII was recovered.

Oxidation of I by action of lead tetraacetate[14] gave the quinone diimide XII as orange-red prisms melting at 260–261°. The same result was achieved when bromine was used as the oxidizing agent, as described by Nef.[9] The significant bands in the infrared spectrum of XII are shown in Table II. The ultraviolet and visible spectra of XII are given in Table I.

Attempts were made to prepare a quinhydrone of I and XII by recrystallizing solutions of equimolar amounts of the two compounds in acetic acid or benzene. When these solutions were cooled, a mixture of I and XII separated. Finally, a melting point diagram of mixtures of I and XII was constructed. This (Figure 1) definitely shows that no compound of I and XII is formed.

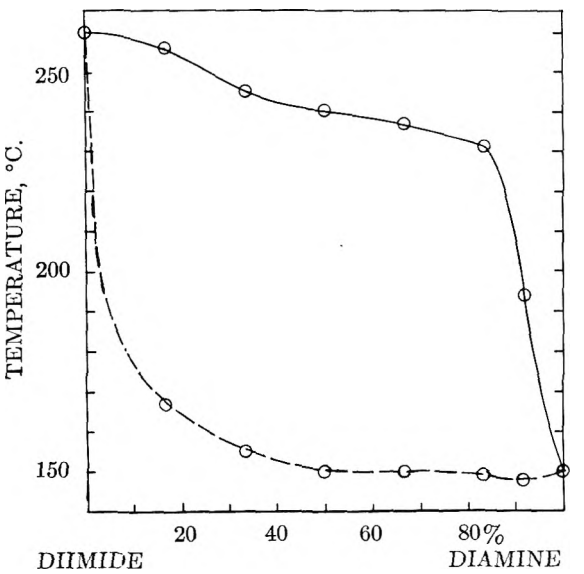


FIG. 1. MELTING-POINT DIAGRAM FOR MIXTURES OF I AND XII. Dotted line, beginning of melting; solid line, complete liquefaction.

Reduction of dinitropyromellitic acid in slightly acidic medium gave a red solution. Ether extracts of this solution were red, and showed a marked yellowish-red fluorescence. The ester I also shows this fluorescence in ultraviolet light. Although the diamino acid was not isolated, the experiment showed that it also was a colored substance.

The ethyl ester II, after crystallization several times from ethanol, formed brick-red prisms

(14) R. Adams and A. S. Nagarkatti, *J. Am. Chem. Soc.*, 72, 4603 (1952).

melting at 138–138.7°, giving excellent analytical values for formula II. The significant bands in the infrared spectrum of II are shown in Table II. The ultraviolet and visible spectra of II are given in Table I. The ester showed a reddish-orange fluorescence in ultraviolet light. Considering the red color of crystalline II and the orange color of crystalline I, a larger difference in λ_{max} might have been expected. However, I was also obtained as a red polymorphic form; two forms of II were not obtained.

Oxidation of II by action of bromine in chloroform gave the quinone diimide XIV as orange yellow needles melting at 159–160°. The significant bands in the infrared spectrum of XIV are shown in Table II. The ultraviolet and visible spectra of XIV are given in Table I. There was a marked difference in the color of the two crystalline quinone diimides XII (orange-red) and XIV (orange-yellow). The values of λ_{max} and ϵ in the visible spectra of the two compounds are, however, almost identical. The difference in visible color might possibly be explained by polymorphism, that is, one form of XII and the other form of XIV were in hand, but no experimental evidence was accumulated to verify this supposition.

DISCUSSION

On the basis of the facts presented above and in the experimental section, it can be concluded that the pure diamino esters I and II, and the dibenzoyl compound XIII are colored that they possess the structures assigned to them, and that the color does not arise from the presence of any impurities or from the presence of any quinhydrones formed from the diamino and diimino compounds. Assuming that compounds III, IV, V, VI, VII, VIII, and XI, as reported in the literature, also have the structures assigned to them and are colored, whereas compound IX is colorless, the question arises as to the cause of the striking and often deep color of these compounds. The color must involve some interaction between the nitrogen atom(s) with the lone pair(s) of electrons, and the carboxyl or ester groups. The number of possible resonance forms involving such interactions in these compounds, such as XV etc. for II, (exclusive of those involving hydrogen bonding) together with the color of the compounds, is shown in Table III.

TABLE III

NUMBER OF RESONANCE FORMS

Esters	Number of Resonance Forms	Color of Solid
I	8	Orange-red
II	8	Red
V	5	Yellow
VI	3	Orange-red, dimorph yellow
VIII	2	Yellow
Acids		
III	3	Brown, → black > 200°
IV	5	Pink
VII	3	Greenish-yellow
IX	2	Colorless
X	2	Unknown
XI (Monoacetyl X)	2	Brown

From the table it appears that for color, at least three resonance forms of this sort must be possible, and in general, the more resonance forms possible, the deeper the color. If the esters I, II, V, VI, and VIII are considered as one group, and the acids III, IV, VII, IX, X, and XI are considered as another group, the change in color with increasing number of resonance forms is shown clearly by each group.

That the ability of the nitrogen atom to function as an electron donor is connected with the color is shown by the fact that the hydrochloride of I is colorless, and is also indicated by a consideration of the oxygen analogs of these compounds, many of which have been described in the literature. Oxygen is not as powerful a donor atom as is nitrogen, therefore it would be expected that the oxygen analogs would be less deeply colored, and this is, indeed, the case. The hydroquinones corresponding to I and II are known;[2,15–17] that corresponding to I is light yellow and melts at 207° (this is also the melting point reported for the quinone); that corresponding to II is reported to crystallize in two forms: "yellowish-green needles" and "bright yellow grains". The needles "change" at 111–115°, then melt at 133.2–133.6°; the "grains" change at 64°, begin to melt at 123–124°, then partially solidify and finally melt at 128.5°. The quinone corresponding to II melts at 148–149°. The monomethyl ether of the hydroquinone corresponding to II[9,18] forms a sodium salt which is yellow with a green fluorescence. All the other dervatives of these hydroquinones—dimethyl ether, diacetate, dibenzoate—are colorless. Hydroquinone tetracarboxylic acid crystallizes with water of crystallization and forms yellow needles which decompose at 150°.[19] None of these compounds shows the deep orange and red colors of I and II. The acids in Table III are not as deeply colored as the esters; this would be expected because ionization of the carbonyl group(s) would make more difficult any type of resonance in which the carbonyl oxygen atom acts as an acceptor.

(15) H. v. Pechmann and L. Wolmann, *Ber.*, **30**, 2570 (1897).

(16) J. U. Nef and W. Muthmann, *J. Chem. Soc.*, **53**, 449 (1888).

(17) J. U Nef, *Ann.*, **258**, 318 (1890).

(18) J. U. Nef, *Ann.*, **258**, 289 (1890).

(19) J. U. Nef, *Ann.*, **237**, 33 (1887).

EXPERIMENTAL[20]

Dinitropyromellitic acid. A solution of potassium carbonate (65.6 g., 0.475 mole) and dinitrodurylic acid (30 g., 0.118 mole) in water (3 l.) was heated on a steam bath while potassium permanganate (117.5 g., 0.744 mole) was added with stirring. Heating was continued for 8 days. Manganese dioxide was removed by filtration and the yellow filtrate was concentrated to a volume of 500 cc. and acidified strongly with hydrochloric and sulfuric acids. The solution was then extracted with six 100-cc. portions of ether, the extracts were combined and evaporated, leaving the white crystalline acid. This was dissolved in water (200 cc.) and converted into the calcium salt by addition of calcium carbonate until there was no further reaction. Ethanol (250 cc.) was added, whereupon the yellow calcium salt (A) separated. This was removed and set aside and the filtrate was evaporated to obtain the calcium salts of tribasic and other acids (B). The salts B were dissolved in water, the solution was strongly acidified and extracted with ether. Removal of the ether left 8 g. of light yellow material, which was again oxidized as described above by action of permanganate (10 g.) in water (200 cc.) containing potassium carbonate (10 g.). This reaction mixture was processed as above and the calcium salt of the tetrabasic acid was combined with A. The combined calcium salts were partially dissolved in water (400 cc.), reprecipitated by addition of ethanol, again partially dissolved in water (250 cc.) and this mixture was strongly acidified and extracted with five 100-cc. portions of ether. The product, obtained by evaporation of the ether, weighed 30.4 g. (74.7%) and melted at 225–230° (dec.).

Tetramethyl ester. Diazomethane was prepared from nitrosomethylurea, according to Arndt.[21] The above acid (20 g.) was added to an ethereal solution of excess diazomethane and the reaction mixture was allowed to stand for 2 hr. The solvent and excess reagent were removed, and the slightly yellow residue was triturated with methanol (50 cc.) and filtered. The crude ester (20.2 g., 90%) melted at 176–178°. Three recrystallizations from methanol-acetone gave a material (14 g.) melting at 179–180°. The analytical sample, recrystallized four times from methanol, melted at 181.8–182.8°.

Anal. Calcd. for $C_{14}H_{12}O_{12}N_2$: C, 42.01; H, 3.02; N, 7.00. Found: C, 42.20; H, 3.30; N, 6.84.

The infrared spectrum of this ester showed absorption bands consistent with the structure assigned to it.

Tetraethyl ester. Diazoethane was prepared from nitrosoethylurethane according to Wilds and Mender.[22] Excess ethereal diazoethane was added to the solid acid (3 g.) and the mixture was allowed to stand overnight at room temperature. The solution was then extracted once with aqueous sodium bicarbonate (100 cc., 2%) and the ether was removed. The residue of ester (2.66 g., 66%) melted at 134.5–135.5°. The analytical sample, crystallized twice from ethanol, melted at 135.5–136°.

Anal. Calcd. for $C_{18}H_{20}O_{12}N_2$: C, 47.37; H, 4.42; N, 6.14. Found: C, 47.56; H, 4.70; N, 6.10.

The infrared spectrum of this ester showed absorption bands consistent with the structure assigned to it.

Reduction of dinitropyromellitic acid. Iron filings (0.5 g., 20 mesh, degreased), water, and acetic acid (0.1 cc.) were heated on the steam bath and a solution of the acid (0.5 g.) in water (10 cc.) was added. The mixture became red immediately; it was heated for 20 min., filtered, and the filtrate was extracted several times with ether. Removal of the ether left only a small amount of red material; the red diaminopyromellitic acid was not isolated from the aqueous layer.

Tetramethyl diaminopyromellitate (I). The tetramethyl dinitro ester (3.134 g., 0.008 mole) was dissolved in acetic acid (30 cc.) and water (0.5 cc.). To the hot solution (steam bath), zinc dust (9.8 g.) was added in small portions over 20 min. The mixture was heated for 10 min., then filtered hot. The insoluble material was washed with three 5-cc. portions of hot acetic acid, and the combined filtrate and washings were poured into water (90 cc.). The product (1.5 g., 56%) was removed; it melted at 148–149°. After three recrystallizations from methanol, the ester melted at 149.4–151°. A column (1.5 × 20 cm.) was packed with alumina (45 g.) wet with petroleum ether (redistilled, b.p. 80–100°), and a solution of I (0.307 g.) in chloroform (30 cc.) was poured into the tube. The column was developed and eluted with petroleum ether–chloroform mixtures, increasing in chloroform content from 5 to 45% (volume). The eluate was separated into three fractions in order A, B, C. A yielded I (0.075 g.) as orange needles melting at 149.6–150.6° after one crystallization from methanol. B and C likewise yielded I (0.128 g.), but along with the orange form melting at 150–151°, there was obtained a small amount of the red form (separated mechanically) which was converted to the orange form at 120–130° and then melted at 149–150°. The sample melting at 150–151° was analyzed.

Anal. Calcd. for $C_{14}H_{16}O_8N_2$: C, 49.41; H, 4.74; N, 8.23. Found: C, 49.55; H, 4.72; N, 8.30.

The significant bands in the infrared spectrum of this material are given in Table II; the ultraviolet and visible spectra are given in Table I. A solution of the ester I in chloroform, when subjected to action of hydrogen chloride gas, deposited a white hydrochloride. When the white solid was removed by filtration, it was immediately transformed into the orange I on contact with the air.

Tetramethyl N,N'-dibenzoyldiaminopyromellitate (XIII). The ester I (1.6 g.) was suspended in aqueous sodium hydroxide (30 cc., 10%) containing benzoyl chloride (4 cc.). The mixture was stirred and heated (steam bath) for 15 min. The cooled mixture was filtered, and a small amount of ether (2 cc.) was poured over the precipitate on the filter. The remaining yellow solid melted at 185–190° and was the monobenzoyl compound. This, when benzoylated again, gave the dibenzoyl derivative XIII. Both compounds were recrystallized several times from dimethylformamide. The dibenzoyl derivative XIII formed slightly yellow needles melting at 264–266° (dec.).

Anal. Calcd. for $C_{28}H_{26}O_{10}N_2$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.11; H, 4.41; N, 5.14.

The significant bands in the infrared spectrum of XIII, and the monobenzoyl derivative, are given in Table II; the ultraviolet absorption spectrum of XIII is given in Table I.

Several attempts to oxidize XIII to a dibenzoylquinone diimide by action of lead tetraacetate in acetic acid, as described below for preparation of XII led only to recovered XIII.

The monobenzoyl derivative, crystallized several times from dimethylformamide, melted at 194.5–195.5° and formed greenish-yellow needles.

Anal. Calcd. for $C_{21}H_{20}O_9N_2$: C, 56.75; H, 4.54; N, 6.30. Found: C, 57.18; H, 4.94; N, 6.39.

Tetracarbomethoxy-p-quinonediimide (XII). (A) The diaminoester I (0.19 g., 0.00056 mole), lead tetraacetate (0.375 g., 0.00085 mole) and acetic acid (10 cc.) were placed in a pear-shaped flask fitted with a stirrer and a reflux condenser protected by a calcium chloride drying tube. The mixture was stirred and heated at 130° for 45 min. The deep red mixture was filtered and the filtrate was poured into water (30 cc.). The product (0.05 g., 26%) was removed, dried, and crystallized three times from dimethylformamide, when it formed orange-red prisms melting at 260–261°.

(20) All melting points were determined on a Kofler micro hot-stage apparatus, and are therefore corrected. Boiling points are uncorrected. Microanalyses by J. H. Cooley, C. B. Koons, and R. L. Lange. Spectrographs by the spectrophotometric laboratory of the School of Chemistry of the University of Minnesota.

(21) F. Arndt, *Org. Syntheses*, **15**, 3, 48 (1935).

(22) A. L. Wilds and A. L. Mender, Jr., *J. Org. Chem.*, **13**, 768 (1948).

(B) The diaminoester I (0.2 g., 0.0006 mole) was dissolved in chloroform, and bromine (0.2 g.) was added. Insoluble material separated at once; the mixture was allowed to stand overnight in an open beaker, when there remained a mixture of red and yellow solids melting at 146–151°. This material was washed with water (30 cc.), dried, again taken up in chloroform (15 cc.) and treated with bromine 0.4 g.). The reaction mixture was allowed to stand for two days, and the solid residue was washed with water (30 cc.) and hot methanol (15 cc.), and then extracted with hot dimethylformamide (10 cc.). The extract was diluted with water and centrifuged. The solid, crystallized four times from dimethyl formamide-water, formed orange-red crystals, weighed 0.05 g. (24%) and melted at 260–261°, alone or when mixed with the product from A above.

Anal. Calcd. for $C_{14}H_{14}O_8N_2$: C, 49.71; H, 4.17; N, 8.28. Found: C, 49.63; H, 4.34; N, 7.50, 8.14.

The significant bands in the infrared spectrum of XII are given in Table II; the ultraviolet and visible spectra are given in Table I.

Equimolar quantities of I and XII were dissolved in hot acetic acid. When the solution was cooled, it deposited two types of crystals, and the mixture melted at 155–258°. In another experiment, but with benzene as the solvent, the same result was obtained. Six mixtures of I and XII, from 92% I and 8% XII to 16% I and 84% XII were studied as to melting point behavior on a Kofler micro hot-stage apparatus. The melting point diagram, given in Figure 1, shows that no compound is formed when mixtures of I and XII are melted. In the figure, the points on the dotted line represent the temperatures at which melting began; those on the solid line represent the temperatures at which melting was complete.

Tetraethyl diaminopyromellitate (II) (1.033 g., 60.5%) was prepared by reduction of the dinitro ester (0.96 g.) in acetic acid (20 cc.) by action of zinc dust (6.02 g.), essentially as described for the preparation of I. The product, crystallized three times from ethanol, formed red prisms melting at 138–138.5°. The analytical sample, crystallized three times again from ethanol, melted at 138.0–138.5°.

Anal. Calcd. for $C_{18}H_{24}O_8N_2$: C, 54.54; H, 6.10; N, 7.07. Found: C, 54.56; H, 6.14; N, 7.08.

The significant bands in the infrared spectrum of II are given in Table II; the ultraviolet and visible spectra are given in Table I.

Tetracarbethoxy-p-quinonediimide (XIV) (0.094 g., 46.5%) was prepared from II (0.203 g.) in chloroform (10 cc.) by action of bromine (0.4 g.) essentially as described for the preparation of XII (B) above, including retreatment of the crude product with bromine. The product was crystallized five times from ethanol, and then formed orange-yellow needles melting at 159–160°.

Anal. Calcd. for $C_{18}H_{22}O_8N_2$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.52; H, 5.66; N, 7.23.

The significant bands in the infrared spectrum of XIV are given in Table II; the ultraviolet and visible spectra are given in Table I.

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Notes

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Triphenylethylene Derivatives. III

TOYOYUKI NAGANO

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In a previous paper[1] we dealt with a novel synthesis of triphenylethylenes, adopting the Friedel-Crafts reaction instead of the Grignard synthesis.

With a view to preparing tris(alkoxyphenyl)-ethylenes, some further work has been performed. A *p,p'*-dialkoxydesoxybenzoin was prepared by the Friedel-Crafts condensation between a *p*-alkoxyphenylacetyl chloride and the corresponding phenyl ether. Desoxyanisoin and desoxyphenetoin (I) thus obtained were converted to the corresponding chlorostilbenes, which were treated with anisole and phenetole to afford the desired triphenylethylenes. The chlorination of these triphenylethylenes was carried out in satisfactory yields by the action of sulfuryl chloride in carbon tetrachloride.

Although the action of an equimolar amount of bromine on I gave α-bromodesoxyphenetoin (II), I was oxidized by 2 equivalents of bromine to phenetil ($EtOC_6H_4COCOC_6H_4OEt$).

The action of sodium ethoxide on II did not yield an ether, but only phenetoin. It has been confirmed by the other investigator[2] that the principal product obtained by the reaction of α-bromodesoxyanisoin with anisole in the presence of aluminum chloride was trianisylethanone, identified by comparison with the product obtained by hydrolysis of trianisylbromoethylene.

EXPERIMENTAL

p-Ethoxyphenylacetic acid. (III). This compound was prepared in 53% yield from *p*-ethoxyacetophenone by a procedure analogous to that used for *p*-methoxyphenylacetic acid.[3] The intermediate thiomorpholide could be crystallized from ethanol as almost colorless needles, m.p. 92–93°, but subsequent hydrolysis was carried out without further purification.

Desoxyphenetoin. (I). A solution of the acid chloride prepared from III (9 g., 0.05 mole) in carbon disulfide (25 ml.) was added dropwise with stirring to a well-cooled mixture (−5°) of phenetol (7.3 g.; 0.06 mole), aluminum chloride (14.7 g.; 0.11 mole) and carbon disulfide (100 ml.) so that vigorous reaction might not occur. After the reaction mixture had stood for 20 hr. below 10° the carbon disulfide layer was removed by decantation, and the residue was treated with ice and concentrated hydrochloric acid. The separated crystals of I were collected and air-dried; weight 10 g. (70.4%), m.p. 105–107°. Two recrystallizations from hot ethanol afforded colorless plates, m.p. 107.5°, reported m.p. 102°.[4]

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.98; H, 6.92.

The oxidation of I with selenium dioxide in glacial acetic acid gave colorless needles, m.p. 151–153°, which showed no depression on admixture with authentic samples of phenetil prepared by Lewis' method.[4]

Similarly, desoxyanisoin was made from *p*-methoxyphenylacetic acid and anisole in 75% yield.

p,p'-Diethoxy-α-chlorostilbene. (IV). A mixture of I (7.1 g.; 0.025 mole), phosphorus pentachloride (5.4 g.; 0.026 mole), and dry benzene (20 ml.) was allowed to stand at room temperature over a period of 15 hr., and then refluxed on a water bath for 1 hr. The resulting red solution was poured into ice water and the products were extracted with an additional 100 ml. of benzene. When the dried extract was evaporated to dryness, and the crystalline residue was treated with a moderate amount of ethanol to remove the noncrystalline part, there remained colorless plates, 4.5 g. (60%), m.p. 103–105°. After two recrystallizations from absolute ethanol, the m.p. reached 105–106°.

Anal. Calcd. for $C_{18}H_{19}O_2Cl$: C, 71.39; H, 6.32. Found: C, 71.36; H, 6.08.

Similarly, *p,p'*-dimethoxy-α-chlorostilbene was obtained from desoxyanisoin as colorless plates (from absolute ethanol); m.p. 117–118°.

Anal. Calcd. for $C_{16}H_{15}O_2Cl$: C, 69.94; H, 5.50. Found: C, 69.98; H, 5.55.

Tris(p-ethoxyphenyl)ethylene. (V). To a cooled mixture of phenetole (0.5 g.; 0.0041 mole), aluminum chloride (0.5 g.; 0.0038 mole), and carbon disulfide (20 ml.) was added IV (1 g.; 0 0.0034 mole) in small portions with stirring. After standing at room temperature for 3 hr., the reaction mixture was treated as usual. The crude product was recrystallized from hot ethanol (20 ml.), giving colorless prisms, m.p. 100–101°. Yield: 0.8 g. (60%). For analysis, small samples were thrice recrystallized from absolute ethanol to give the m.p. of 103–104°, reported m.p. 102°.[5]

Anal. Calcd. for $C_{26}H_{28}O_3$: C, 80.38; H, 7.27. Found: C, 80.58; H, 7.31.

The bromination of V with bromine in carbon tetrachloride afforded *tris(p-ethoxyphenyl)bromoethylene*, which melted at 96–98° after several recrystallizations from absolute ethanol, reported[6] m.p. 81–82°.

Anal. Calcd. for $C_{26}H_{27}O_3Br$: Br: 17.10. Found: Br. 16.83.

Tris(p-ethoxyphenyl)chloroethylene. To a cold solution of V (0.39 g.; 0.0010 mole) in carbon tetrachloride (3 ml.) was added sulfuryl chloride (0.2 g.; 0.0013 mole) drop by drop. The reaction mixture was allowed to stand overnight at room temperature, and then evaporated to dryness on gently warming. The resulting red-colored residue, when treated with a small amount of ethanol, gave a crystalline product (0.40 g.), m.p. 96–98°. On several recrystallizations from ethanol, it gave colorless prisms which melted at 103–104°.

Anal. Calcd. for $C_{26}H_{27}O_3Cl$: C, 73.83; H, 6.43; Cl, 8.38. Found: C, 73.59; H, 6.55; Cl, 8.17.

Action of bromine on I. (A) To a solution of I (0.7 g.; 0.0025 mole) in carbon tetrachloride (15 ml.) was added dropwise a solution of bromine (0.4 g.; 0.0025 mole) in carbon tetrachloride (6 ml.) with vigorous stirring for 30 min. After most

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(2) Oki, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **72**, 1046 (1951) [*Chem. Abstr.*, **47**, 3284 (1953)].

(3) Wiechell, *Ann.*, **279**, 337 (1894).

(4) Lewis, Cramer, and Bly, *J. Am. Chem. Soc.*, **46**, 2063 (1924).

(5) Hey and Carter, Brit. Patent 586,493 (1941).

(6) Carter and Hey, *J. Chem. Soc.*, 154 (1948).

of the solvent was removed under reduced pressure without heating, the residue, after being treated with petroleum ether (20 ml.), gave crystals weighing 0.6 g. Further recrystallization from carbon tetrachloride petroleum ether gave colorless prisms, m.p. 100–102°. The analysis indicated that this material was α-bromodesoxyphenetoin (II).

Anal. Calcd. for $C_{18}H_{19}O_3Br$: Br, 22.00. Found: Br, 21.87.

(B) A mixture of I (0.3 g.) and bromine (0.2 g.) in carbon tetrachloride (3 ml.) was warmed on a water bath until the solvent had evaporated. The residue was crystallized from ethanol (3 ml.), yielding halogen-free compound (0.2 g.). Repeated recrystallization from ethanol gave colorless needles, m.p. 151–153°, which failed to depress the melting point of authentic phenetil.

Phenetoin. A mixture of II (0.4 g.; 0.001 mole) and sodium ethoxide [sodium (0.07 g.; 0.003 mole) in 3 ml. of absolute ethanol] was allowed to stand overnight at room temperature. Then it was poured into water and neutralized with cold 10% hydrochloric acid. Resulting precipitates were collected, washed with water, and dried (0.3 g.). Twice recrystallized from ethanol, the compound had m.p. 88–89°, reported m.p. 86–87°.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.04; H, 6.58.

1,2,2-Trianisylethanone. (A) Trianisylbromoethylene (0.6 g.) was heated with 20 ml. of 50% ethanol in a sealed tube at 100° for 24 hr. After the supernatant fluid was removed, the oily residue was treated with 10 ml. of absolute ethanol denatured with 1% anisole, giving colorless prisms (0.4 g.), which melted at 74–76° to a cloudy liquid and became clear at 79°. Reported[8] m.p. for *1,2,2-trianisylethanone anisolate*, 77–79°.

(B) To a cooled solution of α-bromodesoxyanisoin (1.1 g.) and anisole (1.1 g.) in carbon disulfide (30 ml.), pulverized aluminum chloride (2 g.) was added in small portions with stirring (30 min.), and the mixture was allowed to stand at room temperature for 20 hr. Upon decomposition of the complex in ice and concentrated hydrochloric acid, a viscous yellow liquid was obtained from the organic layer. This could be crystallized from the same solvent as employed in the former case, the crystals thus obtained (0.6 g.) showing no depression of melting point when mixed with the material described under A.

The reduction of the anisolate with sodium borohydride in methanol gave 1,2,2-trianisylethanol, m.p. 107–108°; reported[9] m.p. 107–108°.

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The Color Produced in Acetone Solutions of Nitroaromatics and Sodium Iodide

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It was recently reported by Blatt and Gross[2] that aromatic nitro compounds and alkali iodides in acetone solution develop colors in the visible region which can be used as a qualitative test for aromatic nitro compounds and the number of nitro groups they contain: Acetone solutions approximately 0.1*M* with respect to both the aromatic nitro compound and sodium iodide are very pale yellow if the aromatic nitro compound contains one nitro group; deeper yellow, comparable with the color of 0.3*M* aqueous iron (III) chloride, if the aromatic nitro compound contains two nitro groups; and red-brown, comparable with the color of 3.0*M* aqueous iron (III) chloride, if the aromatic nitro compound contains three nitro groups.

The only earlier report of the color reaction in question is that of Tronow, D'yakonova-Schultz, and Zonova,[3] who examined three trinitro- and two dinitroaromatics, varied the solvent and inorganic iodide widely, and concluded from indirect evidence that the acetone complexes had the probable composition, one aromatic nitro compound: one alkali iodide: three acetone.

EXPERIMENTAL

Reagents and apparatus. 1,3-Dinitrobenzene (DNB) was recrystallized from ethanol until a product with a constant melting point of 90.5–91.5° (uncorr.) was obtained. As a test for water-soluble impurities, a small amount of the product was shaken with distilled water and then filtered. The water was unchanged in *p*H, and tests for nitrate and nitrite were negative. 2,4,6-Trinitrotoluene (TNT) was recrystallized from ethanol until a constant melting point of 80.5–81.5° (uncorr.) was obtained. An earlier observation[4] that TNT when exposed to light develops a red impurity was confirmed. The red color (corresponding to an absorption centered at about 510 mμ) develops more quickly in solutions of TNT in acetone than it does in the dry solid. Solid TNT in a brown bottle can be kept for several weeks without appreciable decomposition; when the red color does develop, it can be removed by one or two recrystallizations. 4,4′-Dinitrobiphenyl, recrystallized from acetone, had a melting point of 241–242° (uncorr.). Mallinckrodt Analytical Reagent acetone was used as solvent without further purification. Mallinckrodt Analytical Reagent sodium iodide was dried at 110° overnight and weighed from a weighing bottle. (Sodium iodide was selected rather than potassium iodide because of its higher solubility in acetone.)

Spectrophotometric measurements were made on a Beckman model DK-1 recording spectrophotometer.

1,3-Dinitrobenzene. 1,3-Dinitrobenzene absorbs strongly in the ultraviolet region of the spectrum. Since this absorption is centered at wave lengths at which acetone is opaque, the measurements in acetone solution were made along the side of the absorption curve. Addition of sodium iodide moves the absorption toward longer wave lengths corresponding to the appearance of the yellow color, and the cut-off becomes much less sharp. (See Figure 1.) The region between about 420 mμ and 550 mμ appeared to be the most fruitful region for study, for at these wave lengths the mixture solutions absorb strongly whereas the solutions of either reactant alone are transparent or nearly so.

(1) Present address: Department of Chemistry, The Ohio State University, Columbus 10, Ohio.
(2) Reported by A. H. Blatt and Norma Gross, at The Office of Ordnance Research Conference on High Nitrogen Compounds, Duke University, March 28–29, 1956.
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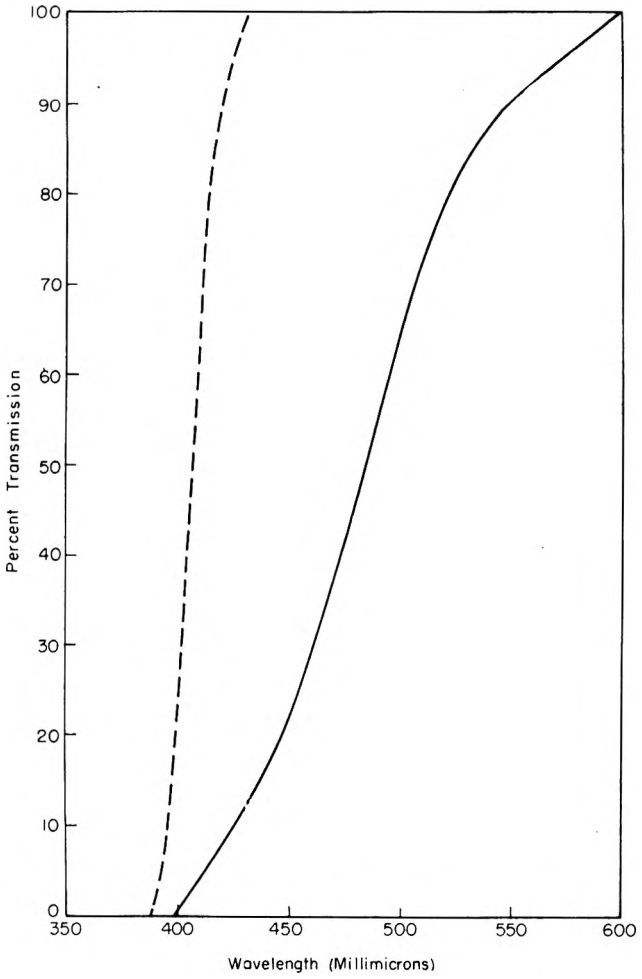

FIG. 1. ABSORPTION SPECTRA OF ACETONE SOLUTIONS 0.05*M* in 1,3-dinitrobenzene (broken line) and 0.05*M* in 1,3-dinitrobenzene and in sodium iodide (solid line). Path length 1 centimeter

The method of continuous variations[5,6] was used in an attempt to establish the molecular combining ratio of the two reactants. In two different experiments, one starting with 0.05*M* reactants and the other with 0.1*M* reactants, taking several different wave lengths each time, curves were obtained which peaked near X = 0.5, indicating a molecular combining ratio of 1:1. The curves of enhancement versus combining ratio were quite rounded, indicating a rather unstable complex.

The ratio 1:1 was checked by a method which we might call the "method of effect of excess."[7,8] Application of this method to the 1,3-dinitrobenzene and sodium iodide mixtures gave results which confirm the 1:1 ratio indicated by the continuous-variations data. The formula will therefore be written NaI·DNB, without any assumptions for the present as to its detailed structure. The complex does not obey Beer's Law, and the deviation is in the direction which would be expected for a complex that dissociates on dilution.

2,4,6-Trinitrotoluene. A similar study was undertaken to establish the combining ratio between 2,4,6-trinitrotoluene and sodium iodide. Both the continuous-variations (using original solutions of 0.02*M* and of 0.1*M*) and the effect-of-excess methods indicate a 1:1 combining ratio in this system also. This compound will therefore be formulated as TNT·NaI.

4,4'-Dinitrobiphenyl. The method of continuous variations was then tried on 4,4'-dinitrobiphenyl and sodium iodide. For original solutions in acetone of concentration of 0.04*M* a 1:1 complex is indicated for this system also. More concentrated solutions were not used because the solubility of 4,4'-dinitrobiphenyl is low.

Effect of water. It was observed that the colors resulting in acetone solution from nitroaromatics and iodides were bleached by the addition of relatively small amounts of water. This effect was quantitatively studied by spectrophotometry. The drop in absorbance is greatest for the first added increments of water. For example, at 450 mμ an acetone solution 0.050*M* in NaI and in DNB (1 cm. path length) was observed to have an absorbance of 0.66. With the same concentrations of NaI and DNB but with 1.1 mole liter^{-1} of water in the acetone solution the absorbance is 0.350, and at 5.6*M* water it is 0.117. Similar results are obtained with TNT and NaI.

When the acetone solutions which had water as well as sodium iodide and 1,3-dinitrobenzene in them were allowed to stand for several days, they gradually took on a purple hue corresponding to the appearance of a new absorption centered at 560 mμ. This new absorption develops most rapidly in the solutions having the most water. The solutions containing no added water maintain the yellow color for long periods of time.

Effect of alkali. The sodium iodide which was used contains some alkaline material, for its concentrated aqueous solutions have a *p*H of between 8 and 9. To determine whether the color might be due to this alkaline constituent, a qualitative experiment was conducted using dilute aqueous solutions of sodium hydroxide and of sodium carbonate. It was found that small amounts of these basic reagents, when added to acetone solutions of the nitroaromatics, had the same effect as equal amounts of water. When larger amounts were added, deeply colored solutions (blue-violet for DNB, cherry-red for TNT) were produced. These colors have been observed previously and have been used for estimation of the amount of nitro compound.[9] The spectra of these solutions show marked similarities as would be expected from the close relationship between the nitro compounds. In each case there are two absorption maxima, with the maximum of shorter wave length being the stronger in each case. The wave lengths of the maxima are 465 mμ and 535 mμ for TNT and 570 mμ and 700 mμ for DNB. The 570 mμ absorption observed here may be the same as the 560 mμ absorption observed in wet acetone solutions of sodium iodide and DNB. Differences in the ionic strength of the solution may be sufficient to account for the small difference in the wave length of the absorption maximum.

The belief that these absorptions are due to the same species is strengthened by the observation that, while the purple color is formed instantly on the addition of relatively large amounts of strong base (sodium hydroxide), the addition of the weaker base sodium carbonate or of very small amounts of sodium hydroxide results in a slower formation of the purple color. (The time required ranges from several minutes to several hours.) With sodium iodide, as noted above, development of the color requires one or more days—which is consistent with the observation that the sodium iodide reagent is only very slightly basic. The presence of at least a small amount of water seems to be

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required for formation of the colors. Canback[10] has suggested that the colored species have quinoid-type structure.

DISCUSSION

In discussing the nature of these colored substances, the first possibility to be considered is that of an oxidation-reduction reaction in which the nitro compound would oxidize the iodide, probably to furnish iodine. It appears that the color is not due to molecular iodine, however, for several reasons which are recountered here. First, comparison of a solution of the nitro-iodide color with an iodine solution of equal intensity shows that there is a difference in hue. Second, a positive iodine reaction by the starch-iodide test cannot be obtained from one of the nitroaromatic iodide solutions although a genuine iodine solution of equal intensity does give a positive reaction. Third, though the color intensity of the nitroaromatic-iodide solutions is substantially decreased by the addition of relatively small amounts of water, the color intensity of an iodine solution in acetone is not nearly so drastically reduced by the addition of comparable amounts of water. Fourth, the intensity of color of a solution of DNB and sodium iodide in acetone decreases strikingly on dilution with more acetone, whereas a solution of iodine in acetone undergoes only the "normal" expected decrease in intensity when diluted. Fifth, a dilute aqueous solution of sodium thiosulfate does not bleach the color to any greater extent than does an equal volume of water. Lastly, a concentrated acetone solution of the colored material produced by 1,3-dinitrobenzene and sodium iodide (2.0 g. DNB and 3.6 g. of NaI in 20 ml. acetone) was prepared, allowed to stand for 24 hr., and then poured into a large excess of cold water. Of the original 2.0 g. of DNB, 1.78 g. were recovered unchanged. These observations make it seem very unlikely that the reaction is an oxidation-reduction.

The 1:1 combining ratio for both 1,3-dinitrobenzene and for 2,4,6-trinitrotoluene suggests that the combination may be through the aromatic ring rather than through the nitro group(s). The crystal radius of iodide ion (2.2 Å) is nearly the same as that of the aromatic nucleus, making it seem geometrically plausible for the iodide ion to be involved with the aromatic ring as a whole. (This does not explain why 4,4′-dinitrobiphenyl, with two aromatic rings, should also have a 1:1 combining ratio.) Since the nitro group withdraws electrons from the aromatic nucleus, the aromatic nucleus might then attempt to regain electrons by forming some sort of loose complex with the iodide ion. It is worth noting in this connection that the intensity of color increases with increasing numbers of nitro groups in the aromatic ring. The color produced by TNT is deeper than that produced by DNB at the same concentration. It would be interesting to see whether aromatic compounds having substituents with electron-attracting power similar to that of nitro group also give this color reaction.

The color is definitely associated with the iodide ion and not the cation, for potassium iodide and ammonium iodide produce the same effect as sodium iodide. Conductivity data[11] indicate that sodium iodide in acetone at concentrations of 0.1*M* or less is appreciably dissociated into the ions, so it is reasonable to assume that iodide ion is acting as an independent species. The color reaction is not restricted to acetone solutions, for methanol solutions have been observed to give similar results.

Acknowledgment. The author would like to express his appreciation to Dr. A. H. Blatt of Queens College, New York, who suggested that this work be done and gave many helpful suggestions and comments.

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(10) T. Canback, *Farm. Revy*, **48**, 153 (1949); *Chem. Abstr.*, **43**, 4650 (1949).

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Studies in the Pyrazole Series. VII.[1] The Base-Induced Scissions of 3,5-Dimethyl-1-carbamylpyrazole and -1-thiocarbamylpyrazole

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We have shown previously[3a,b] that 1 guanyl- and 1-nitroguanylpyrazoles, Ia and Ib, respectively, deguanylate under aminolytic conditions with the formation of substituted guanidines and a 1-unsubstituted pyrazole. The corresponding 1-carbamyl- and 1-thiocarbamylpyrazoles, Ic and Id, respectively, have now been shown to behave similarly. Thus the reactions of Ic with amines formed a variety of substituted ureas, as well as 3,5-dimethylpyrazole (II). While the expected thioureas were analogously obtained from the reactions of Id with such bases as aniline, benzylamine, 4,4-diphenylsemicarbazide, hydrazine hydrate, and phenylhydrazine, the corresponding ammonium thiocyanates were isolated from its reactions with cyclohex-

(1) Part VI, F. L. Scott, A. Ahearne, and J. Reilly, *Rec. trav. chim.*, **76**, 190 (1957).

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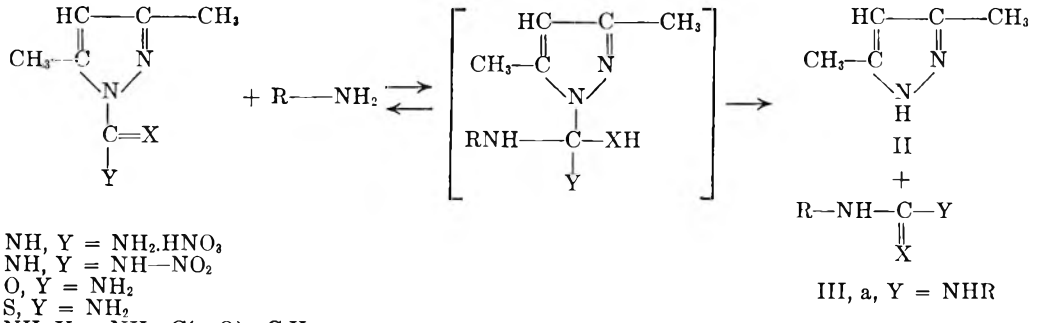
(3) (a) F. L. Scott, D. G. O'Donovan, and J. Reilly, *J. Am. Chem. Soc.*, **75**, 4053 (1953); (b) F. L. Scott, M. T. Kennedy, and J. Reilly, *J. Am. Chem. Soc.*, **75**, 1294 (1953).

ylamine, morpholine, and piperidine. In addition II was isolated in good yield from each of these aminolyses. Some evolution of hydrogen sulfide was also detected in the aminolyses of Id effected with benzylamine, pyrrolidine, pyrrolidone, and phenylhydrazine.

With regard to the mechanism of these reactions three points require comment. First the detected lability of the 1-acylpyrazoles must be attributed primarily to the anionic stability of pyrazolide ion.[4] Secondly, while some of the reaction products obtained with Id suggest elimination processes,[5] the bulk of the present data and other related evidence,[6] suggest that the most probable mechanism for these and similar[3a,b] aminolyses is a carbamyl addition-elimination process as seen in Figure 1.



Ia, X = NH, Y = $NH_2.HNO_3$
Ib, X = NH, Y = NH—NO_2
Ic, X = O, Y = NH_2
Id, X = S, Y = NH_2
Ie, X = NH, Y = NH—C(=O)—C_6H_5
If, X = O, Y = $N(C_6H_5)_2$
Ig, X = NH, Y = NH—SO_2—C_6H_4—CH_3(4)
Ih, X = NH, Y = NH—C(=O)—NH—$C_{10}H_7$(1)
Ij, X = NH, Y = NH—C(=S)—NH—C_6H_5
Ik, Y = NHR

III, a, Y = NHR

FIG. 1

Thirdly, the normal elimination of pyrazolide ion from the intermediary adduct of this latter reaction may receive competition under certain conditions from the expulsion of anion (Y^-) therefrom. This latter event would then result in the formation of pyrazoles of type Ik, and these in turn should readily lead to compounds such as IIIa. We have encountered some products of this type *e.g.*, in the reactions of both aniline and *p*-nitroaniline with Ic, and of aniline and benzylamine with Id. However, in view of the infrequency of IIIa type compounds among the large number of pyrazolyl aminolyses we have examined[3a,b,6] and their possible and demonstrable origination in other ways,[7] we attribute the formation of derivatives such as IIIa to further aminolyses of the initially formed monosubstituted ureas and thioureas. The extent of incursion of IIIa type substances appears to increase with increase in reaction temperature.

Some experiments were also performed herein with azide ion as a deacylating entity. In ethanolic solution the substituted pyrazoles Ie, If, Ig, Ih, and Ij were recovered in *ca.* 80% yields after three hours refluxing with equivalent quantities of sodium azide. After six hours of such treatment, the yield of recovered Ig dropped to 58%. Under the former conditions Ia and Ib were deguanylated by the azide nucleophile and yielded 5-amino- and 5-nitroaminotetrazoles, respectively. Under different experimental conditions *i.e.*, at room temperature but with a much greater reaction time, Id was also deacylated.[8]

EXPERIMENTAL[9]

3,5-Dimethyl-1-carbamylpyrazole (Ic) was prepared by a modification of Posner's method.[10] To a solution of 11.2 g. of

(4) This has not been made explicit in our earlier papers. To support the present statement the following facts may be cited: (a) similar leaving groups have been encountered in related situations, see *e.g.*, H. A. Staab, *Chem. Ber.*, 89, 2088 (1956), and J. Baddiley, J. G. Buchanan, and R. Letters, *J. Chem. Soc.*, 2812 (1956); (b) increasing the electrophilicity of the pyrazole moiety increases its rate of solvolytic 1-deguanylation, see F. L. Scott, *Chimia*, in press, and F. L. Scott and R. Rubin, forthcoming paper in this series; (c) a similar displacement of pyrazolide ion from 1-(2′,4′-dinitrophenyl) pyrazole by base has been recently described, by H. P. Crocker and R. H. Hall, *J. Chem. Soc.*, 4489 (1955); (d) finally the stability of the 1-guanylpyrazolines (F. L. Scott, unpublished data) wherein the acidic character of the pyrazole ring is totally inhibited, also supports this concept.

(5) The isolation of ammonium thiocyanates is not unequivocal evidence for direct eliminations from Id. Such thiocyanic acid derivatives may also arise *via* initial ethanolysis of Id to ethyl thionourethane followed by elimination of thiocyanate ion from this latter substance. Compare *e.g.*, M. Battegay and E. Hegazi, *Helv. Chim. Acta*, **16**, 999 (1933).

(6) See Scott, reference 4 (b) and subsequent papers in this series.

(7) Compare F. L. Scott and M. T. Scott, unpublished results.

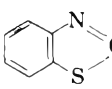
(8) Because we have found (F. L. Scott, A. J. Kocjarski, and J. Reilly, to be published) that thiocarbamyl azide, or rather 5-aminothiatriazole [F. L. Scott, to be published], readily desulfurizes under comparable conditions, and as we encountered no loss of sulfur in the deacylation of Id effected in the presence of sodium azide, we regard this latter deacylation as resulting mainly from ethanolysis.

(9) All melting points are uncorrected. Microanalyses are by Drs. Wieler and Strauss, Oxford, England.

(10) T. Posner, *Ber.*, **34**, 3973 (1901).

TABLE I

AMINOLYSES OF 3,5-DIMETHYL-1-CARBAMYL- AND -1-THIOCARBAMYLPYRAZOLES

Amine	Product (III), with R=	Molecular Formula	M.P., °C.	Yield, %	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
2-Aminobenzothiazole	 [a,b]	$C_8H_7N_3SO$	337[c]	40	49.7	50.2	3.6	3.6
Cyclohexylamine	C_6H_{11}—[a,b]	$C_7H_{14}N_2O$	197[d]	70	59.2	59.1	9.9	9.7
1-Naphthylamine	1-$C_{10}H_7$—[a,b]	$C_{11}H_{10}N_2O$	214[e]	60	71.0	70.8	5.4	5.3
2-Naphthylamine	2-$C_{10}H_7$—[a,b]	$C_{11}H_{10}N_2O$	219[f]	57	71.0	70.6	5.4	5.3
4-Nitroaniline	4-NO_2—C_6H_4—[a,b,g]	$C_{13}H_{10}N_4O_5$	313[h]	97[i]	51.7	51.3	3.3	3.5
n-Octylamine	*n*-C_8H_{17}—[a,b]	$C_9H_{20}N_2O$	100–101[j]	90	62.8	63.2	11.6	11.6
p-Phenylenediamine	4—NH_2—C(=O)—NH—C_6H_4—[a,b]	$C_8H_{10}N_4O_2$	>360[k]	45	49.5	49.2	5.2	5.1
Benzylamine[l]	$C_6H_5CH_2$—[m]	$C_{15}H_{17}N_3SO$[n]	146[o]	56	65.7	66.2	6.6	6.1[p]
Cyclohexylamine[l]	—[q]	$C_7H_{14}N_2S$	101	62	53.2	52.7	8.9	8.8
4,4-Diphenylsemicarbazide[l]	$(C_6H_5)_2N$—C(=O)—NH—[m]	$C_{14}H_{14}N_4SO$	197	34	58.8	59.2	4.9	4.5[r]
Morpholine[l,s]	—[t]	$C_5H_{10}N_2SO$	119–120	63	41.1	41.5	6.8	7.2
Phenylhydrazine[l]	C_6H_5NH—[m]	$C_7H_9N_3S$	202–203[u]	72	50.3	50.3	5.4	5.0[p]
Piperidine[l,s]	—[w]	$C_6H_{12}N_2S$	93	67	50.0	49.9	8.3	8.4

[a] These are represented by the general formula III, with X = O and Y = NH_2. [b] These are reaction products from the appropriate aminolysis of IC in 95% aqueous ethanol, with a 3 hr. reflux period. High yields of II were isolated in each reaction. [c] M.p. >300°, as reported by H. P. Kaufmann, *Arch. Pharm.*, **273**, 22 (1935). [d] J. L. Boivin and P. A. Boivin, *Can. J. Chem.*, **29**, 478 (1951) report this m.p. as 195–196°. [e] Reported[16b] m.p. 215–220°. [f] Reported[16b] m.p. 219–220°. [g] This represents 1,3-di-*p*-nitrophenylurea which is formed in nitrobenzene solution from Ic and *p*-nitroaniline. In ethanolic solution *p*-nitrophenylurea was the sole product isolated from these same reactants and it was formed in only 22% yield. Finally, in toluene as solvent, the major product was again the disubstituted urea (in *ca.* 70% yield), together with *ca.* 5% of the monosubstituted ureide. Each of these reactions involved a 3-hr. reflux period. [h] M.p. 310°, as reported by G. V. Gadhav, *J. Indian Chem. Soc.*, **10**, 391 (1933). [i] This yield is corrected for recovered amine. [j] M.p. 102.5°, reported by J. S. Buck, A. M. Hjort, W. S. Ide, and E. J. de Beer, *J. Am. Chem. Soc.*, **60**, 461 (1938). [k] Previously reported by E. Lellmann, *Ann.*, **221**, 14 (1883) to char without melting. [l] These correspond to aminolyses of Id in ethanolic solution, with a general reflux time of 3 hr. unless otherwise noted. [m] These correspond to III with X = S and in general Y = NH_2. However with benzylamine the product isolated was 1,3-dibenzylthiourea with Y = $NHCH_2C_6H_5$. [n] Physical data correspond to a monohydrate. [o] M.p. 147–148°, reported by G. M. Dyson and H. J. George, *J. Chem. Soc.*, **125**, 1702 (1924). [p] Calcd.: N, 10.2; S, 11.7. Found: N, 10.4; S, 12.1. [q] Apparently, this is cyclohexyl-ammonium thiocyanate; 1-cyclohexylthiourea has been reported to melt at 161–162°, by A. Skita and H. Rolfes, *Ber.*, **53B**, 1242 (1920). [r] Calcd.: N, 19.6; S, 11.2. Found: N, 20.0; S, 11.1. [s] Reflux period: 40 min. [t] This is morpholinium thiocyanate, compare A. Kjaer and K. Rubinstein, *Acta Chem. Scand.*, **7**, 528 (1953). It did not depress on mixture melting point with an authentic sample. This latter sample was prepared by reaction of equimolar quantities of morpholine, potassium thiocyanate, and hydrochloric acid in ethanolic solution at room temperature. The compound thus prepared also had a m.p. 119–120°. [u] Reported[16c] m.p. 200–201°. [v] Calcd.: N, 25.1; S, 19.2. Found: N, 25.0; S, 19.2. [w] This is piperidinium thiocyanate, m.p. 95°, as reported by H. Lecher and A. Goebel, *Ber.*, **55**, 1483 (1922). Again it did not depress on mixture melting point with an authentic sample, prepared similarly to the morpholine derivative, as described above. The melting point of the isomeric 1-thiocarbamylpiperidine has been reported as 128° by O. Wallach, *Ber.*, **32**, 1872 (1899).

semicarbazide hydrochloride in 30 ml. of water was added 10.0 g. of acetylacetone in 10 ml. of absolute ethanol. A vigorous, exothermic reaction resulted and Ic separated in 95% yield. After recrystallization from absolute ethanol or better from benzene-pentane or chloroform-pentane mixtures, it melted at 112°, reported m.p. 111.4–112.4°.

Anal. Calcd. for $C_5H_9N_3O$: C, 51.8; H, 6.5. Found: C, 51.8; H, 6.3.

Essentially, the same technique was employed in the preparation of Id, which was isolated in 85% yield and after crystallization from benzene had m.p. 98–99°. It was markedly unstable.

Anal. Calcd. for $C_6H_9N_3S$: C, 46.5; H, 5.8; N, 27.1; S, 20.6. Found: C, 46.1; H, 5.8; N, 27.0; S, 21.0.

Aminolysis experiments. (1) of Ic.[11] The following is representative of the reactions effected. To a solution of 2.39 g. of Ic dissolved in 30 ml. of 95% ethanol was added a slight excess, 1.8 g., of aniline. The solution was then refluxed for 4 hr. On cooling and diluting the solution with an excess of water a white flocculent precipitate (0.20 g., 5.5% yield)[12] of 1,3-diphenylurea was obtained. This after recrystallization from aqueous ethanol melted at 239–240°, reported[13] m.p. 238–239°.

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.6; H, 5.7. Found: C, 73.4; H, 5.8.

The filtrate on further work-up gave 0.90 g. (37.7% yield) of phenylurea m.p. 146–147°, reported[13] m.p. 144.5–145.6°, which did not depress the melting point of an authentic sample. In addition a quantitative yield of 3,5-dimethylpyrazole (II), m.p. 105–106°, reported[14a] m.p. 107–108°, was isolated and identified by mixture melting point with an authentic sample, and *via* its picrate m.p. 166°, resported[14b] m.p. 166–167°.

(11) We are indebted to Miss M. M. Hearn, M.Sc., for assistance with these experiments.

(12) These yields are based on the quantity of amine employed when diureas are isolated as aminolysis products of Ic (or Id) but on the quantity of substituted pyrazole used when the reaction product is a monosubstituted urea.

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

(14) (a) R. H. Wiley and P. E. Hexner, *Org. Syntheses*, **31**, 43 (1951); (b) R. V. Rothenburg, *J. prakt. Chem.*, **52**, 45 (1895).

Anal. Calcd. for $C_{11}H_{11}N_5O_7$: C, 40.6; H, 3.4; N, 21.5 Found: C, 41.1; H, 3.7; N, 21.5.

It is to be understood that II was similarly isolated and identified in all the pyrazolyl aminolyses effected. The yields of II throughout averaged between 75–85%.

(2) *of Id.* To 2.0 g. of Id dissolved in the minimum quantity of ethanol was added 1.2 ml. of aniline. The mixture was refluxed for 3 hr., during which time it developed a yellow coloration. On standing overnight, 0.76 g. (52% yield)[12] of white flakes, m.p. 148–150° settled out. After crystallization from ethanol these had a m.p. of 152° and corresponded to 1,3-diphenylthiourea, reported[15a] m.p. 154°.

Anal. Calcd. for $C_{13}H_{12}N_2S$: C, 68.4; H, 5.3; N, 12.3; S, 14.0. Found: C, 68.0; H, 5.3; N, 12.2; S, 13.6.

The alcoholic filtrate was allowed to evaporate in a stream of air and the residual solid was then washed with 6 × 20 ml. portions of ether. A further quantity, 0.15 g. (10.3%) of 1,3-diphenylthiourea remained behind, as essentially ether-insoluble. The ethereal liquor on work-up yielded 82% of II, identified as previously described. Most of the remaining aminolyses of both Ic and Id are summarized in Table I.

Some related observations. When treated with Ic under the general conditions described above the following bases were carbamylated: dimethylamine yielded 1,1-dimethylurea, m.p. 182°, reported[13] m.p. 182°, in 64% yield; phenylhydrazine afforded 1-phenylsemicarbazide, m.p. 172°, reported[16a] m.p. 172°, in 90% yield; 4-nitrophenylhydrazine resulted in 1-(4′-nitrophenyl)semicarbazide, m.p. 215°, reported[17] m.p. 211–212°, in 95% yield; and thiosemicarbazide yielded 2-thiobiurea, m.p. 216–218°, reported[18] m.p. 220°, in 82% yield.[19] When the base employed was either diphenylamine, lysine hydrochloride, nitroaminoguanidine, or phthalimide, Ic completely decarbamylated under the usual reaction conditions without forming any appreciable quantities of the corresponding ureides and thus the deacylation encountered was purely solvolytic in origin. A series of experiments were run to put this on a semiquantitative basis. These consisted of refluxing measured quantities of Ic for varying periods of time in 95% ethanol solution, then rapidly cooling the reaction sample and analyzing the liquor for both II and unchanged Ic. From these, a rough rate constant for the solvolytic deacylation of Ic was derived, *viz.* $k_1 = 1.2(\pm 0.2) \times 10^{-3}$ sec.$^{-1}$ This accounts for the non-survival of Ic even with the weakest nucleophiles employed and is in reasonable accord with the more precise rate value as determined by spectrophotometric means.[4b] Incidentally, in the sample analyzed after a minute reflux period, the presence of cyanic acid was suggested in the cooled reaction liquor by means of its [$Co(CNO)_2$.2 KCNO] complex.[20] A similar complex was not formed from a cold solution of pure Ic or II. When Id was refluxed with 1 equivalent of either pyrrolidone or pyrrolidine for 40 min., hydrogen sulfide was vigorously evolved; however only 3,5-dimethylpyrazole, in 60% yield, was identified, as before, on work-up of the reaction liquor. Similarly treated with hydrazine hydrate, with 1 hr. refluxing, Id afforded II in 77% yield and 51% thiosemicarbazide m.p. 181–182°, reported[15b] m.p. 181–183°. Semioxamazide analogously treated, save with a 20-min. reflux period, resulted in a 90% recovery of starting hydrazide, no detectable evolution of either sulfur or hydrogen sulfide, and an 11% yield of II. All the substituted ureides described above were identified by mixture melting point with authentic samples, which were either already available or prepared by standard methods from the literature. Finally, while benzylamine and phenylhydrazine afforded simple displacement products with Id, see Table I, their aminolyses were accompanied by a faint evolution of hydrogen sulfide from the reaction liquor.

Displacements with azide ion. The reaction with Id was as follows: To 5.0 g. of Id dissolved in 200 ml. of cold ethanol was added 2.05 g. of sodium azide dissolved in 20 ml. of water. The mixture was continuously mechanically agitated. At 24-hr. intervals, 44 ml. aliquots were withdrawn. Each aliquot was evaporated to dryness in a stream of air, the residual solid was then dissolved in water and the aqueous liquor extracted with ether. The quantities of II thus isolated from the ethereal extracts and identified as before corresponded to: 0.34 g. (after 24 hr.); 0.40 g. (48 hr.); 0.42 g. (72 hr.); 0.44 g. (96 hr.) and 0.56 g. (120 hr.). Total yield of II obtained, 2.16 g. (71.5%). No other material was isolated (this includes sulfur).[8] The above figures result in a rough rate of deacylation for Id of 7×10^{-5} l. mole^{-1} sec.$^{-1}$ Of the remaining pyrazoles studied only with Ia was a comparable series of experiments run. With this latter pyrazole the solvent employed was water and the reactions were run at reflux temperature. After 1 hr. of such treatment of Ia with an equivalent quantity of sodium azide, 17% Ia was recovered, 54% II was isolated, *via* ether extraction, etc, and 22% of 5-aminotetrazole, m.p. 205°, reported[21a] m.p. 203°, was also obtained.

Anal. Calcd. for CH_3N_5: C, 14.1; H, 3.5; N, 82.4. Found: C, 14.4; H, 3.8; N, 81.9.

After 3 hr. of such refluxing the respective percentages isolated were 13, 39, 35; after 6 hr. they consisted of 10, 51, and 36 and after 9 hr. they corresponded to 7, 52, and 44. These data yielded an approximate value for the second-order rate constant of the azide induced deacylation of Ia in aqueous solution, at 100°, *viz.* $k_2 = 5 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$ From Ib after 3 hr. refluxing in aqueous solution with 1 equivalent of sodium azide was isolated either the sodium salt of 5-nitraminotetrazole, m.p. >360° with very violent explosion, in 46% yield, or, after acidification of the mother liquor, 5-nitraminotetrazole itself, m.p. 137° (with explosion), reported[21b] m.p. *ca.* 140°, in 26% yield.

Anal. Calcd. for $CH_3N_6O_2$: C, 9.2; H, 1.6. Found: C, 10.0; H, 2.1.

The yield of II from both experiments with Ib was 32 and 18% respectively. When the pyrazoles Ie, If, Ig, Ih, and Ij were refluxed for 3 hr. in aqueous ethanolic solution with 1 equivalent of sodium azide they were recovered unchanged in 80, 85, 84, 75, and 82% yields respectively. After 6 hr. refluxing, Ig was recovered in only 58% yield, and II was isolated in 11% yield. However, no tetrazolyl byproducts were identified in the reaction with Ig. Finally when Ic was stirred for 24 hr. in aqueous ethanol with an equimolar quantity of azide ion it was recovered in 70% yield without the detection of any formation of substance II.

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(15) *Organic Reagents for Organic Analysis*, 2nd Edition, Hopkin and Williams, Essex, England, 1950; (a) p. 178; (b) p. 122.

(16) I. Heilbron and H. M. Bunbury, *Dictionary of Organic Compounds*, 4th Edition, Eyre and Spottiswoode, London, 1953; (a) Vol. IV, p. 173; (b) Vol. III, p. 592; (c) Vol. IV, p. 179

(17) E. Hyde, *Ber.*, **32**, 1812 (1899).

(18) S. L. Ganniah and P. C. Guha, *J. Indian Inst. Sci.*, **16A**, 11 (1933).

(19) This percentage has been corrected for recovered amine.

(20) H. E. Williams, *Cyanogen Compounds*, 2nd Edition, p. 400, Arnold and Co., London, 1948.

(21) (a) J. Thiele, *Ann.*, **270**, 54 (1892); (b) see E. Lieber, C. C. Herrick, and E. Sherman, *J. Am. Chem. Soc.*, **74**, 2684 (1952) and previous papers.

Study of the Dithiobiuret-Benzaldehyde Condensation Product

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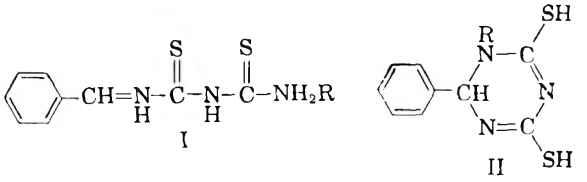
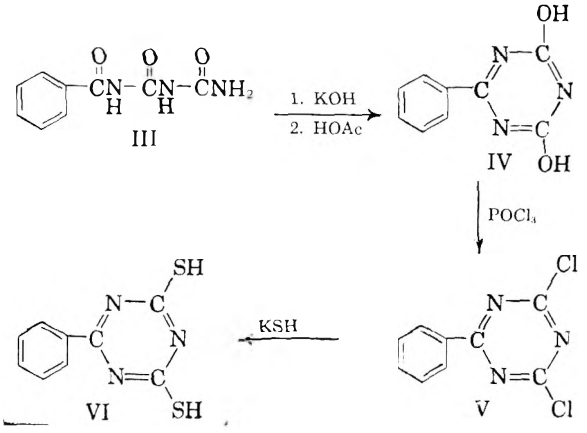
It was previously reported by Foye and Hefferen[2] that compounds of the Tibione type, *p*-$AcNHC_6H_4$-CH=NNHCSNH_2, could be prepared by the condensation of *para*-substituted benzaldehydes with dithiobiuret.



I II

However, Fairfull and Peak[3] recently proved that the products of the reaction between aromatic aldehydes and substituted dithiobiurets were not benzaldithiobiurets, I, as indicated by Foye and Hefferen,[2] but instead the cyclized compound having an *s*-triazine structure, II. They further stated the unsubstituted biuret should behave in a similar manner but they made no attempt to prove this.

Because Fairfull and Peak[3] did not prove the structure of the condensation of benzaldehyde with unsubstituted dithiobiuret and because other groups had postulated the benzal dithiobiuret structure,[2,4] it was felt there was a reasonable doubt as to the structure of the product. The condensation product of benzaldehyde with dithiobiuret was studied and proved conclusively to be 2,4-dimercapto-6-phenyldihydro-*s*-triazine, II (R = H). The approach was to synthesize the known 2,4-dimercapto-6-phenyl-*s*-triazine, VI, by condensing benzoyl chloride with urea to give 1-benzoylbiuret, III.[5] This compound was then treated with potassium hydroxide to afford 2,4-dihydroxy-6-phenyl-*s*-triazine, IV,[5] which on treatment with phosphorous oxychloride gave 2,4-dichloro-6-phenyl-*s*-triazine, VI.[6] The desired product could then be obtained by treating the dichloro compound with potassium hydrosulfide. This yielded compound VI.



III IV V VI

The product obtained from the reaction of benzaldehyde with dithiobiuret was then oxidized and proved to be identical with the known compound, VI, by mixed melting point.

The infrared spectra of 2,4-dimercapto-6-phenyl-*s*-triazine, VI, and the product obtained by the alkaline potassium ferricyanide oxidation of the condensation product were identical when run in KBr disks. These data indicate the dithiobiuret-benzaldehyde condensation product to be 2,4-dimercapto-6-phenyldihydro-*s*-triazine, II, (R = H).

EXPERIMENTAL

1-Benzoylbiuret. Essentially the method of Bloch and Sobotka was used involving the reaction of benzoyl chloride and urea. A white crystalline solid was obtained, m.p. 229–230° dec. (lit. 224–225°).[5]

2,4-Dihydroxy-6-phenyl-s-triazine. IV. This compound was prepared by Bloch and Sobotka by treating 1-benzoylbiuret with aqueous potassium hydroxide. The authors obtained a 74% yield, m.p. 299–300° dec. (lit. 297–300°).[5]

2,4-Dichloro-6-phenyl-s-triazine, V, was prepared by the method of Fairfull and Peak in 65% yield, m.p. 120–121° (lit. 119–120°).[3]

2,4-Dimercapto-6-phenyl-s-triazine, VI, was prepared by the method of Fairfull and Peak in 66% yield, m.p. 244–245° dec. (lit. 248–249°),[3] λ_{max}^{EtOH} 235 (39,600), ϵ_{max} 39,600.

2,4-Dimercapto-6-phenyldihydro-s-triazine. To 135.0 g. (1.00 mole) of dithiobiuret, dissolved in 3 l. of hot glacial acetic acid, was added 170.0 g. (1.60 moles) of benzaldehyde. The mixture was refluxed for 12 hr. concentrated under reduced pressure to 1.5 l., and cooled to 0°. The yellow, crystalline solid was removed, dissolved in sodium hydroxide solution, filtered, reprecipitated with acetic acid, and recrystallized from absolute ethanol to give 84.0 g. (38%) of the condensation product, m.p. 235–236° dec. (lit. 236–238°)[3] λ_{max}^{EtOH} 275, 298, ϵ_{max} 20,200; 21,500.

Anal. Calcd. for $C_9H_9N_3S_2$: C, 48.40%; H, 4.06; N, 18.82; S, 28.72. Found: C, 48.85; H, 3.56; N, 18.60; S, 28.31.

Oxidation of 2,4-dimercapto-6-phenyldihydro-s-triazine to 2,4-dimercapto-6-phenyl-s-triazine. One gram (0.0045 mole) of 2,4-dimercapto-6-phenyldihydro-*s*-triazine was dissolved in a minimum amount of 5% sodium hydroxide. A solution of potassium ferricyanide (2.96 g. of potassium ferricyanide in 10.0 ml. of water) was added dropwise to the above solution at room temperature with constant agitation. After addition was complete the mixture was filtered and acidified with acetic acid to afford a yellow material. This material was washed with water and mixed with 15.0 ml. of dimethyl formamide. The resulting slurry was filtered and the yellow solution was chromatographed on a chloroform-silicic acid column. It was eluted with pure chloroform to give a pure product which on crystallization from water-ethanol (9:1) gave long thin needles, 0.12 g. (12%) m.p. 244–245° dec. (lit. 248–249° dec.).[3]

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(1) In partial fulfillment for the Master of Science Degree, University of Wisconsin.

(2) W. O. Foye and J. J. Hefferen, *J. Am. Pharm. Assoc.*, 42, 31 (1953).

(3) A. E. S. Fairfull and D. A. Peak, *J. Chem. Soc.*, 803 (1955).

(4) A. Claus, *J. prakt. Chem.*, 47, 135 (1893).

(5) E. Bloch and H. Sobotka, *J. Am. Chem. Soc.*, 60, 1656 (1938).

(6) A. Ostrogovich, *Chem. Ztg.*, 36, 739 (1912).

Anal. Calcd. for $C_9H_7N_3S_2$: C, 48.84; H, 3.19; N, 18.99. Found: C, 48.51; H, 2.92; N, 18.53.

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Nitrous Acid Oxidation of Triacyl Pyridoxamine[1]

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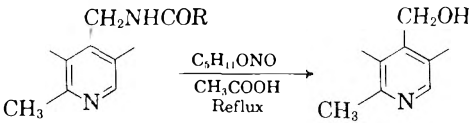
Received December 18, 1956

Based on elemental analysis, it appeared probable that the nitrous acid oxidation product (MDP) of *N,O,O*-tripalmitoylpyridoxamine was a mixture of mono- and di-palmitoylpyridoxine.[2] Since this reaction represented direct conversion of the acylated amino to a hydroxyl group, further studies were carried out with various acyl derivatives of pyridoxamine.

Several workers have synthesized *N*-nitroso derivatives of acylated primary amines and their reactions have been investigated.[3] Heyns *et al.* observed that the nitroso derivatives of *N*-*n*-propylacetamide, *N*-*n*-butylacetamide, and *N*-benzylacetamide could be thermally decomposed to form acetates of the corresponding alcohols.[4]

The transformation of free pyridoxamine to pyridoxine under mild treatment with nitrous acid has been reported.[5,6] The test compounds used were triacetyl-, tridecanoyl, tripalmitoyl-, tribenzoyl- and tri-*p*-nitrobenzoyl-pyridoxamine. When the acyl pyridoxamine was refluxed in a mixture of isoamyl nitrite and glacial acetic acid (1:2 v/v) for 30–60 *min.*, complete replacement of the acylated amino group with a hydroxyl group took place. Evidence for this conversion has been obtained by paper chromatography and microbiological assay using a minute quantity of the test compound.

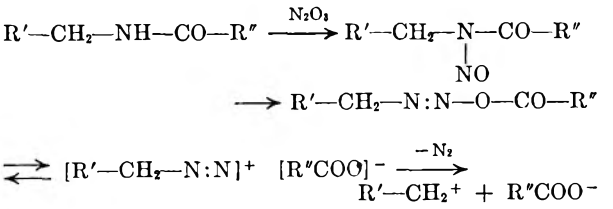
The triacylpyridoxamine was hydrolyzed with 2*N* ethanolic potassium hydroxide by refluxing for 30 min. The resulting hydrolysate contained two



fractions detectable on the papergram with *N*, 2,6-trichloro-*p*-quinoneimine. One was free pyridoxamine and the other was a high R_f fraction, which was probably the corresponding *N*-monoacylpyridoxamine (Table 1). The ester linkages at the 3- and 5-positions must have been cleaved during the alkali treatment, since complete hydrolysis of various *O,O,O*-triacylpyridoxines resulted under identical conditions. If the triacylpyridoxamine was treated with nitrous acid prior to alkali hydrolysis, the only vitamin B_6 component present in the final hydrolysate was found to be pyridoxine (Table 1). Oxidation with nitrous acid under milder conditions gave a mixture of pyridoxamine, pyridoxine, and a high R_f fraction (Table 1). In all cases, pyridoxal was found to be absent.

The theoretical amount of pyridoxine moiety in MDP was calculated from the nitrogen analysis. A portion of MDP was also subjected to microbiological assay. The two values thus obtained were in complete agreement indicating that the nitrogen present in MDP accounted for all of the nitrogen in the pyridoxine molecule. By paper chromatography, it also became clear that MDP contained pyridoxine free from pyridoxamine. However, free pyridoxine, pyridoxal, pyridoxamine as well as the pyridoxamine moiety present in the alkali hydrolysate of tridecanoylpyridoxamine[7] was totally destroyed by refluxing in a mixture of isoamyl nitrite and acetic acid for one hour. This was shown by color test with *N*, 2,6-trichloro-*p*-quinoneimine and by microbiological assay. Protection of one or both of the 3-hydroxyl and 5-hydroxymethyl groups in vitamin B_6, therefore, appeared to be essential in order to prevent destruction of the vitamin fragment. When 3-monopalmitoylpyridoxal[2] or 5-monopalmitoylpyridoxine[2] was similarly treated, the vitamin B_6 moiety withstood the nitrous acid treatment.

The following equations may be of value to explain the conversion of the acylated amino group to



(1) This work was supported by research grant A-257 from the National Institutes of Health, Department of Health, Education, and Welfare. The pyridoxamine used in this study was kindly supplied by Merck and Co. through the courtesy of Dr. Max Tishler.

(2) T. Sakuragi and F. A. Kummerow, *J. Am. Chem. Soc.*, **78**, 839 (1956).

(3) (a) H. v. Pechmann and L. Frobenius, *Ber.*, **27**, 651 (1894); (b) E. Bamberger, *Ber.*, **27**, 914 (1894); (c) G. F. D'Alelio and E. E. Reid, *J. Am. Chem. Soc.*, **59**, 109 (1937); (d) Von R. Husigen and J. Reinertshofer, *Z. Naturforsch.*, **6b**, 395 (1951); (e) K. Heyns and O. Woyrsch, *Ber.*, **86**, 76 (1953); (f) Von R. Husigen and H. Nakaten, *Ann.*, **586**, 84 (1954).

(4) K. Heyns and W. V. Bebenburg, *Ber.*, **86**, 278 (1953).

(5) S. A. Harris, D. Heyl, and K. Folkers, *J. Am. Chem. Soc.*, **66**, 2088 (1944).

(6) E. E. Snell, *J. Biol. Chem.*, **157**, 491 (1945).

(7) Tridecanoyl pyridoxamine was refluxed in 2*N* ethanolic potassium hydroxide for 30 min. After neutralization with ethanolic hydrogen chloride, the precipitate of potassium chloride was removed by filtration and the solvent was evaporated until dryness *in vacuo*. The residue was then used for the nitrous acid oxidation.

TABLE I

PAPER CHROMATOGRAM OF ALKALI HYDROLYSATE OF ACYLPYRIDOXAMINE TREATED WITH NITROUS ACID UNDER VARIOUS CONDITIONS

Test Compound	Treatment[a]	Spots Observed[b] (Solvent: 1-Butanol Saturated with Water)		
		Pyridoxamine (R_f 0.06)	Pyridoxine (R_f 0.24)	High R_f fraction[c]
Triacetylpyridoxamine	A	+	−	− (R_f 0.28)
	E	−	+	−
Tribenzoylpyridoxamine	A	+	−	+ (R_f 0.82)
	E	−	+	−
Tri-*p*-nitrobenzoylpyridoxamine	A	+	−	+ (diffused)
	E	−	+	−
Tridecanoylpyridoxamine	A	+	−	+ (R_f 0.86)
	B	+	−	+
	C	+	+	+
	D	+	+	+
	E	−	+	−
	F	+	−	+
Tripalmitoylpyridoxamine	A	+	−	+ (R_f 0.88)
	E	−	+	−

[a] A few mg. of the test compound was treated as follows: A—Refluxed for 30 min. in 0.5–1.0 ml. of 2*N* ethanolic potassium hydroxide solution. Each of the treatments from B to F was followed by treatment A after thorough removal of the solvent *in vacuo*. B—Dissolved in a mixture of 0.5 ml. of ethanol, 0.5 ml. of isoamyl nitrite, and 2 drops of concentrated hydrochloric acid. Allowed to stand at room temperature for 12 hr. C—Dissolved in a mixture of 0.5 ml. of isoamyl nitrite and 1 ml. of glacial acetic acid. Allowed to stand at room temperature for 120 hr. D—Same as C, but refluxed for 15 min. E—Same as C, but refluxed for 45 min. F—Same as E, but 1 ml. of dioxane was used instead of 1 ml. of glacial acetic acid. [b] Chromogenic reagent was *N*,2,6-trichloro-*p*-quinoneimine. + indicates presence; − indicates absence. [c] Probably the corresponding *N*-monoacyl pyridoxamine.

a hydroxyl group, although no attempt has been made to isolate a nitroso compound as a possible intermediate.

If the chemical conversion observed in the present study was identical with the one reported by Heyns *et al.*,[4] the immediate product from the possible intermediate, *N*-nitroso- *N*,*O*,*O*-triacylpyridoxamine, would be the corresponding triacylpyridoxine. However, when *O*,*O*,*O*-tripalmitoylpyridoxine[2] was refluxed in a mixture of isoamyl nitrite and glacial acetic acid, no chemical change took place and unchanged starting material was recovered. This indicated that MDP could not be derived from tripalmitoylpyridoxine and was probably a product formed directly from the *N*-nitroso intermediate or through some other steps.

EXPERIMENTAL

Microbiological assay of various acyl derivatives of vitamin B_6. Approximately 0.005 to 10 mg. of the test compound was hydrolyzed with a sufficient amount (0.5–10 ml.) of 2*N* ethanolic potassium hydroxide by refluxing for 30 min. This condition was mild enough to prevent alkali destruction of pyridoxine and pyridoxamine,[8,9] but caused about 10–15% destruction of pyridoxal. After cooling, the solution was neutralized to phenolphthalein with alcoholic hydrogen chloride and the solvent was removed thoroughly *in vacuo* using a rotatory evaporator. Complete removal of the alcohol was essential, since inclusion of ethanol in the assay medium caused *drift* or lower readings. The residue was then extracted with hot water and made up to volume for microbiological assay as reported by Atkin *et al.*[10] using *Saccharomyces carlsbergensis* (ATCC 4228). The recovery of vitamin B_6 from triacetyl,- tridecanoyl-, tripalmitoyl-, and tribenzoylpyridoxine was quantitative ranging between 97–104%. The recovery of pyridoxamine from tridecanoyl- and tripalmitoylpyridoxamine varied from 14 to 28% indicating resistance of the amide linkage to hydrolysis. When tridecanoylpyridoxamine was refluxed for 1 hr. in a mixture of isoamyl nitrite and glacial acetic acid (1:2 v/v) prior to alkali hydrolysis, the recovery was increased to 70%. The microbiological assay of MDP was similarly carried out with 7.7 mg. of the sample, which was hydrolyzed with 10 ml. of 2*N* ethanolic potassium hydroxide solution.

Paper chromatography. To separate vitamin B_6 and its derivatives, the ethanolic solution of the sample was acidified to Congo Red with hydrochloric acid and applied to Whatman No. 1 filter paper on a descending system. The solvent used was 1-butanol saturated with water and developed at 30°. To detect the spots, a 1% solution of *N*,2,6-trichloro-*p*-quinonimine in benzene was sprayed on the paper and the paper exposed to ammonia vapor. This solvent system was not satisfactory for the separation of pyridoxine from pyridoxal.[11] Among the three forms of vitamin B_6, however, only pyridoxal revealed a yellow spot with phenylhydrazine in acetic acid. With this chromogenic reagent, absence of pyridoxal in the oxidized triacyl pyridoxamine was confirmed.

Paper chromatography for the fatty acid component in MDP was carried out by the hydroxamate method as reported by Inouye and Noda.[12] The preparation of MDP gave a strong spot of palmitic acid and an extremely faint spot corresponding to acetic acid. The chromogenic reagent, ferric chloride in ethanol, also revealed the spot of pyridoxine.

Test compounds. *N*,*O*,*O*-Tripalmitoylpyridoxamine was

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(9) E. Cunningham and E. E. Snell, *J. Biol. Chem.*, **158**, 491 (1945).

(10) L. Atkin, A. S. Schultz, W. L. Williams, and C. N. Frey, *Ind. Eng. Chem., Anal. Ed.*, **15**, 141 (1943).

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(12) Y. Inouye and M. Noda, *J. Agr. Chem. Soc. Japan*, **23**, 294 (1950).

synthesized as reported previously.[2] The preparation of MDP (C, 72.97; H, 10.19; N, 2.23) was the oxidation product of tripalmitoylpyridoxamine with nitrous acid.[2] Triacetylpyridoxamine was prepared as follows: Approximately 50 mg. of pyridoxamine dihydrochloride was refluxed in a mixture of glacial acetic acid (2.5 ml.) and acetic anhydride (2.5 ml.) for 1.5 hr. The solvent was then removed as much as possible *in vacuo*, and the residue was dissolved in a few ml. of absolute methanol. Upon addition of absolute ether containing dry hydrogen chloride, a precipitate was obtained. M.p. 129.0–130.0°.

Anal. Calcd. for $C_{14}H_{18}N_2O_5 \cdot HCl$: N, 8.47. Found: N, 8.67.

Other triacylpyridoxamines were prepared from pyridoxamine dihydrochloride and the respective acid chlorides in a manner similar to the one described for the synthesis of the tripalmitoyl derivative. *N,O,O*-Tridecanoylpyridoxamine was recrystallized from absolute methanol. M.p. 86.5–87.5°.

Anal. Calcd. for $C_{38}H_{66}N_2O_5$: C, 72.33; H, 10.54; N, 4.44. Found: C, 72.62; H, 10.33; N, 4.54.

N,O,O-Tribenzoylpyridoxamine was recrystallized from 60% ethanol. M.p. 131.0–133.0°.

Anal. Calcd. for $C_{29}H_{24}N_2O_5$: N, 5.83. Found: N, 5.98.

N,O,O-Tri-*p*-nitrobenzoyl pyridoxamine was recrystallized from pyridine-methanol. M.p. 202.0–203.0°.

Anal. Calcd. for $C_{29}H_{21}N_5O_{11}$: N, 11.38. Found: N, 11.34.

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p-Phenylazobenzoyl Chloride for Identification and Chromatographic Separation of Colorless Compounds. III. Phenols

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Received December 26, 1956

The value of *p*-phenylazobenzoyl chloride as a reagent for identification and chromatographic separation of alcohols and amines has been shown in previous communications.[2,3] Since the reactions of alcohols, amines, and phenols are similar in many respects, it seemed desirable to study the usefulness of *p*-phenylazobenzoyl chloride as a reagent for phenols.

Whereas alcohols and amines reacted readily with the reagent to give good yields of esters and amides respectively, in general, the phenols reacted with difficulty and gave small yields of esters. The procedure used in the preparation of the derivatives was very simple. It consisted of heating for 4 hours a solution of the phenol and acid chloride in pyridine. Longer periods of reaction time did not increase the yield of derivatives. With the exception of the derivatives of 2-methylphenol, 3,4-dimethylphenol, 2,4-dimethylphenol, 2,6-dimethylphenol, and 3-ethyl-5-methylphenol all were precipitated from the reaction mixture as solids. Although the yields were low they were adequate for easy identification. The *p*-phenylazobenzoates are highly crystalline derivatives which are easily purified. The melting points of the derivatives are high enough so that only the derivative of 2,6-dimethylphenol was obtained as an oil, and they are separated widely enough to ensure identification. In those several instances where the melting points of derivatives were similar, mixture melting points showed considerable depression and wide spreads.

The aryl-*p*-phenylazobenzoates that have been characterized are recorded in Table I.

The derivatives of phenols which are commonly used for identification are neither colored nor fluorescent. Hence they are not suitable to applications of chromatographic adsorption for the separation of phenol derivatives. The brilliantly colored aryl-*p*-phenylazobenzoates have been found to be suitable derivatives for separation of mixtures by chromatographic adsorption techniques. The adsorbents used in preparing preliminary columns for the separation of the derivatives were as follows: alumina, alumina-celite mixture, silicic acid, and silicic acid–celite. Of these adsorbents silicic acid–celite was the most satisfactory. It afforded better separations of mixtures of derivatives, faster percolation rate and easier desorption of the derivatives. In the case of alumina various percentages of alcohol in Skellysolve B or benzene were required to develop the chromatograms, and to desorb the derivatives it was necessary to heat the adsorbent with a solution of 80% alcohol-water. Under these conditions of desorption the derivatives underwent hydrolysis and transesterification to give a mixture from which the aluminum salt of *p*-phenylazobenzoic acid and ethyl-*p*-phenylazobenzoate were identified.

Table II shows the results obtained by the adsorption of 15 pairs of aryl *p*-phenylazobenzoates on mixtures of alumina-celite and silicic acid–celite. The first member of each separable pair listed in Table II was the most strongly adsorbed derivative. Six pairs marked +++ were separated sufficiently on at least one of the adsorbents to make two zones visible with a colorless zone between. Two pairs marked ++ formed a continuous band on at least one of the adsorbents. Sectioning of this with subsequent elution yielded an almost homogeneous top and bottom section with intervening sections of varying composition. Three pairs marked + formed a continuous band on at least one of the adsorbents, but sectioning of this gave impure top and bottom materials which were of different melting points, showing that a mixture was initially present. Finally, eight pairs marked "minus" gave no separation on one or both of the adsorbents as there was no significant difference in the melting points of the material from the top and bottom sections of the continuous band. Those pairs which

(1) This paper is based on work presented by J. M. T. in partial fulfillment of requirements for an undergraduate research course offered in the Department of Chemistry of Central State College.

(2) E. O. Woolfolk, F. E. Beach, and S. P. McPherson, *J. Org. Chem.*, 20, 391 (1955).

(3) E. O. Woolfolk and E. H. Roberts, *J. Org. Chem.*, 21, 436 (1956).

TABLE I

ESTERS OF *para*-PHENYLAZOBENZOIC ACID

Phenol Used	M.P., °C.[a] Corrected	Yield,[b] %	Formula	Nitrogen[c] Calcd.	Found
Phenol	148.0–150.0	45*	$C_{19}H_{14}N_2O_2$	9.27	9.30
2-Methylphenol	110.0–111.5	17	$C_{20}H_{16}N_2O_2$	8.86	8.68
4-Methylphenol	134.5–136.5	13	$C_{20}H_{16}N_2O_2$	8.86	8.70
2,3-Dimethylphenol	134.0–136.0	14	$C_{21}H_{18}N_2O_2$	8.48	8.33
3,4-Dimethylphenol	104.0–107.0	26	$C_{21}H_{18}N_2O_2$	8.48	8.23
2,4-Dimethylphenol	110.0–113.0	20	$C_{21}H_{18}N_2O_2$	8.48	8.61
2,5-Dimethylphenol	95.5– 97.5	24	$C_{21}H_{18}N_2O_2$	8.48	8.30
3,5-Dimethylphenol	104.5–106.5	36	$C_{21}H_{18}N_2O_2$	8.48	8.53
2,6-Dimethylphenol	Oil				
4-Ethylphenol	117.0–118.0	48	$C_{21}H_{18}N_2O_2$	8.48	8.57
3-Ethyl-5-methylphenol	159.0–161.0	9	$C_{22}H_{20}N_2O_2$	8.14	8.31
2-Isopropyl-5-methylphenol (thymol)	85.0– 88.0	9	$C_{23}H_{22}N_2O_2$	7.82	7.82
o-Chlorophenol	120.0–121.0	55	$C_{19}H_{13}ClN_2O_2$	8.32	7.99
m-Chlorophenol	127.5–128.5	36	$C_{19}H_{13}ClN_2O_2$	8.32	8.15
p-Chlorophenol	153.0–154.0	13	$C_{19}H_{13}ClN_2O_2$	8.32	8.34
o-Bromophenol	126.5–127.5	80	$C_{19}H_{13}BrN_2O_2$	7.35	7.15
m-Bromophenol	124.5–126.0	58	$C_{19}H_{13}BrN_2O_2$	7.35	7.11
p-Bromophenol	167.5–168.5	32	$C_{19}H_{13}BrN_2O_2$	7.35	7.22
2,4,6-Tribromophenol	116.0–119.0	8	$C_{19}H_{11}Br_3N_2O_2$	5.20	5.09
2,4,6-Tribromo-3-methylphenol	130.0–132.0	34*	$C_{20}H_{13}Br_3N_2O_2$	5.07	4.98
o-Iodophenol	125.5–127.5	8	$C_{19}H_{13}IN_2O_2$	6.54	6.65
o-Nitrophenol	136.5–137.0	30	$C_{19}H_{13}N_3O_4$	12.10	10.39
m-Nitrophenol	160.5–162.5	33	$C_{19}H_{13}N_3O_4$	12.10	10.79
p-Nitrophenol	203.0–206.0	9	$C_{19}H_{13}N_3O_4$	12.10	10.15
p-Phenylphenol	213.5–214.0	50*	$C_{25}H_{18}N_2O_2$	7.40	7.44
o-Phenylphenol	141.0–144.0	5	$C_{25}H_{18}N_2O_2$	7.40	7.34
p-Phenylazophenol	213.5–214.0	19	$C_{25}H_{18}N_4O_2$	13.79	13.89
α-Naphthol	118.0–119.0	20	$C_{23}H_{16}N_2O_2$	7.95	8.09
β-Naphthol	190.0–193.0	18	$C_{23}H_{16}N_2O_2$	7.95	7.82
2-Carbomethoxyphenol (methyl salicylate)	100.5–102.5	17	$C_{21}H_{16}N_2O_4$	7.77	7.76

[a] Melting points taken on Kofler Micro Hot Stage. [b] Yields marked with asterisk are on products purified only by recrystallization; otherwise reported on products purified by chromatography then recrystallized. [c] Microanalyses by the Dumas method were performed by the Du Good Chemical Laboratories, St. Louis, Mo.

were not investigated on one of the adsorbents are marked O in the appropriate column.

TABLE II

CHROMATOGRAPHIC SEPARATION OF ESTERS OF *p*-PHENYLAZOBENZOIC ACID

Mixture[a]		Alumina-Celite	Silicic Acid–Celite
o-Bromophenol	*o*-Iodophenol	0	+++
o-Bromophenol	*m*-Bromophenol*	–	–
o-Bromophenol	*p*-Bromophenol	–	–
m-Bromophenol	*p*-Bromophenol	–	–
m-Chlorophenol	*m*-Bromophenol*	–	+++
o-Chlorophenol	*o*-Bromophenol*	–	+++
o-Chlorophenol	*o*-Iodophenol	0	+++
m-Chlorophenol	*p*-Chlorophenol	0	–
o-Chlorophenol	*p*-Chlorophenol	+++	+++
m-Chlorophenol	*o*-Chlorophenol	++	+++
p-Methylphenol	*o*-Methylphenol	++	++
α-Naphthol	β-Naphthol	–	–
o-Nitrophenol	*m*-Nitrophenol*	–	+
p-Nitrophenol	*o*-Nitrophenol	0	+
o-Phenylphenol	*p*-Phenylphenol	0	+

[a] The pairs marked with an asterisk on desorption of the bands from alumina-celite gave materials which did not melt below 300° (aluminum salt of *p*-phenylazobenzoic acid).

Previous chromatographic studies[3,4] have shown that adsorption affinities of *ortho*-substituted benzenes are markedly less than those observed for the *meta* and *para* isomers and that the *meta* and *para* isomers have about the same adsorption affinities. However, it was found that within an *ortho*, *meta*, and *para* series of the derivatives prepared in this work no appreciable differences were exhibited in their relative adsorption affinities (see Table II). Further, in the case of three pairs (*o*-nitrophenol, *m*-nitrophenol; *o*-chlorophenol, *p*-chlorophenol; *o*-phenylphenol, *p*-phenylphenol) it was found that the *ortho* isomer was the most strongly adsorbed derivative. An examination of these experiments indicates the order of influence of a halogen substituent on the degree of adsorption affinity of these derivatives to be Cl > Br > I.

EXPERIMENTAL

Reagents. 2-Methylphenol, 4-methylphenol, 2,3-dimethylphenol, 2,4-dimethylphenol, 2,5-dimethylphenol, 3,5-di-

(4) For a recent study of steric factors as a definite influence in the behavior of *ortho*-substituted benzenes on chromatographic columns see J. K. Carlton and W. C. Bradbury, *J. Am. Chem. Soc.*, 78, 1069 (1956).

methylphenol, 4-ethylphenol, and 3-ethyl-5-methylphenol were kindly furnished by Dr. R. A. Friedel, U. S. Bureau of Mines, Bruceton, Pa.

2,4,6-Tribromophenol and 2,4,6-tribromo-3-methylphenol were prepared as described by Shriner and Fuson.[5]

The remaining phenols were commercially available grades and were used without further purification, except phenol and 1-naphthol which were redistilled.

The solvents Skellysolve B and benzene were redistilled, and ethyl alcohol and ethyl acetate were used as purchased.

The adsorbents used in preparing the chromatographic columns were silicic acid (Mallinckrodt, prepared by the method of Ramsey and Patterson), alumina (Aluminum Company of America, Grade F-20) and celite-535 (Johns-Manville). *p*-Phenylazobenzoyl chloride is manufactured by Distillation Product Industries.

Preparation of aryl p-phenylazobenzoates. A mixture of acid chloride (approximately 0.1 g.), phenol (0.0003*M* excess), and 3 to 6 ml. of pyridine was refluxed gently for 4 hr. The reaction product was poured with stirring into ice and 50 ml. of 10% sodium carbonate solution. If the crude reaction product separated as a solid, it was filtered off and washed with water and dried. The crude product was dissolved in Skellysolve B or a mixture of Skellysolve B and benzene and chromatographed on a mixture of silicic acid–celite (2 to 1 by weight) on which the free acid was strongly adsorbed. The derivative was then recrystallized. Chromatography of the crude derivatives of the following phenols gave two colored bands with a colorless band in between: 2,3-dimethylphenol, 3,4-dimethylphenol, *o*-chlorophenol, *m*-chlorophenol, *p*-chlorophenol, *o*-bromophenol, *m*-bromophenol, *p*-bromophenol, *o*-nitrophenol, *m*-nitrophenol, and *p*-nitrophenol. Of these two bands the lower one gave sharp melting points and good analyses. When the reaction product separated out as an oil, it was extracted with ether. The ether extract was washed successively with water and a saturated sodium chloride solution, dried over sodium sulfate, and the ether was removed. The residue was chromatographed, then recrystallized. The red-colored esters crystallized from Skellysolve B or mixtures of Skellysolve B and benzene as crystalline solids or fine needles.

Chromatographic separations. A typical chromatographic separation of a mixture of two components was conducted as described below. A tube 20 mm. × 400 mm. was connected to a suction flask. A 50 to 50 mixture by volume of alumina and celite or a 2 to 1 mixture by weight of silicic acid and celite was prepared for use as the adsorbent. While tapping the sides of the tube with cork rings, the tube was filled with the adsorbent to a height of approximately 290 mm. Then full suction of the water aspirator was applied to the suction flask which caused the adsorption column to decrease to approximately 268 mm. in height. The adsorbent was then wetted with Skellysolve B. In order to obtain a suitable percolate rate it was necessary to apply full suction with silicic acid and celite but only partial suction was required for alumina and celite.

The mixture of esters (10 to 20 mg. of component) was dissolved in the minimum volume of warm Skellysolve B or solutions of benzene in Skellysolve B and was adsorbed on the column. The chromatogram was developed by passing Skellysolve B, then solutions of benzene in Skellysolve B, and finally solutions of ethyl acetate in Skellysolve B through the adsorbent. The adsorbent was dug out of the column by a long narrow spatula and eluted with absolute ethanol if the adsorbent was silicic acid–celite or 95% ethanol if it was alumina-celite. When a continuous band was obtained, the band was arbitrarily dug out in several sections. The pure components were obtained from the top and bottom sections whereas the intervening sections were mixtures. The eluents were concentrated, filtered into a tared flask, and the last traces of solvent removed *in vacuo* under a stream of nitrogen. Melting points of the residues were determined.

(5) R. C. Shriner and R. C. Fuson, *Identification of Organic Compounds.* John Wiley and Sons, Inc., New York, N. Y., 2nd ed., 1947, p. 174.

Acknowledgment. We are indebted to the National Science Foundation for financial aid in the pursuance of this work.

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Reduction with Hydroxylating the Organism, *Curvularia lunata*

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With the aim of obtaining a 14α-hydroxy derivative, 4,6-pregnadiene-17α,21-diol-3,11,20-trione[1] was incubated with *C. lunata*, an organism reported to hydroxylate certain steroids at C-7,[2] C-11[3] and C-14.[4] Paper chromatography showed two major spots absorbing ultraviolet light, of which only the less polar stained with triphenyltetrazolium reagent.[5] The more polar substance thus no longer had the dihydroxy acetone side chain.

Column chromatography permitted isolation of both compounds. The less polar was shown by infrared spectrum and melting point to be the starting material. The more polar substance, obtained in 20–25% yield was considered to be a 17,20,21-triol on the basis of the strong polarity and the altered staining chracteristics, since such reductions have been observed with other microorganisms.[6] The substance analyzed for 4,6-pregnadiene-17α,20ξ,21-triol-3,11-dione with methanol of crystallization, and had infrared and ultraviolet spectra and a molecular rotation change which agreed with the assigned structure.

Acetylation gave a diacetate confirming introduction of a new acylable hydroxyl group. The direction of the molecular rotation change, +556, supports the structure and demonstrates[6] that the transformation product is 4,6-pregnadiene-17α,-20β,21-triol-3,11-dione. The evidence thus confirms this conversion as a reduction by an organism

(1) V. R. Mattox, E. L. Woroch, G. A. Fleischer, and E. C. Kendall, *J. Biol. Chem.*, **197**, 261 (1952).

(2) C. Meystre, E. Vischer, and A. Wettstein, *Helv. Chim. Acta*, **38**, 381 (1955).

(3) G. M. Shull and D. A. Kita, *J. Am. Chem. Soc.*, **77**, 763 (1955).

(4) G. M. Shull, D. A. Kita, and J. W. Davisson, U. S. Patent 2,702,812 (1955).

(5) W. J. Mader and R. R. Buck, *Anal. Chem.*, **24**, 666 (1952).

(6) F. Carvajal, O. F. Vitale, M. J. Gentles, H. L. Herzog, and E. B. Hershberg, to be published.

known previously only to hydroxylate or epoxidize steroids.[7]

EXPERIMENTAL[8]

Preparation of 4,6-pregnadiene-17α,20β-21-triol-3,11-dione. The organism used in this study was a strain of *Curvularia lunata* (NRRL No. 2380), maintained in this laboratory for more than a year on Sabouraud agar slants at 28–30° for 14 to 20 days at each culture generation. In the conversion studies subcultures were prepared from well sporulated slant cultures, 7 to 14 days old. Such a culture was washed with 5–10 ml. of Sabouraud liquid medium and used for inoculation of Erlenmeyer flasks filled with 100 ml. of the following medium: proteose peptone No. 3 (Difco), 0.5 g.; cerelose, 2 g.; soybean oil meal, 0.5 g.; potassium dihydrogen phosphate, 0.5 g.; sodium chloride, 0.5 g.; yeast extract (Difco), 0.3 g.; tap water, 100 ml. The medium had *p*H 5.6 and was sterilized for 15 min. in an autoclave. The inoculated flasks were shaken on a rotary shaker for 48 hr. at 28°. Samples of 25 mg. (1.1 g. total) of 4,6-pregnadiene-17α, 21-diol-3,11,20-trione were dissolved in 2 ml. of ethanol and added to the heavy black 48-hr. culture. After additional shaking for 48 hr., the whole culture was removed, blended with a knife-blade mixer and extracted three times with equal volumes of chloroform. The chloroform extracts were pooled and evaporated on a steam bath. The residue was analyzed by paper chromatography.

Chromatography of the residue on activated Florosil gave a fraction eluted with 25–50% methylene chloride in ether (140 mg.), purified by crystallization from methanol, m.p. 238–240°; λ_{max}^{MeOH} 281 mμ (ε = 24,000); λ_{max}^{Nujol} 2.87 μ, 2.93 (OH), 5.87 (11,20 C=O), 6.10 (3 C=O), 6.17, 6.29 ($\Delta^{4,6}$), identical with starting material.

The major amount of substance (250 mg.) was obtained by elution with 1.5–2% methanol in methylene chloride. Crystallization from methanol gave a methanol solvate of 4.6-pregnadiene-17α,20β,21-triol-3,11-dione, sinters 125°, m.p. 208–209°, $[\alpha]_D^{25}$ 126° (dioxane), λ_{max}^{MeOH} 282 mμ (ε = 22,800), λ_{max}^{Nujol} 2.95 μ, 3.08 (OH), 5.86 (11 C=O), 6.11 (3 C=O), 6.19, 6.28 ($\Delta^{4,6}$).

Anal. Calcd. for $C_{21}H_{28}O_5 \cdot CH_3OH$: C, 67.32; H, 8.22. Found: C, 67.58; H, 8.06.

The molecular rotation change from the starting material is −475°, agreeing in sign with changes which occur on reduction of a C-20 carbonyl to a hydroxyl group.[6] Analysis of the infrared spectrum showed the presence of three hydroxyl groups.

A separate run gave a polymorphic form, m.p. 204–205°, whose infrared spectrum in Nujol mull differed. When observed in bromoform solution, the spectrum was λ_{max} 2.72 μ, 2.81 (OH), 5.84 (11 C=O), 6.04 (3 C=O), 6.17, 6.25 ($\Delta^{4,6}$), identical with that of the other form.

4,6-Pregnadiene-17α,20β,21-triol-3,11-dione 20,21-diacetate. A sample of 100 mg. of the purified transformation product was treated with 3 ml. of acetic anhydride in 4 ml. of pyridine at room temperature for 18 hr. The solution was poured into dilute acid and extracted with methylene chloride. The residue from evaporation of the dried solution was crystallized from aqueous methanol to give a solvate, which, on drying *in vacuo*, had a melting point of 208.5–210°, $[\alpha]_D^{25}$ 237° (dioxane).

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.34; H, 7.39.

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(7) G. M. Shull, 130th Meeting of the AMERICAN CHEMICAL SOCIETY, September, 1956, Atlantic City, N. J., reported that E. J. Agnello, *et al.*, had found a similar reduction as a by-product of the action of *C. lunata*.

(8) All melting points are corrected. Analyses and optical data were obtained by the Physical Chemistry and Microanalytical Departments of these laboratories. Interpretations of infrared spectra were performed by Dr. Jo-Yun Chen.

Synthesis of Spirolactams from Nitrocycloalkanes

RICHARD K. HILL

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During an investigation of the Beckmann rearrangement of spiroketoximes,[1] it became necessary to prepare authentic samples of a series of spirolactams with the nitrogen atom bound directly to the spiro carbon. Two methods of preparation of such compounds have been reported; one is that of Lukes and Blaha,[2] who obtained 1-methyl-1-azaspiro[5,5]undecanone-2 in low yield by the action of the Grignard reagent of 1,5-dibromopentane on *N*-methylglutarimide. The other, which appeared to be more capable of extension to a variety of ring sizes, is the reduction of suitable nitroesters. Three foreign patents[3–5] and more recent work by Moffett[6] report the preparation of 1-azaspiro[4,5]decanone-2 by the hydrogenation of ethyl β-(1-nitrocyclohexyl)propionate.

In extending this second method, nitrocyclopentane and nitrocyclohexane were reacted with methyl or ethyl acrylate, using Triton B as the catalyst,[7] to yield the addition products I and V. Hydrogenation over Raney nickel at room temperature and subsequent cyclization by heating gave good yields of the spiropyrrolidones IX and XII.

To increase the size of the lactam ring, it was necessary to extend the length of the ester side chain. In one trial, the nitro-ester V was reduced with lithium aluminum hydride and the resulting amino alcohol converted to its *O,N*-di-*p*-toluenesulfonate. Heating this with potassium cyanide in an attempt to displace the *O*-tosylate gave no nitrile, however.

The chain lengthening was readily accomplished by the Arndt-Eistert homologation. Hydrolysis of the nitro-esters gave the corresponding acids, II and VI, which were converted successively to the

(1) R. K. Hill and R. T. Conley, *Chemistry and Industry*, 1314 (1956).

(2) R. Lukes and K. Blaha, *Chem. Listy*, **46**, 726 (1952).

(3) Swiss patent 227,125 (1942).

(4) French patent 880,400 (1943); *Chem. Zentr.*, **114**, 218 (1943 II).

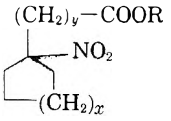
(5) Dutch patent 57,433 (1946).

(6) R. B. Moffett, abstracts of papers, 130th Meeting, ACS, Atlantic City, N. J., September, 1956, 4N.

(7) H. A. Bruson, U. S. Patent **2,390,918**; *Chem. Abstr.* **40**, 2456 (1946).

TABLE I

NITRO ACIDS AND ESTERS

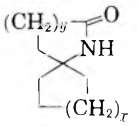


No.	X	Y	R	Formula	M.P. or B.P., °C.	% Nitrogen Calcd.	% Nitrogen Found
I	1	2	CH_3	$C_9H_{15}NO_4$	B.p. 100/0.4 mm.	6.96	6.95
II	1	2	H	$C_8H_{13}NO_4$	M.p. 59.5–60.5[a]	7.48	7.47
III	1	3	C_2H_5	$C_{11}H_{19}NO_4$	B.p. 108–109/0.2 mm.	6.11	6.36
IV	1	4	C_2H_5	$C_{12}H_{21}NO_4$	B.p. 95–97/0.01 mm.	5.76	5.70
V	2	2	C_2H_5	$C_{11}H_{19}NO_4$	B.p. 117–118/0.6 mm.	6.11	6.00
VI	2	2	H	$C_9H_{15}NO_4$	M.p. 93.7–94.2	6.96	6.65
VII	2	3	C_2H_5	$C_{12}H_{21}NO_4$	B.p. 128/0.1 mm.	5.76	6.03[b]
VIII	2	3	H	$C_{10}H_{17}NO_4$	M.p. 96.5–97	6.51	6.29[c]

[a] Recrystallized from 60–70° pet. ether. [b] Calcd.: C, 59.24; H, 8.70. Found: C, 59.21; H, 8.60. [c] Calcd.: C, 55.80; H, 7.96. Found: C, 56.18; H, 8.09.

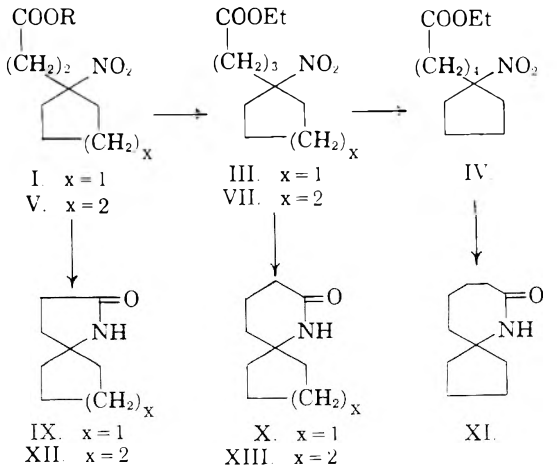
TABLE II

SPIROLACTAMS



Lactam	X	Y	M.P., °C.	Calculated % C	Calculated % H	Calculated % N	Found % C	Found % H	Found % N
IX	1	1	125.6–126.2	69.03	9.41	10.06	69.28	9.37	9.80
X	1	2	106.5–107	70.55	9.87	9.14	70.78	9.72	8.85
XI	1	3	112.7–113.5	71.81	10.25	8.38	71.66	10.17	8.13
XII[a]	2	1	132.2–132.3[b]	70.55	9.87	9.14	70.41	9.84	9.12
XIII	2	2	117–118	71.81	10.25	8.38	71.71	10.05	8.10

[a] References 3–6. [b] Lit.[4] m.p. 132–133°.



acid chloride, diazoketone, and ethyl esters III and VII. Raney nickel hydrogenation, followed by refluxing in ethanol, again gave good yields of the spiropiperidones X and XIII.

A repetition of the Arndt-Eistert reaction on the nitro-acid II gave the corresponding valerate IV, which on reduction and cyclization yielded the homopiperidone XI.

A second possible approach to the synthesis of these spirolactams was briefly tested. Analogous to the acid-catalyzed lactonization of β,γ-, γ,δ-, or δ,ϵ-unsaturated acids would be the cyclization of the corresponding amides to lactams. In the one experiment tried, γ-(1-cyclohexenyl)butyramide, XIV, was quantitatively converted by heating briefly in polyphosphoric acid to the spiropiperidone XIII. It appears that this reaction may offer a convenient synthesis of lactams, and experiments are in progress to test its generality.

The properties of the nitro-acids and esters and the spirolactams prepared in this work are shown in Tables I and II.

Lactams XII and XIII were tested for analgesic activity through the courtesy of Dr. Howard J. Glenn of Abbott Laboratories. In a modified Wolff, Hardy, and Goodell procedure in dogs, neither showed any increase in pain threshold.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns hot stage microscope, and are uncorrected. Microanalyses were performed by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England. Since the same procedure was often used to prepare several compounds, details are given below for representative experiments.

Ethyl-β-(1-nitrocyclohexyl)propionate (V). To a mechanically stirred solution of 129.2 g. (1.0 mole) of nitrocyclohexane, 50 ml. of *t*-butyl alcohol, and 12 g. of a 35% methanolic solution of Triton B was added dropwise, over 2 hr., 100.1 g. (1.0 mole) of redistilled ethyl acrylate. The reaction was mildly exothermic, and the temperature was maintained at 35–40° with a cold water bath. When the addition was completed, the mixture was stirred at room temperature for 5 hr. and allowed to stand overnight. The mixture was acidified with dilute hydrochloric acid and extracted with chloroform. After washing with water and drying over magnesium sulfate, the extracts were concentrated and the residue distilled through a short Vigreux column. The nitroester distilled as a pale green oil at 139–141°/3 mm., 117–118°/0.6 mm., and weighed 210.5 g. (91.6%).

β-(1-nitrocyclohexyl)propionic acid (VI).[8] The nitro-ester (54 g.) was refluxed with a solution of 40 g. of sodium hydroxide in 350 ml. of water for 10 hr. After cooling in ice, the solution was acidified with concentrated hydrochloric acid and allowed to stand in the refrigerator. The collected solid weighed 39 g. (83%). Recrystallized from water, it yielded white plates, m.p. 93.0–93.6°. Recrystallization from ethanol-water raised the melting point to 93.7–94.2°.

Ethyl γ-(1-nitrocyclohexyl)butyrate (VII). Thionyl chloride was purified by successive distillations from cholesterol, quinoline, and linseed oil. The nitro-acid (20 g.) was refluxed with 100 ml. of thionyl chloride for 4 hr., and the excess thionyl chloride was evaporated, finally by distilling 50 ml. of dry benzene from the solution. The acid chloride was generally used without further purification; in one run it was distilled *in vacuo*, b.p. 105–109°/0.1 mm. When a sample was treated with water, it regenerated the original acid.

A solution of the acid chloride in 60 ml. of anhydrous ether was added to an ethereal solution of excess diazomethane. After standing overnight, the ether was removed at reduced pressure, leaving the diazoketone as an orange oil. It was heated to reflux in 200 ml. of absolute ethanol, while over a period of 48 hr. a slurry of silver oxide (from 10 g. of silver nitrate) in ethanol was added in portions. The mixture was filtered and the filtrate distilled. The nitro-ester was collected at 128–131°/0.1 mm., and weighed 17.8 g. (73.6%).

1-Azaspiro[4,5]decanone-2 (XII).[3-6] A solution of 40 g. (0.175 mole) of ethyl-β-(1-nitrocyclohexyl)propionate in 125 ml. of ethanol was hydrogenated over Raney nickel at 38 pounds pressure and room temperature. After 6 hr., 0.55 mole of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate refluxed overnight. Distillation of the alcohol left a solid residue, which was collected and washed with a little ether. The crystals weighed 22 g. and melted at 132–132.5°. A second crop of 3.9 g. was isolated from the filtrate by sublimation, bringing the total yield to 96%. The lactam was easily purified by recrystallization from 60–70° petroleum ether or by sublimation at 100°/0.03 mm., though the melting point remained unchanged.

3-(1-Aminocyclohexyl)propanol-1. A solution of 25.9 g. (0.113 mole) of ethyl β-(1-nitrocyclohexyl)propionate in 25 ml. of anhydrous ether was added with stirring over 2 hr. to a solution of 11.8 g. (0.31 mole) of lithium aluminum hydride in 200 ml. of ether. After stirring and refluxing for 2 hr., the mixture was treated with 20 ml. of ethyl acetate, then with saturated aqueous sodium sulfate. Magnesium sulfate was added to coagulate the alumina, and the mixture filtered and washed with hot ethanol. The filter cake was digested three times with hot alcohol, and the combined filtrates dried over magnesium sulfate. Concentration and vacuum distillation gave the amino-alcohol as a pale green oil, b.p. 98–100°/0.15 mm., weighing 11.0 g. (62%). After standing for a few hours, it crystallized to white plates, which, recrystallized from ether, melted at 69.5–70.5°.

Anal. Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.80; H, 12.01; N, 8.97.

The *O,N-diacetate*, prepared with acetic anhydride in pyridine, melted at 96.5–97.5° after successive recrystallizations from cyclohexane and ether.

Anal. Calcd. for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 65.54; H, 9.41; N, 5.93.

The *O,N-di-p-toluenesulfonate* was prepared by the Hinsburg procedure.[9] After two recrystallizations from ethanol, it melted at 176.5–177.5°.

Anal. Calcd. for $C_{23}H_{31}NO_6S_2$: C, 59.33; H, 6.71; N, 3.01; S, 13.77. Found: C, 59.49; H, 6.63; N, 2.95; S, 13.53.

γ-(1-cyclohexenyl)butyramide (XIV). γ-(1-cyclohexenyl-butyric acid[10] (8.2 g.) was esterified with an ethereal solution of diazomethane from 25 g. of nitrosomethylurea. After removal of the ether, the residual ester was taken up in 60 ml. of methanol, saturated at 0° with dry ammonia, and heated at 125° overnight in a sealed bomb. After charcoal treatment and filtration, the methanol was evaporated to a small volume and the amide precipitated with water. Recrystallized from ethyl acetate-petroleum ether, it melted at 97–98°.

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.66; H, 10.04; N, 8.05.

Acid cyclization of amide. Two hundred fifty mg. of γ-(1-cyclohexenyl)butyramide was stirred into 12 g. of polyphosphoric acid and heated at 120–130° for 10 min. This solution was poured into a mixture of ice and sodium hydroxide solution, stirred until homogeneous, and extracted with chloroform. The extracts were washed with water, dried over sodium sulfate, and evaporated. The solid residue weighed 250 mg., and after recrystallization from 60–70° petroleum ether, melted at 116.5–118°, alone or admixed with a sample of 1-azaspiro[5,5]undecanone-2 (XIII).

Acknowledgments. It is a pleasure to thank Dr. R. W. H. Gentry of the Explosives Department, E. I. du Pont de Nemours & Company, for generous gifts of the nitrocycloalkanes used in this work.

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(8) H. Hopff, O. von Schickh, and G. Wiest, German patent 851,342 (1952).

(9) No evidence was found for the formation of a spiropyrrolidine tosylate analogous to the cyclization reported by R. F. Brown and N. M. Van Gulick, *J. Am. Chem. Soc.*, 77, 1079 (1955).

(10) J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 1637 (1935).

Preparation of Dialkylanilines by the Reaction of Bromobenzene with Sodium Amide and Dialkylamines[1]

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Reactions have been reported[3] of the monobro-

(1) Financial assistance from the Office of Ordnance Research, U. S. Army, is gratefully acknowledged.

(2) American Enka Fellow, 1954–55; R. J. Reynolds Fellow, 1955–56. This note is based on the Ph.D. thesis of T. K. Brotherton, October, 1956.

(3) Bunnett and Brotherton, *J. Am. Chem. Soc.*, 78, 155 (1956).

monaphthalenes with sodium amide in refluxing piperidine to form, in high total yields, mixtures of the two *N*-naphthylpiperidines. There is evidence that these reactions proceed by the elimination-addition (benzyne) mechanism.[3,4] In connection with the above work, bromobenzene was submitted to the action of the sodium amide-piperidine reagent and *N*-phenylpiperidine was obtained in 99% yield. This observation suggested that the reaction of bromobenzene with sodium amide in refluxing secondary amines might be a general method for the preparation of dialkylanilines. We have found that the method is indeed general, but yields are for the most part not especially high. Our results are summarized in Table I.

TABLE I

YIELDS OF DIALKYLANILINES FROM BROMOBENZENE, SODIUM AMIDE, AND DIALKYLAMINES

Secondary Amine Used	Reflux Time, Hr.	Yield of Dialkylaniline, %
Piperidine	2	99
	1	82
	0.17	51
Diethylamine	2	53
	3.75	46
	16	64
Diisopropylamine	2	22[a]
Di-*n*-butylamine	2	67
Morpholine	2	46[b]

[a] 58% of bromobenzene was recovered. [b] 8% of bromobenzene was recovered.

The reaction of bromobenzene with sodium amide in refluxing aniline was also tried. Diphenylamine (25%) and triphenylamine (4%) were obtained, along with small amounts of other products which were not identified.

Reactions of this general type have been reported before. Thus, Wittig and Merkle[5] obtained a 16% yield of *N*-phenylpiperidine from iodobenzene and lithium piperidide in ether. Even more similar to the present work is the preparation, by Seibert and Bergstrom,[6] of *N*-cyclohexylaniline in 42% yield by the reaction of bromobenzene with potassium amide in cyclohexylamine at 120–130°.

Presumably all these reactions occur by the benzyne mechanism. If so, the recovery of much bromobenzene from the reaction with diisopropylamine would suggest that it is a dialkylamide ion rather than a simple amide ion (NH_2^-) which removes a proton from the position *ortho* to the bromine, and that the diisopropylamide ion is relatively inefficient in this function owing to front-side steric hindrance.[7] The fact that smaller yields were obtained with other dialkylamines than with piperidine is perhaps a further consequence of front-side steric interactions which retard the combination of benzyne with the bulkier dialkylamide ions (or dialkylamines), allowing time for the benzyne to undergo side reactions with eventual formation of tarry by-products.[8]

N-Phenylpiperidine is also formed by the reaction of bromobenzene with sodium metal in refluxing piperidine; however, in this case the yield is only 67%.

Earlier[4] it was found that the sodium amide–piperidine reagent acts upon 1-bromo-2-methylnaphthalene to form 2-methylnaphthalene in 81% yield. A similar debromination has now been observed in the reaction of 2-bromomesitylene with this reagent: mesitylene is formed in 53% yield with 24% recovery of unreacted 2-bromomesitylene. 2-Bromomesitylene, like 1-bromo-2-methylnaphthalene, is structurally unable to be converted into a benzyne derivative. In the reaction of such a compound with the sodium amide–piperidine reagent, reductive debromination appears to occur more readily than direct displacement of the bromine by piperidide ion.

EXPERIMENTAL

Reaction of bromobenzene with sodium amide and piperidine. A mixture of sodium amide (7.8 g., 0.2 mole) and piperidine[9] (30 cc.) was refluxed for 15 min. Bromobenzene (15.7 g., 0.1 mole) was then added dropwise through the top of the condenser. A vigorous reaction ensued with the evolution of ammonia, but the reaction subsided when all the bromobenzene had been added. The resulting mixture was refluxed for 2 hr., cooled, and cautiously treated with 25 cc. of water and 25 cc. of benzene. The layers which formed were separated and the benzene layer was washed with three 25-cc. portions of 10% hydrochloric acid. The acid extracts were combined and made strongly basic by the addition of concentrated sodium hydroxide solution. The oil layer which formed was taken up in 15 cc. of ether and the aqueous layer was washed with an additional 15 cc. of ether. The two ether solutions were combined and distilled; the main fraction of the distillate was 16.05 g. (98.8%) of *N*-phenylpiperidine, b.p. 93–97° (3–4 mm.), n_D^{25} 1.5593. (Authentic *N*-phenylpiperidine was found to have b.p. 98° (5 mm.), n_D^{25} 1.5606.) The identity of the product was further verified by formation of the methiodide, m.p. 146.5–148° not depressed on admixture with authentic *N*-phenylpiperidine methiodide.[10]

Reactions by the same procedure but with shorter periods of reflux (after addition of the bromobenzene) gave lower yields of *N*-phenylpiperidine as shown in Table I. When the reagents were mixed with no prior refluxing of the sodium amide and piperidine, no detectable amount of *N*-phenylpiperidine was formed during 10 min. refluxing or during 24 hr. at room temperature.

Reactions of bromobenzene with sodium amide and other dialkylamines. Each amine was a commercial product (generously furnished by Union Carbide Chemicals Co.)

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which was dried by azeotropic distillation with benzene and then purified by distillation. The procedure (including quantities of reactants) was in each case as described for the reaction with piperidine. Characteristics of the products were as follows: *N,N*-Diethylaniline: b.p. 62–66°/3 mm., n_D^{24} 1.5394 (lit.[11,12] b.p. 70°/3 mm., n_D^{22} 1.5410). *N,N*-Diisopropylaniline: b.p. 95.5°/12 mm., n_D^{20} 1.5222 (lit.[13] b.p. 98–100°/13 mm). *N,N*-Di-*n*-butylaniline: b.p. 103.5–106° (3.5 mm.), n_D^{20} 1.5182. The picrate, crystallized from ether, had m.p. 124° (lit.[14] m.p. 124°) not depressed on admixture with the picrate of authentic *N,N*-di-*n*-butylaniline. *N*-Phenylmorpholine: b.p. 87–92°/3–4 mm., m.p. 52–53° after crystallization from an ethanol-ether mixture (lit.[15] m.p. 57–58°).

Reaction of bromobenzene with sodium amide and aniline. Bromobenzene (15.7 g., 0.1 mole), sodium amide (11.7 g., 0.3 mole) and 35 cc. of purified aniline were allowed to react by the procedure described for the reaction with piperidine. After water had been added to the reaction mixture, it was made acidic by addition of hydrochloric acid and then was extracted with five 150-cc. portions of benzene. The combined benzene washings were distilled until the boiling point reached 80° and then were treated with anhydrous hydrogen chloride. The purple solid which formed was collected on the suction filter and then was treated with sodium hydroxide solution. The resulting product was separated by steam distillation. Diphenylamine (4.3 g., 25.4%), m.p. 52–52.5°, not depressed on admixture with authentic diphenylamine, was so obtained. The benzene filtrate was distilled and two fractions of interest were obtained: a yellow oil, b.p. 100–106° (2–3 mm.), wt. 3.9 g., and a mushy solid, b.p. 106–161° (2–3 mm.), wt. 2.8 g. By trituration of the first fraction with petroleum ether (b.p. 30–60°), 1.1 g. of a sublimable white solid, m.p. 205–210° with decomposition, was obtained, but this product was not identified. Cooling the filtrate to −78° caused 0.61 g. of a sublimable solid, m.p. 33–35°, to separate; this was not identified. From the second fraction, 0.33 g. (4.4%) of triphenylamine, m.p. 126–127° not depressed on admixture with authentic triphenylamine, was obtained by crystallization from petroleum ether (b.p. 30–60°). A yellow oil, n_D^{18} 1.6431, remained on evaporation of the mother liquor from the triphenylamine crystallization.

Reaction of 2-bromomesitylene with sodium amide and piperidine. 2-Bromomesitylene (19.9 g., 0.1 mole), sodium amide (7.8 g., 0.2 mole) and 30 cc. of piperidine were allowed to react by the procedure described above for the bromobenzene-sodium amide-piperidine reaction. From the neutral product fraction, 6.4 g. (53.2%) of mesitylene, b.p. 75–78° (40 mm.), n_D^{24} 1.4987 (authentic mesitylene has b.p. 79.8°/40 mm., n_D^{18} 1.4954) and 4.8 g. (24.1% recovery) of 2-bromomesitylene, b.p. 106–109°/17 mm., n_D^{24} 1.5480 (authentic 2-bromomesitylene has b.p. 108–110°/17–18 mm., n_D^{34} 1.5484). No basic product could be isolated.

Reaction of bromobenzene with piperidine and sodium metal. Sodium metal (2.3 g., 0.1 mole) and piperidine (20 cc.) were combined and heated at reflux for 15 min. Bromobenzene (7.9 g., 0.05 mole) was then added through the condenser and the resulting mixture was refluxed for 2 hr. Water (25 cc.) was cautiously added to the cooled reaction mixture; there was little evidence of residual sodium. The neutral and basic product fractions were separated by common extraction procedures. The basic fraction yielded 5.2 g. (66.7%) of *N*-phenylpiperidine, b.p. 95–98° (5 mm.), n_D^{25} 1.5590. The neutral fraction furnished 0.9 g. of an unidentified yellow oil b.p. 65–68° (40 mm.).

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Preparation of Tetramethylene Dibromide and Chlorobromide

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In the course of a synthetic study relatively large quantities of tetramethylene dibromide and chlorobromide were required, and an attempt was made to develop inexpensive methods for the preparation of these substances.

For the preparation of tetramethylene dibromide, the reaction of tetramethyleneglycol with hydrogen bromide (yield, 70%),[1] with hydrogen bromide in the presence of concentrated sulfuric acid,[2,3] or with phosphorus tribromide (55–60%)[4] has been described. Since tetrahydrofuran has become easily available, its reaction with hydrogen bromide (71%)[5–7] or with hydrogen bromide and concentrated sulfuric acid (77–82%)[8,9] has been suggested as an attractive alternative. A third method is the bromination of butane in the presence of zinc acetate (85%).[10] It has now been found that the reaction of tetrahydrofuran with sodium bromide and concentrated sulfuric acid represents the easiest method. Under the conditions specified herein, this reaction gives a yield of 86%.

Most of the syntheses of tetramethylene chlorobromide have been based on tetrahydrofuran and consist of two steps, its transformation into tetramethylene chlorohydrin (50–60%) and the treatment of the latter with phosphorus tribromide

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(98%).[11-14] A modification of this method is the procedure of Normant and Voreux,[15] in which the intermediate is the acetate of tetramethylene chlorohydrin. Furthermore, the chlorination of *n*-butyl bromide with atomic chlorine or sulfuryl chloride has been suggested as a method for the preparation of tetramethylene chlorobromide; in this reaction a yield of 35% is obtained.[16]

Attempts have been made to improve the conversion of tetramethylene chlorohydrin into the chlorobromide. However, the use of sodium bromide and concentrated sulfuric acid, or the application of phosphorus and bromine to this step, did not give better overall yields (58%; 40%) for the conversion of tetrahydrofuran into tetramethylene chlorobromide. Eventually, it was found that the treatment of tetrahydrofuran with a mixture of sodium chloride, sodium bromide, and concentrated sulfuric acid gives in a single step a 44% yield of the desired substance, which is accompanied by a 10% yield of tetramethylene dibromide. In our experience, this represents the easiest method for the preparation of tetramethylene chlorobromide.

EXPERIMENTAL

Tetramethylene dibromide. To a solution of sodium bromide (500 g; 4.85 mole) in water (600 ml.), there were added tetrahydrofuran (144 g.; 2.0 mole) and, with efficient agitation, concentrated sulfuric acid (750 ml.). The temperature was kept at 70–72°. The mixture was heated on the steam bath for 8 hr., then the two liquid layers were decanted from the solid phase and separated. The aqueous layer and the solid phase were washed with benzene (500 ml.), and the benzene extract was combined with the organic layer. The combined product was washed with sodium carbonate solution, sodium bisulfite solution, and water, dried, and distilled. Thus, 71 g. (86%) of the dibromide, b.p. 194–196°, was obtained.

Tetramethylene chlorobromide. (1) To a solution of sodium bromide (65 g.; 0.64 mole) in water (150 ml.), tetramethylene chlorohydrin (54.3 g.; 0.5 mole) and concentrated sulfuric acid (190 ml.) were added successively with efficient agitation. The temperature rose to 60–70°. The mixture was heated for 3 hr. on the water bath with continued agitation and kept at room temperature for 12 hr. Benzene was added and the organic layer separated, washed with 5% sodium hydroxide solution, sodium sulfite solution, and water, and then dried. Distillation gave 63.6 g., boiling at 87–95° (35 mm.). Fractionation of the product gave 49.9 g. (58%) of tetramethylene chlorobromide, b.p. 173–177°, n_D^{20} 1.4870, and 9.5 g. (9%) of tetramethylene dibromide, b.p. 193–195°, n_D^{20} 1.5162.

(2) To a mixture of crude tetramethylene chlorohydrin, prepared from 228 g. (3.2 mole) of tetrahydrofuran[17] and 33 g. (1.07 mole) of red phosphorus, bromine (240 g., 1.5 mole) was added within 3 hr., with cooling and agitation. The reaction product was poured into ice water and the organic layer separated, washed with sodium bicarbonate solution and water, and dried. Distillation under 30 mm pressure (b.p. 80–85°) and at atmospheric pressure (b.p. 172–176°) gave 221 g. (43%) of tetramethylene chlorobromide, n_D^{20} 1.4872.

(3) Sodium bromide (124 g., 1.2 mole) and sodium chloride (76 g.; 1.3 mole) were dissolved in water (400 ml.), and tetrahydrofuran (72 g.; 1.0 mole) and, with agitation, concentrated sulfuric acid (400 ml.) were added, the latter at such a rate that the temperature did not exceed 70°. The mixture was then heated for 3 hr. at 100°, kept for 12 hr. at room temperature, and extracted with benzene or ether (250 ml.), and the extract was washed with 5% sodium hydroxide solution, sodium bisulfite solution, and water, dried and distilled. The product which collected between 65 and 100° at 6 mm. pressure was washed again with 20% sodium hydroxide solution and fractionated: 173–177°, tetramethylene chlorobromide, n_D^{20} 1.4870, yield, 75.5 g. (44%); 193–195°, tetramethylene dibromide, n_D^{21} 1.5162, yield, 22.7 g. (10%).

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Heterocyclic Analogs of Terphenyl: 3,6-Diaryl-1,2,4,5-Tetrazines

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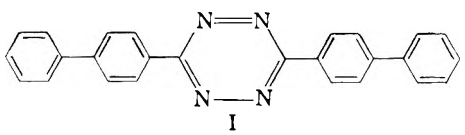
As part of a study of the heterocyclic analogs of terphenyl and quaterphenyl, which are of interest as solutes in liquid scintillation counting systems, we have devised improved syntheses for two previously known 3,6-diaryl-1,2,4,5-tetrazines (3,6-diphenyl[3] and 3,6-di-*m*-tolyl[4]) and synthesized for the first time 3,6-di-*p*-biphenylyl-1,2,4,5-tetrazine (I) as well as the corresponding dihydrotetrazines.



I

The preparation of these compounds has been accomplished by a variation of the original Pinner synthesis in which the imido ester of an aromatic nitrile was reacted with hydrazine in an aqueous solution of either ammonium hydroxide or potassium hydroxide. Under these reaction conditions

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a complex mixture of products is formed and the desired dihydro-1,2,4,5-tetrazine is difficult to separate from the mixtures. In our variation of this procedure the reaction is carried out under anhydrous conditions in a mixture of methanol and triethylamine. The dihydrotetrazine precipitates from this reaction mixture, the reaction time is shortened, and the overall yields are improved to around 50%. Attempts to prepare those diaryltetrazines containing electron attracting substituents and 3,6-dipyridyl-1,2,4,5-tetrazine were unsuccessful by either procedure.

The infrared spectra of these 3,6-diaryl-1,2,4,5-tetrazines show a very strong ring stretching vibration at 1375–1390 cm.$^{-1}$ which appears to be a characteristic of the tetrazine ring since it is absent from the spectra of the corresponding dihydrotetrazines. Another rather unique feature of these spectra is a strong band at 913–925 cm.$^{-1}$. A similar band was found in the spectrum of azobenzene at 920 cm.$^{-1}$ but was absent from the spectrum of both freshly recrystallized hydrazobenzene and the dihydro derivative of 3,6-di-*p*-biphenylyl-1,2,4,5-tetrazine. Although this would seem to indicate a connection between this frequency and the azo linkage, data for additional compounds is needed to establish this definitely. When examined by previously described techniques[5,6] none of these compounds showed relative pulse heights in excess of 0.12.

EXPERIMENTAL

Details are given for the preparation of a typical dihydrotetrazine and tetrazine. Similar procedures were used in the preparation of 3,6-diphenyl-1,2,4,5-tetrazine, m.p. 195° (reported,[1] 192°), yield 55%, and 3,6-di-*m*-tolyl-1,2,4,5-tetrazine, m.p. 151° (reported,[2] 150–52°), yield 53%.

1,2-Dihydro-3,6-di-p-biphenyl-1,2,4,5-tetrazine. Dry hydrogen chloride gas was bubbled for 12 hr. into a solution of 10 g. (0.058 mole) *p*-biphenylcarbonitrile in 200 ml. of anhydrous methanol. At the end of this time the methanol solution was kept at 0° for 4 hr. to cause precipitation of the crystalline methyl *p*-biphenylimidate hydrochloride. This slurry of the imido ester hydrochloride in methanol was added very slowly and cautiously to a solution of 5 g. 95% hydrazine in 200 ml. anhydrous methanol and 100 g. triethylamine. After the addition was complete the mixture was heated on a steam bath until precipitation of the yellow-orange dihydrotetrazine was complete. The precipitate was immediately filtered and washed with distilled water. Recrystallization from toluene yielded 6 g. (53.5%) of yellow-orange plates melting at 160° with resolidification. No attempt was made to obtain analytical data on this compound since it is so readily oxidized by air.

3,6-Di-p-biphenyl-1,2,4,5-tetrazine. To a solution of 5 g. of isoamyl nitrite in 100 ml. 95% ethanol was added 6 g. of 1,2-dihydro-3,6-di-*p*-biphenyl-1,2,4,5-tetrazine. This mixture was refluxed for 4 hr., cooled to room temperature, and filtered. The product was recrystallized from toluene to yield 5 g. (83.5%) of fuchsia needles, m.p. 297° (corr.).

Anal. Calcd. for $C_{26}H_{18}N_4$: C, 80.80; H, 4.70; N, 14.50. Found: C, 80.56; H, 4.56; N, 14.55.

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The Pinacol Rearrangement[1]

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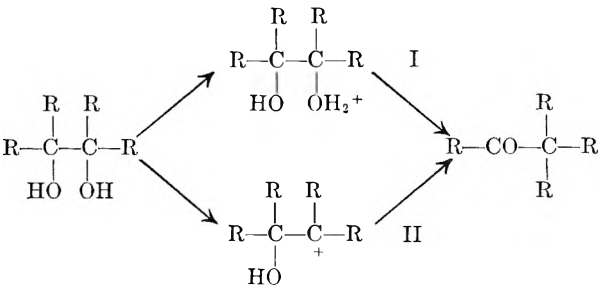
The pinacol rearrangement is acid-catalyzed and could conceivably proceed through an intermediate protonated glycol (I) or the free alkyl cation (II). Duncan and Lynn[3] concluded that for pinacol



itself (2,3-dimethyl-2,3-butanediol) the reaction proceeded *via* I. This conclusion was based on the observation that $d \log k = -d H_0$. However, the comparison was made using values of H_0 measured at 25° with values of log k measured at 70–150°.

We have now measured the rate of conversion of pinacol to pinacolone from 39–75% sulfuric acid at 25 ± 0.01°. The data, which are summarized in Table I, show that the relation $d \log k = -dH_0$ is precisely followed.

The conclusions of Duncan and Lynn can be extended as follows. The hypothesis has been developed[4] that if the transition state were of type I with the positive charge residing principally on the OH_2 group, $d \log k$ would equal $-d H_0$. For transition states of type II, $d \log k$ would equal $-d C_0$. For transition states intermediate between I and II, $d \log k$ would have values intermediate between

(1) Grateful acknowledgment is made of the support of this research by a grant from the Petroleum Research Fund of the American Chemical Society.

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TABLE I

RATE CONSTANTS FOR THE PINACOL REARRANGEMENT AS A FUNCTION OF SULFURIC ACID CONCENTRATION

H_2SO_4, %	$k \times 10^6$ (Sec.$^{-1}$)	$\frac{d \log k}{d\ \%\ H_2SO_4}$	$\frac{-d H_0}{d\ \%\ H_2SO_4}$
38.71	1.75	0.083	0.081
43.98	4.92	.089	.093
51.37	22.6	.105	.108
54.01	45.6	.108	.110
60.25	205	.110	.110
64.36	511	.110	.115
69.09	2010	.115	.121
74.37	8450	.125	.127

$-dH_0$ and $-dC_0$. The symbols H_0 and C_0 refer to the Hammett acidity function based on base-protonated base equilibria and an acidity function (C_0) based on alcohol-carbonium ion equilibria.

The precision of the relation $d \log k = -d H_0$ (Table I) is interpreted to mean that the transition state is of type I as concluded by Duncan and Lynn. Also there is a relatively small amount of stretching of the C—O bond and relatively little delocalization of the positive charge in this transition state. These conclusions apply strictly to the case under study, pinacol to pinacolone. When R is phenyl for example, the reaction path should more closely approach path II if not actually proceeding through the free carbonium ion, II.

EXPERIMENTAL

The rate of conversion of pinacol (2,3-dimethyl-2,3-butanediol) to pinacolone (3,3-dimethyl-2-butanone) has been studied from 39–75% sulfuric acid. The progress of the reaction was followed by calculating the concentration of pinacolone from the optical density at 270 mμ.

The rate constants calculated from the general relation for first-order reaction, $\log c/c_0 = kt$, were remarkably constant from 0% to over 90% completion. Deviations from the average values were rarely greater than 2%. Duplicate runs also generally agreed within 2%. The final optical density was within 5% of that calculated for complete conversion of pinacol to pinacolone based on the extinction coefficients of pure pinacolone and the initial concentration of pinacol employed.

The completeness of the reaction and freedom from side reactions was checked in another way. The 2,4-dinitrophenylhydrazone of pinacolone was isolated in yields of 99% and 91% from the kinetic runs in 53% and 61% sulfuric acid, respectively.

The extinction coefficients of pinacolone varied with the percent sulfuric acid. For example, at 270 mμ the value ranged from 28.0 at 22% sulfuric acid to 41.1 at 69% acid. The extinction coefficients from 220 to 280 mμ and from 22% to 70% sulfuric acid as well as other experimental details have been published in a thesis.[5]

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(5) Ph.D. Thesis of C. Perizzolo, Pennsylvania State Univ., 1957.

3-(*N*,*N*-Dialkylcarboxamido)piperidinoalkanes[1]

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Received January 14, 1957

As reported earlier,[2] we have undertaken the synthesis of a series of pyridine- and piperidinecarboxylic acid derivatives in connection with an investigation directed toward the elucidation of the pharmacodynamic characteristics of this group of compounds. The compounds reported in this and the preceding[2] communications were planned as to permit the pharmacological evaluation of gradual changes in chemical structure. We anticipate that such correlation will contribute toward a better understanding of the fundamental principles governing relationships between molecular constitution and biological response, and allow a better insight into the chemotherapeutic potentialities of pyridine- and piperidinecarboxamides.

EXPERIMENTAL

The compounds listed in Table 1 were prepared by the following procedures.

Procedure A1: 1,1-Bis[3-(N,N-diethylcarboxamido)pyridinium]methane dibromide (IV). Reaction mixtures consisting of 53.5 g. (0.300 mole) of pyridine-3-(*N*,*N*-diethylcarboxamide) (I) and 23.1 g. (0.150 mole) of dibromomethane in 200 ml. of anhydrous benzene, or multiples thereof, were refluxed for a total of 51–94 hr. The crystalline reaction product was filtered off and recrystallized from ethanol-ethyl acetate.

Procedure A2: 1-Decyl-3-(N,N-diethylcarboxamido)pyridinium bromide (XI). An excess (106.8 g., 0.483 mole) of 1-bromodecane and 36.0 g. (0.202 mole) of I were heated at 93–95° or refluxed in anhydrous benzene (200 ml.) for a total of 34–35 hr. The excess alkyl halide and the solvent were decanted or removed under reduced pressure, the residue was washed with anhydrous ethyl ether, and recrystallized from ethanol-ethyl acetate.

Procedure B: 1,10-Bis[3-(N,N-diethylcarboxamido)piperidino]decane dihydrobromide (XIII). The quaternary derivative was obtained by Procedure A1. The crude 1,10-bis[3-(*N*,*N*-diethylcarboxamido)pyridinium]decane dibromide, obtained from 45.0 g. (0.150 mole) of 1,10-dibromodecane and 53.5 g. (0.300 mole) of I, was washed with anhydrous ethyl ether, and dissolved in 100–200 ml. of warm water. The aqueous solution was washed with two 50 ml. portions of benzene, treated with charcoal, and filtered through Celite (Johns-Manville filter-aid). The filtrate was subjected to hydrogenation at room temperature, in the presence of platinum oxide (Adams' catalyst), at maximum pressures of 50–55 p.s.i. Hydrogen absorption ceased after about 9 hr. The platinum oxide was filtered off, and the water was removed under reduced pressure (max. pot temp. 50°). The residual moisture was removed from the reaction product by azeotropic distillation under reduced pressure with about 800 ml. of anhydrous benzene. The crystalline residue was recrystallized from ethanol-ethyl acetate.

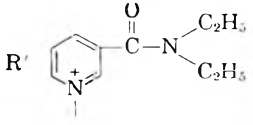
Procedure C: 1-Cyclopentyl-3-(N,N-diethylcarboxamido)-

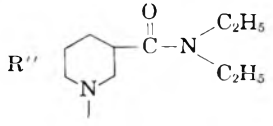
(1) This investigation is supported by grants from the Geschickter Foundation for Medical Research.

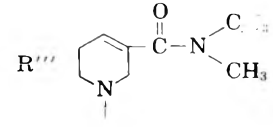
(2) A. Lasslo, W. M. Marine, and P. D. Waller, *J. Org. Chem.*, **21**, 958 (1956).

TABLE I

Compound No.	Alkane	Substitution	Method of Preparation	Yield, %[a]	B.P., °C., at Mm. Hg	n_D, °C.	Salt	M.P., °C.[b]	Analyses[c] C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	Br, % Calcd.	Br, % Found	Cl, % Calcd.	Cl, % Found	N, % Calcd.	N, % Found
III	Methane	1-(R‴)	D	48.8	96–8 0.10–0.15	26.5 1.5021	HCl	158.5–159.5	52.80	52.49	8.37	8.43	—	—	17.32	17.2	13.69	13.7
IV	Methane	1,1-Bis(R′)	A1	60.5	—	—	$2Br^-$	214.0–215.0	47.56	47.39	5.70	5.74	30.14	30.20	—	—	10.56	10.30
V	Ethane	1-(R″)	B	95	—	—	HBr	135.5–136.0	49.14	49.02	8.59	8.54	27.25	27.2	—	—	9.55	9.26
VI	Ethane	1,2-Bis(R″)	B	51.1	—	—	2HBr	273.0–274.0	47.48	47.24	7.97	8.02	28.73	28.6	—	—	10.07	10.1
VII	Cyclopentane	1-(R″)	C	74.5	141–2 0.35–0.37	26 1.4950	HCl	161.5–162.0	62.36	62.35	10.12	10.25	—	—	12.27	12.35	9.70	9.6
VIII	Cyclohexane	1-(R″)	C	13.5	152 0.50–0.52	27 1.4971	—	—	72.13	72.04	11.35	11.27	—	—	—	—	10.52	10.40
IX	Hexane	1-(R″)	B	97.7	—	—	HBr	175.0–176.0	55.00	55.16	9.52	9.47	22.88	22.9	—	—	8.02	8.0
X	Hexane	1,6-Bis(R″)	B	64.7	—	—	2HBr	253.5–254.5	50.98	50.97	8.56	8.58	26.09	26.3	—	—	9.15	8.80
XI	Decane	1-(R′)	A2	95	—	—	Br^-	91.0–92.0	60.14	60.30	8.83	8.75	20.01	20.0	—	—	7.01	7.00
XII	Decane	1-(R″)	B	66.3	—	—	HBr	157.5–158.0	59.24	59.11	10.19	10.16	19.71	19.90	—	—	6.91	6.90
XIII	Decane	1,10-Bis(R″)	B	97.7	—	—	2HBr	223.0–224.0	53.89	53.86	9.05	9.05	23.90	23.8	—	—	8.38	8.35







[a] Crude yield. [b] Melting points uncorrected. [c] Analyses by Drs. G. Weiler and F. B. Strauss, Oxford, England.

piperidine hydrochloride (VII). A reaction mixture consisting of 60.0 g. (0.402 mole) of bromocyclopentane, 61.6 g. (0.335 mole) of piperidine-3-(*N,N*-diethylcarboxamide) (II),[2] 62.0 g. (0.449 mole) of anhydrous potassium carbonate, and 150 ml. of anhydrous benzene was heated at reflux temperature, with mechanical agitation, for a total of 124 hr. Upon cooling, the solid constituents of the reaction mixture were filtered off, the filtrate was washed with aqueous 40% potassium hydroxide, and dried over anhydrous magnesium sulfate. The dry benzene solution was filtered, the benzene was removed, and the residue was fractionated under reduced pressure. The base was converted to the hydrochloride by treating it with anhydrous HCl in anhydrous ethyl ether. The salt was purified by recrystallization from ethanol-ethyl acetate.

Procedure D: 1-Methyl-1,2,5,6-tetrahydro-3-(N,N-dimethylcarboxamido)pyridine hydrochloride (III). 1-Methyl-1,2,-5,6-tetrahydropyridine-3-carboxylic acid was prepared from arecoline according to Jahns' procedure.[3] To 30.0 g. (0.213 mole) of the acid, 245.7 g. (2.065 moles) of thionyl chloride was added, the mixture was heated gradually to reflux temperature, and the resulting solution was refluxed for 16 min. The excess thionyl chloride was removed under reduced pressure (max. pot temp. 40°). The residual thionyl chloride was removed from the reaction product by azeotropic distillation under reduced pressure with two 400 ml. portions of anhydrous benzene. Then 200 ml. of anhydrous benzene was introduced into the reaction vessel, and the solid acid chloride was finely dispersed with mechanical agitation. To this dispersion, a solution of 100 g. (2.219 moles) of dimethylamine in 200 ml. of anhydrous benzene was added gradually, while the reaction mixture was maintained at room temperature. After the addition, the mixture was stirred an additional 2 hr. at room temperature and an additional 5 hr. at 50–55°. The resulting slurry was treated with aqueous 40% sodium hydroxide and the base extracted with benzene. The combined benzene extracts were dried over anhydrous sodium sulfate, filtered, the benzene was removed, and the residue was fractionated under reduced pressure. The base was converted to the hydrochloride by treating it with anhydrous HCl in anhydrous ethyl ether. The salt was purified by recrystallization from ethanol-ethyl acetate.

The following monoalkylcarboxamido derivatives were prepared by Procedure D: *1-Methyl-3-(N-methylcarboxamido)-1,2,5,6-tetrahydropyridine hydrochloride* (*XIV*). The base distilled at 129–131°/0.5 mm. Hg; n_D^{27} 1.5197 (yield 41.0%). The compound melted at 184.0–185.0°.

Anal. Calcd. for $C_8H_{15}ClN_2O$: C, 50.39; H, 7.93; Cl, 18.60; N, 14.70. Found: C, 50.40; H, 8.00; Cl, 18.55; N, 14.70.

1-Methyl-3-(N-ethylcarboxamido)-1,2,5,6-tetrahydropyridine hydrochloride (*XV*). The base distilled at 128–132°/0.09 mm. Hg; n_D^{27} 1.5107 (yield 42.2%). The compound melted at 163.0–164.0°,

Anal. Calcd. for $C_9H_{17}ClN_2O$: C, 52.80; H, 8.37; Cl, 17.32; N, 13.69. Found: C, 52.96; H, 8.39; Cl, 17.3; N, 13.8.

In tests on blood pressure and upon the autonomic nervous system as defined by changes in response to acetylcholine, epinephrine, tetramethylammonium bromide, and carotid occlusion (in chloralose anesthetized dogs), several compounds induced ganglionic blockade, some adrenergic blockade, and some effected hypotension of an as yet undetermined nature. The pharmacological evaluation is not complete at the time of this writing.

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(3) E. Jahns, *Arch. Pharm.*, **229**, 680 (1891).

Nitriles in Nuclear Heterocyclic Syntheses. I. Dihydro-1,3-oxazines[1]

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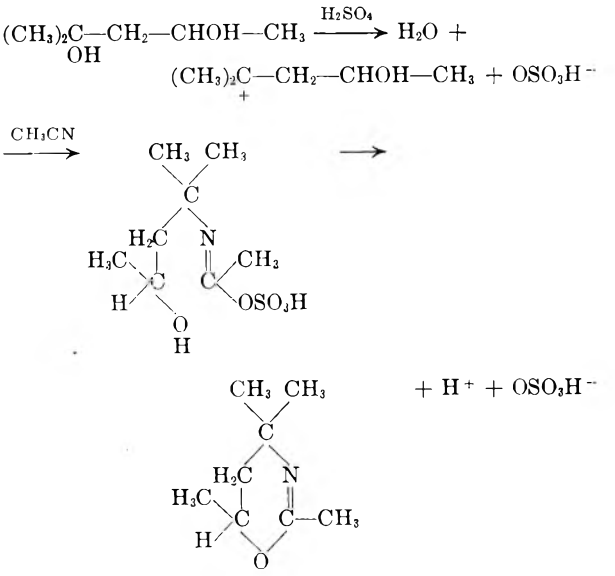
The acid-catalyzed reaction of secondary and tertiary alcohols with nitriles has been shown to result in formation of a variety of *N*-substituted amides.[2] Interaction of 2-methyl-2,4-pentanediol with acetonitrile has now been found to yield a dihydro oxazine instead of the expected diamide. It is suggested that primary reaction of a tertiary carbonium ion with the nitrile in the ordinary manner is followed by cyclization with displacement of —OSO_3H as follows:



Confirmation of the identity of the product was obtained by comparison with authentic 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine.[3] Further proof consisted in comparison of the caprylate of the amine resulting from alkaline cleavage of this dihydro oxazine with that of an authentic specimen of 4-amino-4-methyl-2-pentanol.

Two additional dihydro oxazines, 4,4,6-trimethyl-2-phenyl-5,6-dihydro-1,3-oxazine and 4,4,6-trimethyl-2-benzyl-5,6-dihydro-1,3-oxazine were prepared in the same manner by substituting benzo-

(1) Abstracted from part of a thesis submitted by Emma-June Tillmanns to the Graduate Faculty of New York University in partial fulfilment of the requirements for the degree of Doctor of Philosophy, February 1954.

(2) J. J. Ritter and J. Kalish, *J. Am. Chem. Soc.*, **70**, 4048 (1948); F. R. Benson and J. J. Ritter, *J. Am. Chem. Soc.*, **71**, 4128 (1949); L. W. Hartzel and J. J. Ritter, *J. Am. Chem. Soc.*, **71**, 4130 (1949); H. Plaut and J. J. Ritter, *J. Am. Chem. Soc.*, **73**, 4076 (1951).

(3) M. E. Smith and H. Adkins, *J. Am. Chem. Soc.*, **60**, 407 (1938).

nitrile and phenylacetonitrile respectively for acetonitrile.

This novel variant of the alkene-nitrile reaction has since been extended to the synthesis of Δ^1-pyrrolines, dihydropyridines, and other *N*-heterocyclic systems which will be reported in the near future.

EXPERIMENTAL

2,4,4,6-Tetramethyl-5,6-dihydro-1,3-oxazine(I). Acetonitrile (55 ml., 1.05 mole) was added dropwise with stirring to 500 g. of 92% sulfuric acid at 6–7° during 0.5 hr. Then 128 ml. (118.2 g., 1 mole) of 2-methyl-2,4-pentanediol was added dropwise with stirring over 4 hr. at 8–10°. The resulting solution was poured with stirring on 1 kg. of cracked ice and the mixture was half-neutralized with 40% sodium hydroxide solution, then extracted with several portions of chloroform. The acid layer was then made alkaline with 40% sodium hydroxide and the basic oil which separated was extracted with several portions of ether. The combined ether extracts were dried over anhydrous potassium carbonate, and after removal of the ether the residual oil was distilled through a 30-cm. vacuum-jacketed Vigreux column. There was obtained 61.4 g. (44%) of a water-soluble colorless liquid with ammoniacal odor, b.p. 56°/24 mm. (146–147°/750 mm.), n_D^{25} 1.4370; reported[3] b.p. 146.8–147°, n_D^{25} 1.4358.

Anal. Calcd. for $C_8H_{15}ON$: N, 9.93. Found, 9.95. The picrate melted at 153–154° (uncorr.); reported,[3] 152–153°.

Alkaline cleavage of I. The method of Smith and Adkins[3] was used to treat 24 g. (0.17 mole) of I. A colorless amine(II) was obtained in 75% yield (15 g.), b.p. 174–175°, n_D^{20} 1.4350. A specimen of 4-amino-4-methyl-2-pentanol[4] distilled at atmospheric pressure at 174–175°, n_D^{20} 1.4340. The caprylates of II and 4-amino-4-methyl-2-pentanol were prepared by mixing 1 mmole of each with 1 mmole of caprylic acid. The mixtures solidified almost immediately and the resulting solids were recrystallized twice from dry acetone. The melting point of each was 84–85° and the mixed melt showed no depression.

4,4,6-Trimethyl-2-phenyl-5,6-dihydro-1,3-oxazine. Benzonitrile (20.6 g., 0.2 mole) was added dropwise with stirring to 100 g. of 92% sulfuric acid at 2–4° over 20 min. Then 23.6 g. (0.2 mole) of 2-methyl-2,4-pentanediol was added dropwise with stirring at 3–6° during 2 hr. The product was isolated in the same manner as for I. A pale yellow oil (19.1 g., 47%), b.p. 103–106°/3 mm. was obtained. Two recrystallizations from ethanol-water (the compound was dissolved at room temperature and the solution was then strongly cooled) gave colorless crystals, m.p. 34–35° (reported,[5] 32°).

Anal. Calcd. for $C_{13}H_{17}ON$: N, 6.90. Found, 7.01. The picrate melted at 159–161° (corr.); reported,[6] 162.5–164°.

4,4,6-Trimethyl-2-benzyl-5,6-dihydro-1,3-oxazine. The procedure for this preparation was similar to the one above. Phenylacetonitrile (11.7 g., 0.1 mole) was added to 50 g. of 92% sulfuric acid followed by 11.8 g. (0.1 mole) of 2-methyl-2,4-pentanediol. A yellow oil (5.7 g., 26%) was obtained, b.p. 116–119°/5 mm., n_D^{20} 1.5125.

Anal. Calcd. for $C_{14}H_{19}ON$: N, 6.45; found, 6.39. The picrate melted at 125–126°.

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(4) M. Kohn, *Monatsh.*, 25, 141 (1904).
(5) M. Kahan, *Ber.*, 30, 1319 (1897).

Amines. III. Characterization of Some Aliphatic Tertiary Amines[1]

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The literature on simple aliphatic tertiary amines and their characterization is surprisingly sparse. Even the commercially available triethylamine[3] has not been reported characterized by such common derivatives as the methiodide or the methotosylate. Frequently when methiodide derivatives have been prepared and reported—there are at least five references to the methiodide of *N*-ethyldimethylamine,[4] two each for that of *N*,*N*-diethylmethylamine[4a,4b] and of *N*-isopropyldimethylamine[4a,5] and one for that derivable from *N*-*tert*-butyldimethylamine[6]—no melting data were given. The present investigation was undertaken to provide systematic and comparative characterization of a series of closely related simple aliphatic tertiary amines. This included the fully *N*-methylated ethyl-, diethyl-, isopropyl-, diisopropyl-, and *tert*-butylamines, and triethylamine. Although the *tert*-butyldimethylamine is the only new compound, the other amines, except for triethylamine, have been poorly characterized in the literature.

The tertiary methylamines were prepared by the Eschweiler-Clarke method.[7] The preparative data are presented in Table I. Physical constants, including freezing points, refractive indices, densities, molar refractivities, and Eykman constants are summarized in Table II. The chemical derivatives are listed in Tables III and IV.

EXPERIMENTAL

Eschweiler-Clarke N-methylation. Reactions were carried out in a magnetically stirred glass system closed except for a gas effluent tube which carried off the evolved carbon dioxide

(1) Previous paper, J. Radell, L. Spialter, and J. Hollander, *J. Org. Chem.*, 21, 1051 (1956).
(2) Dr. Joseph A. Pappalardo, of the University of Dayton, worked on this investigation under the Summer Expert Employment Program of the Wright Air Development Center.
(3) Available from Union Carbide Chemicals Co., 30 East 42nd Street, New York 17, N. Y.
(4) (a) N. Collie and S. B. Schryver, *J. Chem. Soc.*, 57, 767 (1890); (b) L. Wagner, *Z. Kryst. Mineral.*, 43, 148 (1907); (c) R. Müller, *Ann.*, 108, 1 (1858); (d) W. Lossen, *Ann.*, 181, 364 (1876); (e) Z. H. Skraup and Wiegmann, *Monatsh.*, 10, 107 (1889).
(5) H. Malbot and A. Malbot, *Bull. soc. chim. France*, [3], 7, 136 (1892).
(6) W. Hanhart and C. K. Ingold, *J. Chem. Soc.*, 997 (1927).
(7) (a) W. Eschweiler, *Ber.*, 38, 880 (1905); (b) H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, *J. Am. Chem. Soc.*, 55, 4571 (1933); (c) M. L. Moore, *Org. Reactions*, 5, 307 (1949).

TABLE I

PREPARATIVES DATA FOR VARIOUS TERTIARY AMINES

Amine Prepared	Moles of Reactants: Parent amine	Formic acid	Formaldehyde	Yield, %[a]	Boiling Point, °C. Found (740 Mm.)	Analyses[b] Calcd./Found C	H	N
$EtN(Me)_2$	1[c]	5	2.2	38	35.8–35.9[d]	65.69	15.16	19.15
						65.62	15.32	19.40
$(Et)_2NMe$	1[e]	5	2.2	79	65.1–65.3[f]	68.90	15.03	16.07
						68.72	15.09	15.94
i-$PrN(Me)_2$	1[g]	10	4.4	71	65.5–65.7[h]	68.90	15.03	16.07
						68.85	14.95	15.80
i-$PrN(Me)_2$	1[g]	5	2.2	35[a]	—	—	—	—
$(i$-$Pr)_2NMe$	1[i]	5	2.2	79	111.7–112.0[j]	72.97	14.87	12.16
						73.09	14.76	12.47
t-$BuN(Me)_2$	1[k]	5	2.2	76	89.6–89.9	71.21	14.94	13.84
						71.39	14.72	14.10

[a] The yields are based on weights of distillate fractions with an average boiling range of 1.4°, except for the 35% yield in the 2nd i-$PrN(Me)_2$ run. [b] All analyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. [c] Ethylamine (Sharples). [d] Lit. values (unspecified pressures): 37.5°, M. Kohn and O. Morgenstern, *Monatsh.*, **28,** 479 (1907); 36–38°, ref. (6); 37–39°, F. Schlegel, *Ber.*, **64B,** 1739 (1931). [e] Diethylamine (Sharples). [f] Lit. values (unspecified pressures): 63–65°, B. Emmert, *Ber.*, **42,** 1507 (1909); 66°, G. M. Robinson and R. Robinson, *J. Chem. Soc.*, **123,** 532 (1923); 66–69°; A. P. Terent'ev, A. N. Kost, and S. M. Gurvich, *Zhur. Obshchei Khim.*, **23,** 615 (1953). [g] *iso*-Propylamine (Union Carbide Chemical). [h] Lit. values (unspecified pressures): 67–67.5°, A. Skita and F. Keil, *Monatsh.*, **53/54,** 753 (1929). [i] Di-*iso*-propylamine (Sharples). [j] Lit. values (unspecified pressures): 109–112°, J. Klages, G. Nober, F. Kircher, and M. Bock, *Ann.*, **547,** 1 (1941). [k] *tert*-Butylamine (Rohm and Haas).

TABLE II

PHYSICAL CONSTANTS FOR VARIOUS TERTIARY METHYLAMINES

Amine	F.P.	n_D^{25}	n_D^{20}	d_4^{25}	d_4^{20}	Molar Refractivity, 25° Calcd.[a]	Found	Eykman Constant[b]
$EtN(Me)_2$	−140	1.3702	1.3720	0.6694	0.6751	24.46	24.73	0.7391 ± 0.0014
$(Et)_2NMe$	−196 (glass)[c]	1.3865	1.3891	0.7016	0.7061	29.09	29.01	0.7357 ± 0.0002
i-$PrN(Me)_2$	−196 (glass)[c]	1.3874	1.3905	0.7106	0.7151	29.09	28.90	0.7287 ± 0.0005
$(i$-$Pr)_2NMe$	−196 (glass)[c]	1.4082	1.4109	0.7495	0.7535	38.35	37.94	0.7257 ± 0.0003
t-$BuN(Me)_2$	− 90	1.4021	1.4041	0.7377	0.7419	33.72	33.41	0.7261 ± 0.0004

[a] Bond refractivity values used were those for the sodium-D line given by Y. K. Syrkin and M. E. Dyatkina, *Structure of Molecules and the Chemical Bond*, p. 201, Interscience Publ. Inc., New York, 1950. [b] See ref. (12). The values here represent the mean values over the range 20 to 25°. [c] These could not be crystallized.

through a reflux condenser and thence a gas flowmeter.[8] The formalin solution was added to the amine dissolved in 88% formic acid. Sufficient heat (60 to 90°) was applied to maintain carbon dioxide evolution of 200–500 cc./min. In less than an hour gas evolution ceased and the system was heated at reflux temperature for 4 hr. The product was worked up by acidification, concentration by evaporation, alkalization, distillation, drying over potassium hydroxide, and final fractionation from sodium in a dry nitrogen, carbon dioxide-free atmosphere. Table I contains preparative conditions and yields. To maintain purity, the products were divided into 1–5 ml. portions and sealed under nitrogen in individual ampoules.

Physical constants. Freezing points were determined by chilling samples in sealed ampoules with liquid nitrogen-cooled pentane mixtures and repeatedly observing freezing and melting points. Temperature values are estimated to be better than ±5°. As indicated in Table II, three of the amines could not be induced to crystallize, but froze to glassy supercooled liquids at the temperature of liquid nitrogen.

Refractive index measurements were made with a thermostated American Optical Spencer Abbe refractometer. Densities were determined with a pycnometer.

(8) Flowrater, range of 100 to 3000 cc./mm., manufactured by the Fischer and Porter Co., Hatboro, Pa.

Chemical derivatives. The methiodides and methotosylates[9] were satisfactorily prepared by both conventional procedures,[10] with the additional precaution in the solventless method of using small quantities and special care because of the high amine reactivity and exothermicity on quaternization. The methotosylates were recrystallized from ethyl acetate containing some methanol. All crystals were dried in a vacuum oven at 60 to 90°.

On exposure to the laboratory atmosphere over a 3 to 4 day period, all of the methiodides acquired a yellow color except the one from *tert*-butyldimethylamine. The intensity of the yellow color, in decreasing order, was $Et_3N = Et_2NMe > EtNMe_2 > i$-$PrNMe_2 = i$-$Pr_2NMe > t$-$BuNMe_2$.

Melting points of the methiodides were determined on a Kofler micro hot stage and represent corrected values. Those for the methotosylates had to be determined in sealed capillary tubes by the Thiele tube method because of the pronounced hygroscopicity of these latter derivatives.

(9) These are the quaternary ammonium derivatives arising from reaction of a tertiary amine with methyl iodide and methyl *p*-toluenesulfonate, respectively.

(10) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, p. 149, John Wiley and Sons, Inc., New York, 2nd Ed., 1940.

TABLE III

METHIODIDES OF TERTIARY AMINES

Amine	M.P. (Corr.)[a]	Formula	Analyses, % Calcd./Found C	H	N	I
$EtN(Me)_2$	300–301[b,c]	$C_5H_{14}NI$	27.92	6.56	6.51	59.01
			27.87	6.31	6.64	58.94
$(Et)_2NMe$	298–299[b,c]	$C_6H_{16}NI$	31.45	7.04	6.11	55.40
			31.42	6.76	6.29	55.22
i-$PrN(Me)_2$	294–295[b]	$C_6H_{16}NI$	31.45	7.04	6.11	55.44
			31.49	6.94	6.36	55.45
$(i\text{-}Pr)_2NMe$	252–253[b]	$C_8H_{20}NI$	37.36	7.84	5.45	49.35
			37.39	7.73	5.52	49.44
t-$BuN(Me)_2$	240–241[b]	$C_7H_{18}NI$	34.58	7.46	5.76	52.20
			34.73	7.30	5.92	52.46
$(Et)_3N$	280–281[b]	$C_7H_{18}NI$	34.58	7.46	5.76	52.20
			34.51	7.19	5.93	52.05

[a] A Kofler micro hot stage apparatus was used. [b] Decomposes. [c] Sublimes.

TABLE IV

METHOTOSYLATES OF TERTIARY AMINES

Amine	M.P.[a]	Formula	Analyses, % Calcd./Found C	H	N	S
$EtN(Me)_2$	185–188	$C_{12}H_{21}O_3NS$	55.57	8.16	5.40	12.36
			55.77	8.18	5.67	12.56
$(Et)_2NMe$	132–135	$C_{13}H_{23}O_3NS$	57.11	8.48	5.12	11.73
			57.20	8.20	5.06	11.78
i-$PrN(Me)_2$	187–190	$C_{13}H_{23}O_3NS$	57.11	8.48	5.12	11.73
			57.00	8.58	5.18	11.72
$(i\text{-}Pr)_2NMe$	109–111	$C_{15}H_{27}O_3NS$	59.77	9.03	4.65	10.64
			60.65	8.96	4.74	10.22
t-$BuN(Me)_2$	184–187	$C_{14}H_{25}O_3NS$	58.50	8.77	4.87	11.15
			58.43	8.44	4.95	11.48
Et_3N	88–91	$C_{14}H_{25}O_3NS$	58.50	8.77	4.87	11.15
			58.04	9.22	5.02	11.11

[a] Melting points are uncorrected and were obtained in sealed capillary tubes.

DISCUSSION

The physical properties of the aliphatic tertiary amines, as listed in Table II, appear rather similar to those of highly branched alkanes of comparable molecular weight and structure. The densities and refractive indices are, respectively, about 0.04–0.05 and 0.01–0.02 units higher than those of the hydrocarbon analogs wherein the amino-nitrogen has been replaced by the C-H group.[11] The Eykman constants[12] for the amines are 0.025–0.030 units lower. The amines except for the case of ethyldimethylamine, are also lower-melting. For this reason and others, such as chemical stability, ease and low cost of synthesis, they may be useful as low temperature thermometric, heat exchange, hydraulic, or lubricative fluids.

Agreement between calculated (from bond refractivities) and found values for molar refractivity is not as good as one might expect in view of the simplicity of the tertiary amine structures and absence of hydrogen bonding, unsaturation, etc., which disturb additive molecular parameters in the case of more complex molecules. The agreement is no better (and is sometimes worse) when atomic

(11) American Petroleum Institute Research Project 44 at National Bureau of Standards, *Selected Values of Properties of Hydrocarbons*, U. S. Government Printing Office, Washington, D. C., Nov. 1947.

(12) The Eykman equation [J. F. Eykman, *Rec. trav. chim.*, 14, 185 (1895)] is a temperature-invariant relation between the density and index of refraction of a liquid. The equation has the form:

$$\frac{n^2 - 1}{n + 0.4} \times \frac{1}{d} = C_e$$

where n and d are the refractive index and liquid density, respectively, at the same temperature, and C_e, the Eykman Constant, which is a fixed parameter characteristic for a particular compound. Critical evaluations of this equation have been given by S. S. Kurtz, Jr., S. Amon, and A. Sankin [*Ind. Eng. Chem.*, 42, 174 (1950)] and R. R. Dreisbach [*Ind. Eng. Chem.*, 40, 2269 (1948)]. These authors show its superiority in temperature invariance over the well-known Lorentz-Lorenz molecular refractivity equation.

refractivity values of other authors[13] are used. The refractivity increment per methylene group appears to be less than the estimated value of 4.65 generally given.[13]

The Eykman constant was computed over the range 20–26° and appears constant within the estimated limits of experimental error.

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(13) (a) W. Hückel, *Theoretische Grundlagen der Organischen Chemie*, 4th Ed., Vol. II, p. 142, Akademische Verlag., Leipzig, Germany, 1943. (b) A. I. Vogel, *A Textbook of Practical Chemistry*, 3rd Ed., p. 1035, Longmans, Green and Co., Inc., New York, N. Y., 1956. (c) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, 2nd Ed., p. 107, John Wiley and Sons, Inc., New York, N. Y., 1940.

High Temperature Chlorination of Dioxane to Give Trichloroacetyl Chloride

N. B. LORETTE

Received February 7, 1957

Several workers[1–4] have reported the chlorination of *p*-dioxane at temperatures of 130–160° to give a number of chlorinated dioxanes. Boeseken, *et al.*[2] noted that the ring was broken and that "acid chlorides were probably present" when dioxane was subjected to prolonged chlorination at 130–150°.

When trichloroacetyl chloride was isolated from the products of a dioxane chlorination experiment, the work described below was carried out to determine the extent to which trichloroacetyl chloride was formed. Although the experiment was stopped before the ultimate yield of trichloroacetyl chloride was obtained, sufficient information was obtained to show that trichloroacetyl chloride is a major product of the prolonged high temperature chlorination of dioxane. The factors which account for the different results of the previous and present work are the temperature, which was kept near or above 160° when trichloroacetyl chloride was formed, and the large excess of chlorine which was used in this work.

(1) C. L. Butler and L. H. Cretcher, *J. Am. Soc.*, **54**, 2987 (1932).

(2) J. Boeseken, F. Tellegen, and P. C. Henriquez, *J. Am. Chem. Soc.*, **55**, 1284 (1933).

(3) J. J. Kucera and D. C. Carpenter, *J. Am. Chem. Soc.*, **57**, 2346 (1935).

(4) R. K. Summerbell, R. R. Umboeffer, and G. R. Lappin, *J. Am. Chem. Soc.*, **69**, 1352 (1947).

EXPERIMENTAL

Two hundred and sixty g. (2.95 moles) of *p*-dioxane was heated to 90° in a flask equipped with a condenser, an inlet tube, and a thermometer. Chlorine was added at a rate of 20 to 30 g. per hr. At the end of 60 hr. the pot temperature had risen to 115° and the net weight increase was 530 g. Infrared analysis indicated less than 2% carbonyl chloride present. Chlorination was continued at 155–160° for 11 hr. Distillation of the crude products at 75 mm. gave 144 g. of trichloroacetyl chloride, b.p. 47–48, n_D^{24} 1.4662, confirmed by the infrared spectrum. The residue was then chlorinated for 15 hr. at 165–180° after which reduced pressure distillation yielded 88 g. of trichloroacetyl chloride. Again the distillation residue was chlorinated at 175–190° for 10 hr.; no condenser was used and the vent gases were passed directly into a cold trap. During this period 160 g. was collected. Distillation of the condensate gave 84 g. of trichloroacetyl chloride. The pot residue solidified on cooling. Infrared and chlorine analysis showed the solid to be hexachloroethane. The total yield of trichloroacetyl chloride was 316 g. (1.74 moles).

An attempt was made to distill the reaction residue (462 g.) at 2 mm. The column and condenser immediately plugged with hexachloroethane. According to the infrared spectrum, the residue contained above 20% hexachloroethane.

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Preparation of Malonaldehyde bis-Bisulfite, Sodium Salt

L. D. SASLAW AND V. S. WARAVDEKAR

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Malonaldehyde (I) reacts with 2-thiobarbituric acid to give a characteristic pink coloration. This reaction is useful for the estimation of 2-deoxysugars and nucleosides containing 2-deoxysugars. For this purpose, it is considered important to have a stable derivative of I, since I has been reported[1] as an unstable crystalline monomer. This report is concerned with the preparation of a stable crystalline bisulfite addition compound suitable for investigations of reactions of I.[2]

EXPERIMENTAL[3]

A suspension of 10 ml. of malonaldehyde bis(dimethyl acetal)[4] in 5.5 ml. of 3.7% aqueous hydrochloric acid was shaken for 1 min. in a water bath at 60° to effect dissolution. The resulting yellow solution was kept at room temperature for 40 hr. and then cooled to 4°. A freshly prepared saturated solution of sodium *meta*-bisulfite was chilled in an ice bath

(1) R. Hüttel, *Ber.*, **74**, 1825 (1941).

(2) U. S. Patent No. 2,671,800 has been granted for a related process for preparing bisulfite addition products of malonaldehyde [*Chem. Abstr.*, **49**, 4014 (1955)]. However, no proof of identity of the proposed compounds is recorded, and apparently no physical or chemical studies were undertaken to characterize the compounds.

(3) Microanalyses for C, H, S, and Na were performed by Dr. W. C. Alford and his associates.

(4) Obtained from Kay-Fries Chemicals, Inc., 180 Madison Ave., New York 16, N. Y.

and 40 ml. was mixed with the malonaldehyde solution. After 5 hr. at 4°, the slowly separating crystals were collected and washed successively with cold 15 ml. aliquots of saturated bisulfite solution and 50% ethanol. Substantial quantities of crystals were obtained by mixing the mother liquor with an additional 40 ml. of saturated bisulfite solution and storing for several days in a refrigerator.

The sodium salt of malonaldehyde *bis*-bisulfite (II) was recrystallized, after storage at 4°, from saturated aqueous solution by the dropwise addition of 1/4 volume of absolute ethanol. A second crop was obtained by bringing the total ethanol concentration to about 50%. The combined crops were washed with cold 70% ethanol and anhydrous ether and stored overnight in a vacuum desiccator over calcium chloride. The colorless oblong hexagonal plates (40% yield) darkened above 185° without melting.

Anal. Calcd. for $C_3H_6O_8S_2Na_2.2H_2O$: C, 11.39; H, 3.19; S, 20.28; Na, 14.54; H_2O, 11.39. Found: C, 11.57; H, 3.30; S, 20.16; Na, 14.58; wt. loss (vac. oven, 70°), 11.39.

Concentrated aqueous solutions of II exhibit a maximum in the ultraviolet at 265 mμ. Distillates of concentrated aqueous solutions of II exhibit a maximum at 245 mμ and also give the red color, characteristic of I, with aqueous ferric chloride.[5]

Reaction with 2-thiobarbituric acid aids in identification of I. Three ml. of an aqueous solution of 5.5 micrograms of II and 12 mg. of 2-thiobarbituric acid, in a test tube fitted with a tear-drop condenser, was immersed in boiling water for 20 min. Examination of the visible absorption spectrum of the pink solution, with the use of a Warren Spectracord, revealed a maximum at about 530 mμ which was in agreement with spectra reported by other workers.[6,7]

A highly sensitive method of estimating 2-deoxysugars based upon oxidation with periodate and subsequent estimation of the resulting I with 2-thiobarbituric acid has been developed. The usefulness of the bisulfite compound in enzymic studies based upon the observations of others[8,9,10] has been explored. These studies will form the subject of separate communications.

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(5) L. Claisen, *Ber.*, **36**, 3664 (1903).
(6) S. Patton and G. W. Kurtz, *J. Dairy Sci.*, **34**, 669 (1951).
(7) W. G. Jennings, W. L. Dunkley, and H. G. Reiber, *Food Research*, 20, 13 (1955).
(8) F. Bernheim, K. M. Wilbur, and C. B. Kenaston, *Arch. Biochem.* and *Biophys.*, **38**, 177 (1952).
(9) A. Ottolenghi, K. M. Wilbur, and F. Bernheim, *Arch. Biochem.* and *Biophys.*, **56**, 157 (1955).
(10) C. W. Shuster, *Proc. Soc. Exp. Biol. Med.*, **90**, 423 (1955).

Some Quaternary Salts of Pyridazine

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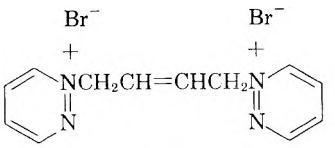
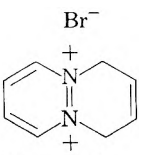
Received February 13, 1957

The reaction of either *cis*- or *trans*-1,4-dibromo-2-butene with pyridazine in mole ratios varying from 1:4 up to 4:1, in methanol, carbon tetrachloride, or acetone, and at different concentrations, gave only *trans*-1,4-dipyridazinium-2-butene bromide (I).



I



II Br⁻

There was no evidence for the formation of the *cis* isomer, of *N*-(4-bromo-2-butenyl)pyridizanium bromide, of *N,N'*-di-(4-bromo-2-butenyl)pyridazinium bromide, of 9,10-diaza-1,4-dihydronaphthalene bromide (II), or of products that might result from allylic rearrangement of 1,4-dibromo-2-butene before or during reaction with pyridazine.

Attempts to prepare simpler diquaternary salts of pyridazine were equally unsuccessful. When pyridazine was heated with an excess of either methyl iodide or ethyl bromide at temperatures up to 100°, only the monoquaternary salts were obtained.

It has been pointed out[1] that compounds containing more than one tertiary nitrogen, phosphorus, or arsenic atom frequently do not give the maximum number of quaternary groups on reaction with alkyl halides. This behavior has been ascribed to the proximity of the positive charge produced when the first tertiary group forms a quaternary salt. However, hydrazine forms numerous diacid salts,[2] and both *p*-phenylenediamine[3] and 2,2'-dipyridyl[4] readily form diquaternary salts. Hence it cannot be predicted that the presence of a charge necessarily will prevent the introduction of an adjacent like charge or one separated by a conjugated system.

EXPERIMENTAL

trans-1,4-Dipyridazinium-2-butene bromide (I). To 25.6 g. (0.12 mole) of *cis*-1,4-dibromo-2-butene[5] dissolved in 35 cc. of carbon tetrachloride was added dropwise with cooling and stirring a solution of 5.5 g. (0.069 mole) of pyridazine[6] in 20 cc. of carbon tetrachloride. During the course of the addition a small amount of brown solid separated. The mixture was allowed to stand in an ice bath for 4 hr. during which time more solid was deposited. The carbon tetrachloride was decanted and the solid crystallized from 1-propanol to give 9.7 g. (71%) of gray hygroscopic crystals that melted with decomposition at 177–178°. Recrystallization for analysis raised the decomposition point to 179–180°.

Anal. Calcd. for $C_{12}H_{14}Br_2N_4$: C, 38.52; H, 3.77; Br, 42.73; N, 14.98. Found: C, 38.8; H, 3.5; Br, 42.6; N, 14.9.

Infrared spectrum, Nujol mull: maxima at 6.32, 7.05, 8.41, 9.16, 9.91, 10.0, and 12.56 μ. The lack of a band near 6μ indicates that the double bond is *trans* and symmetrically substi-

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(2) L. F. Audrieth and B. A. Ogg, *The Chemistry of Hydrazine*, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 177.
(3) A. W. Hofmann, *Proc. Roy. Soc.* (*London*) **12**, 642 (1863).
(4) F. Blau, *Monaish.*, **10**, 382 (1889).
(5) A. Vallette, *Ann. chim.*, (12) **3**, 644 (1948).
(6) N. Clausen-Kaas, S. Li, and N. Elming, *Acta Chem. Scand.*, **4**, 1233 (1950).

tuted.[7] The same product was obtained in each of the following runs: (a) 0.028 mole of pyridazine was added to a solution of 0.0054 mole of *trans*-1,4-dibromo-2-butene and the mixture heated to refluxing; (b) a solution of 0.059 mole of pyridazine in 100 cc. of carbon tetrachloride was added dropwise with stirring and cooling to a solution of 0.24 mole of *cis*-1,4-dibromo-2-butene; (c) a solution of 0.016 mole of pyridazine in 620 cc. of acetone was added dropwise to 0.018 mole of *cis*-1,4-dibromo-2-butene in 560 cc. of acetone at room temperature.

N-Methylpyridazinium iodide. A mixture of 5.5 g. (0.069 mole) of pyridazine and 34 g. (0.24 mole) of methyl iodide was heated in a sealed tube at 100° for 12 hr. After chilling in an ice bath, two phases were present, a dark upper phase containing yellow crystals, and a light red bottom phase of methyl iodide. The total content was added to 40 cc. of acetone, the mixture chilled in an ice bath, and filtered. The yellow prisms weighed 11.3 g. (75%) and melted with decomposition at 93–94°. Crystallization from 1-propanol gave yellow hygroscopic needles, m.p. 95–96° (dec.).

Anal. Calcd. for $C_5H_7IN_2$: C, 27.04; H, 3.18; I, 57.16; N, 12.62. Found: C, 27.3; H, 3.2; I, 56.6; N, 12.4.

Infrared spectrum, Nujol mull: maxima at 6.30, 6.88, 10.18, and 12.84 μ. The same product was obtained in the absence of solvent at 0° and in methanol solution at 110°.

N-Ethylpyridazinium bromide. A mixture of 2.21 g. (0.0028 mole) of pyridazine and 14.5 g. (0.13 mole) of ethyl bromide was heated in a sealed tube at 110° for 20 hr. On cooling an upper light yellow phase separated from a lower dark red phase of ethyl bromide. The upper phase solidified on further cooling in an ice bath. The mixture was filtered in a dry box and the solid washed with dry acetone. Crystallization from 1-propanol gave pale tan plates that melted in a sealed tube at 118–120° (dec.). The product was very hygroscopic and all transfers were made in a dry box.

Anal. Calcd. for $C_6H_9BrN_2$: C, 38.11, H, 4.80; Br, 42.27; N, 14.82. Found: C, 37.9; H, 4.8; Br, 42.0; N, 15.0.

Infrared spectrum, Nujol mull: maxima at 6.30, 8.44, 10.08, and 12.84 μ.

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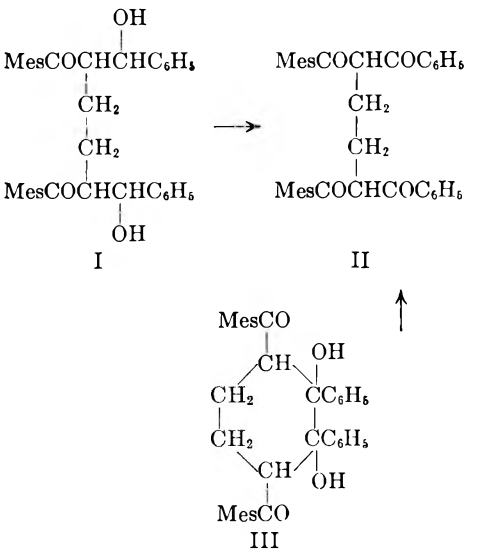
(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 34.

Isomerization of 1,4-Dibenzoyl-1,4-dimesitoylbutane[1]

REYNOLD C. FUSON AND H. SCOTT KILLAM

Received February 14, 1957

1,4-Dibenzoyl-1,4-dimesitoylbutane (II), prepared from the diol I by the action of chromic anhydride in glacial acetic acid, was found to melt at 201–203°.[2] The same substance was obtained by the oxidation of the cyclic glycol III by way of a compound melting at 124–126°. Evidence has now been found which indicates that this intermediate compound and that melting at 201–203° are diastereoisomers.



Repetition of the oxidation of the linear glycol I was accomplished without difficulty, but more extensive purification raised the melting point to 133°. When this material, or the less pure sample, is recrystallized repeatedly from ethanol, it is transformed into the high-melting compound (m.p. 201–203°).[3] This change can be accomplished also merely by heating the low-melting isomer in benzene. It seemed probable that the change from the low- to the high-melting isomer is an epimerization, realized by way of an enol form. As was to be expected on this basis, treatment with sodium methoxide was found to bring about the conversion. In these experiments the high-melting isomer was always obtained as a colorless powder.[3] It was observed also that this isomer could not be formed by seeding solutions of the low-melting isomer.

EXPERIMENTAL

Chromic anhydride oxidation. A solution of 1 g. of the linear glycol I was prepared by shaking it with 25 ml. of glacial acetic acid for 30 min. at room temperature. The chromic anhydride reagent, made from 1.1 g. of the anhydride, 10 ml. of glacial acetic acid, and 3 ml. of water, was added in portions over a period of 5 min. during which time the reaction mixture was swirled vigorously. The brown solution was allowed to stand at room temperature, with occasional agitation, for 2 hr.; during the latter part of this time the tetraketone II separated in the form of pale yellow needles. The product was washed on the filter, first with cold glacial acetic acid and then with cold water. The water caused the separation of a second crop of the tetraketone from the filtrate. The two crops of material were recrystallized separately from ether–petroleum ether mixtures. In each case the product formed pale yellow needles, m.p. 133–134°.[3]

Anal. Calcd. for $C_{38}H_{38}O_4$: C, 81.69; H, 6.86. Found: C, 81.74; H, 6.82.

The infrared spectrum contains absorption bands corresponding to a conjugated (1677 cm.$^{-1}$) and to an unconjugated carbonyl group (1705 cm.$^{-1}$). There is no evidence of

(1) This investigation was supported in part by a grant from the Office of Ordnance Research, U. S. Army (Contract No. DA-11-022-ORD-874).

(2) R. C. Fuson and R. W. Hill, *J. Org. Chem.*, 19, 1575 (1954).

(3) R. C. Fuson and R. W. Hill, *J. Org. Chem.*, 21, 1553 (1956).

the presence of hydroxyl groups. The expected absorption for a mesityl group and a phenyl group is shown.

Isomerization was observed when the tetraketone was recrystallized repeatedly from ethanol or 1-propanol. When 0.5 g. of the compound was boiled with ethanol for a few minutes it was converted to a colorless powder which still melted at 133–134°. When the contact with boiling ethanol was prolonged, the product was a colorless powder melting at 199–200° (corr.). Under the same conditions the sample described earlier[2] was found to melt at 199–200° (corr.). A mixture of the two samples melted at 199–200° (corr.).

Anal. Calcd. for $C_{38}H_{38}O_4$: C, 81.69; H, 6.86. Found: C, 81.44; H, 7.18.

The infrared spectrum is identical to that obtained for the low-melting product.

The isomerization was accomplished also by use of sodium methoxide. The reagent was made by shaking 0.5 g. of the methoxide with 10 ml. of methanol and removal of undissolved methoxide by filtration. The reagent was added to a methanolic solution of 0.1 g. of the tetraketone (m.p. 133–134°). The solution, which immediately became pale yellow, was allowed to stand for 15 min. at room temperature. Dilute hydrochloric acid was added until a permanent turbidity was produced. The product, which separated during 2 hr. of refrigeration, crystallized from ethanol as a colorless powder melting at 199–200° (corr.). A mixture melting point with the sample described above was not depressed.

The same two tetraketones were obtained by oxidation of the cyclic glycol III with periodic acid. When the oxidation product was recrystallized from an ether–petroleum ether mixture, pale yellow crystals melting at 133–134° were obtained. When the recrystallization solvent was ethanol, however, the product separated as a colorless powder. This product and its mixture with the high-melting tetraketone from the linear glycol melted at 199–200° (corr.).

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Reaction of Cyanogen with Organic Compounds. IX. Allyl Amines

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Received December 6, 1956

Several years ago it was shown in this laboratory[3,4] that saturated primary and secondary aliphatic amines react with cyanogen at low temperature and atmospheric pressure to yield oxamidines and cyanoformamidines. We report here the similar behavior of the unsaturated compounds allylamine and diallyl amine:

$$2\ CH_2{=}CHCH_2NH_2 + (CN)_2 \longrightarrow CH_2{=}CHCH_2NHC(=NH)C(=NH)NHCH_2CH{=}CH_2$$

$$(CH_2{=}CHCH_2)_2NH + (CN)_2 \longrightarrow (CH_2{=}CHCH_2)_2NC(=NH)CN$$

These compounds are important in our current study of the chemistry of oxamidines because they possess nitrogen-free reactive centers somewhat removed from the C=NH and C≡N groups.

Physically the allyl derivatives are quite similar to their saturated analogs.[3,4] The oxamidine is a white, crystalline solid, soluble in water, ethanol, carbon tetrachloride, acetone, and ether, and insoluble in petroleum ether. It quickly turns brown in air, but forms a stable, crystalline dihydrochloride. The cyanoformamidine is a colorless liquid when freshly distilled but darkens on standing, even in the ice chest. Its hydrochloride is a stable, white solid.

The behavior of the new compounds toward bromine was investigated. From *sym*-diallyloxamidine, or better from its hydrochloride, was obtained a white, crystalline compound which gave the correct analysis for

$$CH_2BrCHBrCH_2NHC(=NH)C(=NH)NHCH_2CHBrCH_2Br\cdot 2HCl$$

Both diallylcyanoformamidine and its hydrochloride decolorized bromine solutions readily but the gummy products could not be purified. A quantitative bromination with KBr-$KBrO_3$ solution indicated that four equivalents of bromine reacted with one mole of cyanoformamidine.

Difficulty was experienced in determining the chlorine content of *N*-diallylcyanoformamidine hydrochloride. Both Mohr and Volhard methods gave consistent results about 3% higher than theoretical. However, titration of the hydrochloride with standard sodium hydroxide gave an equivalent weight corresponding to the calculated value. It is conceivable that the cyanoformamidine forms a complex with $AgNO_3$ thus consuming part of the precipitant.

Although *sym*-diallyloxamidine can be obtained by the conventional method of cyanogenating an aqueous solution,[3] the most successful method employs petroleum ether, from which the product precipitates as formed.

EXPERIMENTAL

Cyanogen was prepared, purified and dried by the method described by Woodburn, Morehead, and Bonner.[4]

sym-Diallyloxamidine dihydrochloride. A solution of 10 g. of allylamine in 25 g. of petroleum ether was placed in an ice bath and maintained at 0° while cyanogen gas was bubbled in. After some time light-colored crystals of product appeared. Cyanogenation was discontinued soon thereafter, since experience showed that further cyanogenation converted the crystals to a brown liquid.

The crystals were filtered, dissolved in diethyl ether, and the solution saturated with dry hydrogen chloride. The precipitated hydrochloride was purified by dissolving it in ethanol and reprecipitating with ether. White crystals, melt-

(1) Present address: Foramino, Inc., Kenova, W. Va.

(2) Present address: Durez Plastics Division, Hooker Electrochemical Co., Walck Road, North Tonawanda, N. Y.

(3) Woodburn, Morehead, and Chen, *J. Org. Chem.*, 15, 535 (1950).

(4) Woodburn, Morehead, and Bonner, *J. Org. Chem.*, 14, 555 (1949).

ing with decomposition at 260° were obtained. The yield (based on amine) was 39%.

Anal. Calcd. for $C_8H_{14}N_4 \cdot 2HCl$: C, 40.3; H, 6.7; N, 23.5; Cl, 29.8. Found: C, 40.5; H, 7.2; N, 23.7 Cl, 29.8.

Crystals of *the free base* could be kept for a short time at room temperature in a tightly stoppered bottle. Exposed to air they turned brown in a few hours. They melted between 65–75°, were very soluble in water, ethanol, acetone, carbon tetrachloride, and ether, but insoluble in petroleum ether.

N-diallylcyanoformamidine. A solution of 20 g. of diallyl amine in 40 ml. of anhydrous ethyl acetate was cooled to 40° and treated with cyanogen until the mixture turned yellow. After standing in the ice chest for 2 days, it was heated to 75° in a water bath under the hood to remove any unreacted cyanogen. Ethyl acetate was distilled off at atmospheric pressure and the remaining mixture was fractionated at 16 mm. pressure. Unreacted diallylamine weighing 9.8 g. was recovered. The yield of diallylcyanoformamidine boiling at 102–104°/16 mm. was 9.5 g. which on the basis of the diallylamine which reacted was 66.9%. The liquid was colorless and had a refractive index, n_D^{20}, of 1.4903.

The *hydrochloride* was prepared by saturating an ether solution of diallylcyanoformamidine with dry hydrogen chloride. The white solid was filtered, washed with cold ether, and dried in a vacuum desiccator over concentrated sulfuric acid. The crystals melted at 136–138° with decomposition.

Anal. Calcd. for $C_8H_{11}N_3 \cdot HCl$: C, 51.8; H, 6.52; N, 22.6; equiv. wt., 185.5. Found: C, 52.0; H, 6.95; N, 22.2; equiv. wt. (by NaOH titration), 186.4.

It was also possible to prepare the hydrochloride by cyanogenating diallylamine in petroleum ether. The cyanoformamidine, which settled out as an insoluble layer, was separated, washed with petroleum ether, dissolved in diethyl ether, and saturated with dry hydrogen chloride. This procedure eliminated the time-consuming distillation of the cyanoformamidine involved in the other procedure.

sym-Bis(2,3-dibromopropyl)oxamidine dihydrochloride. To 1 g. of *sym*-diallyloxamidine dihydrochloride dissolved in water was added bromine water until a yellow color persisted. Sufficient normal NaOH solution was added to remove excess bromine and to liberate the free base of the brominated product. The solution was extracted with ether, the extract dried, and saturated with gaseous hydrogen chloride. The crystalline product was recrystallized from ethanol. It melted at 212°.

The same product was obtained by adding a carbon tetrachloride solution of bromine to a carbon tetrachloride solution of *sym*-diallyloxamidine. The gummy precipitate was dissolved in ethanol and saturated with hydrogen chloride. Cooling in a dry ice chest caused the separation of crystals which melted at 212°.

Anal. Calcd. for $C_8H_{14}N_4Br_4 \cdot 2HCl$: C, 17.2; H, 2.9; N, 10.0; Br, 57.2; Cl, 12.7. Found: C, 17.5; H, 3.2; N, 10.3; Br, 57.0; Cl, 13.0.

The hydrochloride neutralized with dilute sodium hydroxide gave a solid presumed to be the *free base* which melted at about 112°.

Bromination of N-diallylcyanoformamidine. (a) Attempts to isolate the product of the bromination of *N*-diallylcyanoformamidine in carbon tetrachloride, ether, or ethanol solution produced only a gummy material. This, dissolved in ethanol and saturated with hydrogen chloride likewise failed to produce crystals. (b) *N*-diallylcyanoformamidine hydrochloride, dissolved in water, decolorized bromine water readily but gave a gummy product on which no analysis was attempted. (c) Two samples of *N*-diallylcyanoformamidine, quantitatively brominated with KBr-$KBrO_3$-HCl mixture, consumed respectively 3.90 and 3.89 equivalents of bromine per mole.

Acknowledgment. Acknowledgment is made to The Edwal Laboratories, Inc., Ringwood, Ill., for their gift of diallylamine.

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Trifluoroacetates of Ethylene Glycol

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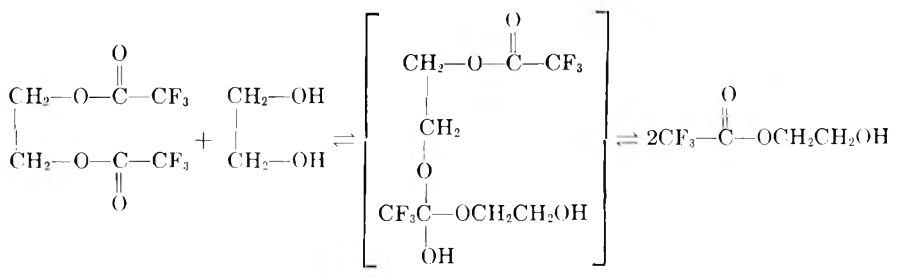
When an excess of ethylene glycol is reacted with either trifluoroacetic acid or trifluoroacetic anhydride and the reaction mixture is distilled at atmospheric pressure, an apparently homogeneous product is obtained. This product has a constant boiling point of 151–152°; n_D^{25} 1.3450. If this product is arbitrarily divided during distillation into successive fractions, all of the fractions have the same index of refraction and the same infrared spectrum.

Nevertheless, this product gives a saponification equivalent of 144, a value intermediate between those calculated for 2-trifluoroacetoxyethanol (158) and 1,2-bis(trifluoroacetoxy)ethane (127). It may be shown that this product is, in fact, a mixture by subjecting it to vapor phase chromatography at 145°, whereby it is separated into its two components, initially present in a ratio of 1.33 to 1 and having retention times of 10.5 min. and 7.6 min. respectively. This product is a mixture of 2-trifluoroacetoxyethanol and 1,2-bis(trifluoroacetoxy)ethane and results from an equilibration, at the temperature of distillation, according to the following equation:



By selecting appropriate reaction conditions it is possible to prepare both the pure ditrifluoroacetate and the pure monotrifluoroacetate. The former is readily obtained by treating ethylene glycol, in the cold, with a large excess of trifluoroacetic anhydride; the latter may be obtained by adding trifluoroacetic anhydride in benzene in the presence of *N,N*-dimethylaniline to an excess of glycol and carrying out the distillation of the product at reduced pressure. Pure 1,2-bis(trifluoroacetoxy)ethane is stable to distillation at atmospheric pressure, but when it is heated with glycol at 65°, a mixture of the two trifluoroacetates is obtained. Alternatively, if the pure monotrifluoroacetate is heated at 150° for 2 hr. in a sealed tube, a mixture of glycol, the monotrifluoroacetate and the ditrifluoroacetate is obtained. The reactions involved here are ester interchange reactions.[1] The ditrifluoroacetate requires glycol for equilibration, but the monotrifluoroacetate has both the ester and alcohol function and can react with itself. The reaction is probably particularly facile in this case because of the strong electron withdrawal from the carbonyl carbon atom by the trifluoromethyl group.

EXPERIMENTAL

Reaction of ethylene glycol with trifluoroacetic anhydride. Ethylene glycol (25.6 g.; 0.41 mole) was added, in several portions with shaking, to a cooled solution of trifluoroacetic anhydride (43 g.; 0.20 mole) in dry benzene (100 ml.). After standing overnight the reaction mixture was distilled at atmospheric pressure through a Vigreux column; yield, 52 g.; b.p., 150–155°; n_D^{25}, 1.3487. After redistillation this product had b.p., 151–152°; n_D^{25}, 1.3450; saponification equivalent found, 144, 145. The same procedure with just one equivalent of the glycol gave 41 g. of product; b.p., 151–152°; n_D^{25}, 1.3330; saponification equivalent, 135.

1,2-Bis(trifluoroacetoxy)ethanol. A large excess of trifluoroacetic anhydride (90 g.; 0.43 mole) was added slowly to ethylene glycol (5.5 g.; 0.08 mole) cooled in an ice bath. After standing overnight the mixture was distilled at atmospheric pressure; yield, 16.1 g. (79%); b.p., 152–154°; n_D^{25}, 1.3293. This product was dissolved in ether, washed with sodium bicarbonate solution, dried, and redistilled; b.p., 151–153°; n_D^{25}, 1.3286. Vapor phase chromatography indicated that this product contained at least 95% of one component, which had a retention time of 8.15 min.

Anal. Calcd. for $C_6H_4O_4F_6$: Sapon. equiv., 127. Found: Sapon. equiv., 124.

2-Trifluoroacetoxyethanol. Ethylene glycol (38 g.; 0.61 mole) was added with shaking to a cooled mixture of trifluoroacetic anhydride (43 g.; 0.20 mole) and *N,N*-dimethylaniline (18 g.; 0.15 mole) dissolved in dry benzene (100 ml.). Distillation at 10 mm. yielded 34.2 g. of crude product, b.p., 51–61°. This crude product was twice redistilled through a Vigreux column to yield finally 18.3 g. (58%) of 2-trifluoroacetoxyethanol; b.p., 48° at 8 mm.; n_D^{25}, 1.3520.

Anal. Calcd. for $C_4H_5O_3F_3$: Sapon. equiv., 158. Found: Sapon. equiv., 160.

Equilibration experiments. (1) 1,2-Bis(trifluoroacetoxy)-ethane (5 g.) was mixed with ethylene glycol (3.6 g.) and kept in an oil bath at 65° for 20 hr. The mixture was distilled directly, yielding 4 g. of product; b.p., 151–160°; n_D^{25}, 1.3548. This product was dissolved in ether. The ether solution was washed 3 times with water, dried over magnesium sulfate, and the ether was removed. Redistillation gave 3 g.; b.p. 149–151°; n_D^{25}, 1.3445.

In a typical experiment starting with 2-trifluoroacetoxyethanol, 10 ml. of the monoester was treated as indicated below and then divided by distillation into 3 arbitrary fractions of approximately 3 ml. each and a residue. During the distillation the bath temperature was not permitted to exceed 75°. In a control experiment, in which the monoester received no prior treatment, the successive fractions obtained had the following indices at 25°: 1, 1.3510; 2, 1.3535; 3, 1.3534; 4, 1.3545.

(2) The monoester was heated in a sealed tube at 150° for 2 hr. Distillation, as above, gave fractions having the following indices at 25°: 1, 1.3382; 2, 1.3390; 3, 1.3485; 4, 1.3650.

(3) Distillation of the monoester at atmospheric pressure without prior treatment, gave fractions having the following indices at 25°: 1, 1.3468; 2, 1.3488; 3, 1.3508; 4, 1.4150.

(4) Treatment of the monoester with a trace of sodium for 20 hr. at room temperature resulted in the following fractions: 1, 1.3495; 2, 1.3500; 3, 1.3512; 4, 1.3528. In this case the fourth fraction was obtained by distilling to dryness since the sodium salt was insoluble.

Treatment of the monoester with a trace of *p*-toluenesulfonic acid for 20 hr. at room temperature gave fractions having the following indices of refraction at 25°: 1, 1.3490; 2, 1.3498; 3, 1.3512; 4, 1.3668.

In the vapor phase chromatography experiments, a Perkin-Elmer Model 154 instrument (column "A", 20 p.s.i. He) was used.

Acknowledgment. The authors are indebted to Mr. George H. Dorian, Yale University, for advice and assistance in the work involving vapor-phase chromatography.

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(1) M. Harfenist and R. Baltzly, *J. Am. Chem. Soc.*, **69**, 362 (1947); L. Farkas, O. Schächter, and B. H. Vromen, *J. Am. Chem. Soc.*, **71**, 1991 (1949).

Preparation of Dimethyl β-Ketoadipate

JEROME KORMAN

Received November 6, 1956

Although its use has been generally restricted to the preparation of substituted phenanthrene derivatives,[1,2] β-ketoadipic ester can be an important intermediate for the synthesis of many interesting compounds.

Numerous procedures for the preparation of the methyl and ethyl esters have appeared in the literature, but none is completely satisfactory.[3] In addition to poor yields all suffer the disadvantage of being quite lengthy, and require the preparation and purification of intermediates. The ester has been prepared by: (a) Acylation of the sodio deriva-

(1) J. C. Bardhan, *J. Chem. Soc.*, 1848 (1936).

(2) W. E. Bachmann and R. E. Holmen, *J. Am. Chem. Soc.*, **73**, 3660 (1951).

(3) An excellent critique and complete experimental data have been assembled by R. E. Holmen, Dissertation, The University of Michigan, 1948 (University Microfilm Publication No. 1173).

tive of acetoacetic ester with β-carbalkoxypropionyl chloride with subsequent removal of the acetyl group by ammonolysis;[4] (b) Acylation of the magnesium enolate of malonic ester with the same acid chloride, followed by decarbalkoxylation by thermal decomposition in the presence of β-naphthalenesulfonic acid;[5,6] and (c) Saponification and decarboxylation or cleavage of the acylated intermediate (prepared by any method above) to the β-ketoadipic acid, followed by esterification.[3]

While the magnesium enolate method (b) appears to be the most facile, this laboratory has never been able to realize the yields reported, nor were the results consistent. Successful decomposition of the tricarboxylic ester intermediate presented the most difficulty and in many cases only tar resulted.

It has been found that the desired compound can be readily prepared in quantity by employing the procedure for the synthesis of ethyl diacetylacetate.[7] In this particular case, the magnesium enolate of methyl acetoacetate and β-carbomethoxypropionyl chloride were used. The resulting intermediate was treated with gaseous ammonia as in method (a). In spite of the relatively low yield (38% over-all) the procedure has certain merits. No isolation of intermediate is required, and except for the final distillation, the preparation can easily be completed in one day. The method is quite satisfactory for the methyl ester; in one experiment using the corresponding ethyl esters only a 25% overall yield of diethyl β-ketoadipate was obtained. This was not investigated further.

EXPERIMENTAL[8]

Dimethyl β-ketoadipate. To 30 g. (1.23 moles) of magnesium metal turnings and 287 g. (2.47 moles) of methyl acetoacetate in 800 ml. of dry benzene was added all at once 565.8 g. (3.76 moles) of β-carbomethoxypropionyl chloride[9] and the mixture refluxed for 3.5 hr. on the steam bath. Provision was made for the removal of hydrogen chloride, which was evolved. During this time additions of fresh magnesium metal were made as follows: 7.5 g. after 1.5 hr. and 15 g. after 2.5 hr. After cooling, as much of the benzene solution as possible was decanted, and the residue treated with water and ether. The solutions were combined after filtering from unused magnesium. The separated organic layer was washed with water, 5% sodium bicarbonate solution, and finally with water, and dried over anhydrous sodium sulfate. The filtered solution was cooled to 0° and dry ammonia passed in for 40 min. After standing at room temperature for 30 min., the reaction mixture was washed with water until neutral and dried over anhydrous sodium sulfate. Removal of the solvent and distillation through a 30-cm. Vigreux column gave 174.5 g. (37.8%) of product boiling at 114–126°/0.8 mm. with most of the material distilling at 119–120° (reported 122° at 0.5 mm.[1]); n_D^{23} 1.4414. It gave a reddish-brown color with ferric chloride solution.

Anal. Calcd. for $C_8H_{12}O_6$: C, 51.06; H, 6.43. Found: C, 51.03; H, 6.45.

The *1-phenyl-3-(β-carbomethoxyethyl)-pyrazolone* was obtained in 70% yield upon heating an equimolar mixture of the adipic ester and phenylhydrazine on the steam bath for 2 hr. After recrystallization from a mixture of ethyl acetate and petroleum ether, it melted at 79–80°.

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.50; H, 5.79; N, 11.60.

Saponification and decarboxylation of a sample, and treatment of the resulting oil with semicarbazide hydrochloride, gave the semicarbazone of levulinic acid, m.p. 183–184.5° (reported 184–185°[1]).

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(4) *Cf.* ref. 1,3: P. Ruggli and A. Maeder, *Helv. Chim. Acta*, 25, 936 (1942); J. R. Stevens and R. H. Beutel, *J. Am. Chem. Soc.*, 65, 449 (1943); R. Robinson and J. S. Watt, *J. Chem. Soc.*, 1536 (1934).

(5) B. Riegel and W. M. Lilienfeld, *J. Am. Chem. Soc.* 67, 1273 (1945).

(6) Presumably acylation of *t*-butyl malonate and thermal decomposition in the presence of *p*-toluenesulfonic acid according to the method of D. S. Breslow, E. Baumgarten, and C. R. Hauser, *J. Am. Chem. Soc.*, 66, 1286 (1944) would be a source of product.

(7) A. Spassow, *Org. Syntheses*, Coll. Vol. III, 390 (1955).

(8) Melting points are uncorrected.

(9) J. Cason, *Org. Syntheses*, Coll. Vol. III, 169 (1955).

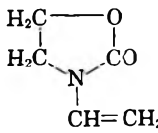
N-Vinyl-2-oxazolidone

ERHART K. DRECHSEL

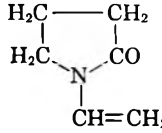
Received December 19, 1956

Widespread attention has been focused upon the rapid growth of the synthetic water-soluble polymer field.[1] In this connection, polyvinylpyrrolidone (PVP) has been given special recognition because of its original use as a blood plasma extender and because of its versatility in many industrial applications. Structurally related compounds are thus of considerable interest.

A recent German patent application[2] describes a process for the preparation of *N*-vinyl-2-oxazolidone and prompts a preliminary disclosure of our own research with this material. The structural similarity between this compound and *N*-vinyl-2-pyrrolidone is shown below:



N-vinyl-2-oxazolidone
(cyclic carbamate)



N-vinyl-2-pyrrolidone
(cyclic amide)

In spite of the structural similarity, these compounds and their polymers belong to different chemical families. The substitution of an oxygen atom for a methylene group within the heterocyclic ring (see formulas above) contributes an additional

(1) Symposia on Water-Soluble Polymers, Polymer and Cellulose Divisions, American Chemical Society, Dallas Meeting, April 8–13, 1956.

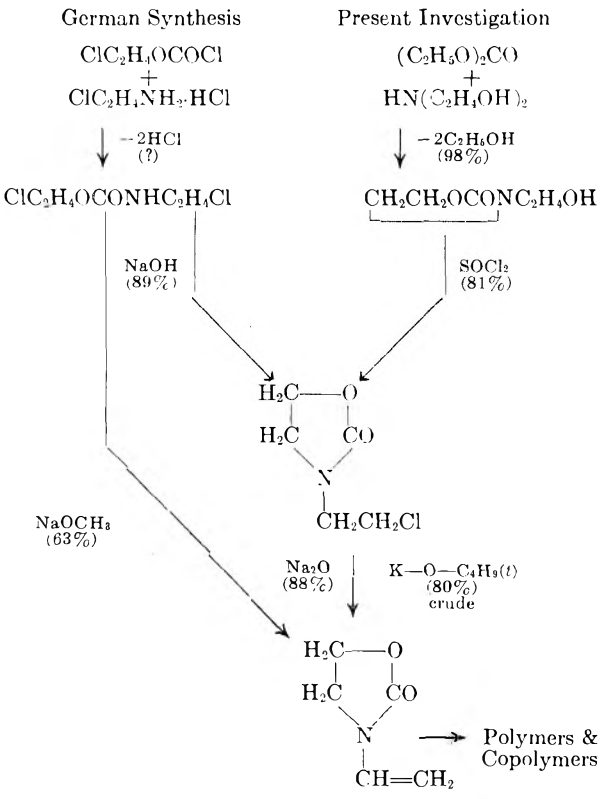
(2) W. Arend and H-G. Trieschmann, German Patent application Klasse 12p Gruppe 3, B340321Vb/12p; Filed 1/8/55, Published 3/29/56.

TABLE I

Compound (Where R Is)	2-Oxazolidone $CH_2CH_2OCON-R$ B.p.	Mm.	n_D^{25}	Ref.	2-Pyrrolidone $CH_2CH_2CH_2CON-R$ B.p.	Mm.	n_D^{25}	Ref.
—H	200°	21		(4)	245°	760	1.486	(5)
	(M.p. 90–91°)			(3)	(M.p. 25°)			(5)
$-C_2H_4OH$	162°	1.0	1.482		142–143°	2.3		(6)
$-C_2H_4Cl$	100°	0.1	1.490		118–119.5°	7.0		(6)
$-CH=CH_2$	70°	0.1	1.494		94–96°	13–14	1.510	(7)
	100–105°	1.3		(2)	148°	100		(7)
	(M.p. *ca.* −15°)				(M.p. 13.5°)			(7)
$[-CH(-)-CH_2-]_n$	Polymers and copolymers are readily formed. Homopolymers are water-soluble. Homopolymers are complexing agents.							

pair of unshared electrons to the molecular structure and provides a basis for differences in chemical and physical properties. Moreover, hydrolysis of the polymers leads to entirely dissimilar products; *e.g.*, polyvinyloxazolidone (PVO) yields an ethanolamine derivative while PVP yields a γ-aminobutyric acid derivative. The properties of both monomers and their key intermediates, together with qualitative polymer characteristics, are shown in Table I; infrared data on the oxazolidone derivatives are shown in Fig. 2.

FIG. 1



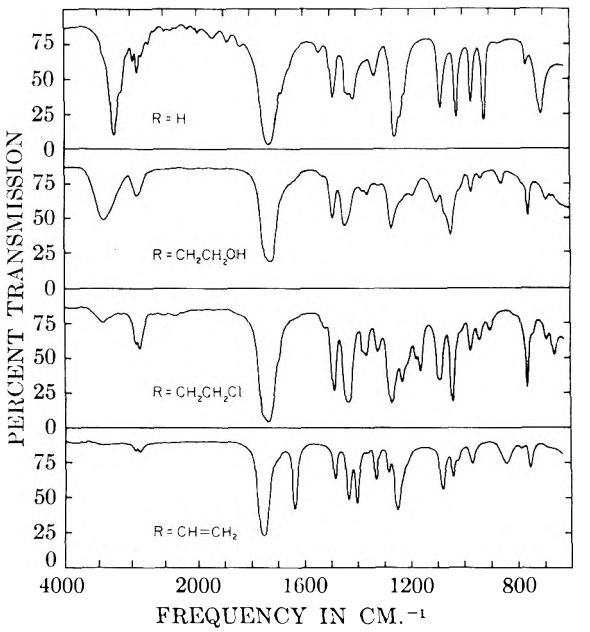


FIG. 2. INFRARED SPECTRA OF KEY OXAZOLIDONE INTERMEDIATES, $CH_2CH_2OCON-R$

Inspection of the vinyloxazolidone structure indicates several possible synthetic routes based upon readily available raw materials. Unfortunately, several attempts at direct vinylation of the parent oxazolidone heterocycle with acetylene were unsuccessful. This observation is confirmed by the German application.

The synthesis of *N*-vinyl-2-oxazolidone herein reported was developed some time ago and in some respects parallels a laboratory synthesis for *N*-vinyl-2-pyrrolidone.[6] The relationship between our method for preparing *N*-vinyl-2-oxazolidone and the German one is shown in Figure 1.

(3) S., Gabriel, *Ber.*, **21**, 568 (1888); *Beilstein* **27**, 135 (259).
(4) L. Knorr, and P. Rössler, *Ber.*, **36**, 1281 (1903).
(5) General Aniline & Film Data Sheet B-105 (August 1953).
(6) B. Puetzer, *et al.*, *J. Am. Chem. Soc.*, **74**, 4959 (1952).
(7) General Aniline & Film Data Sheet B-104 (August 1954).

EXPERIMENTAL

N-(2'-Hydroxyethyl)-2-oxazolidone. To 472 g. (4.0 moles) of diethyl carbonate under agitation 420 g. (4.0 moles) diethanolamine was slowly added. The resulting reaction mixture was then heated to reflux and ethanol taken off using a 10-in. column packed with refractory material and fitted with a variable take-off head. In this way, 84% of the ethanol was stripped out with a pot temperature mainly between 110°–120°, and gradually rising to 135°. The remaining ethanol was separated using reduced (aspirator) pressure. The crude product was treated with finely divided decolorizing carbon and filtered hot to yield 513 g. (98.0%) of clear, light-colored *N*-(2'-hydroxyethyl)-2-oxazolidone.

This product was quite suitable for use in subsequent reactions. Initial batches readily distilled at 162°/1.0 mm., n_D^{25} 1.4823; but later runs demonstrated a tendency to decompose during distillation. These data compare favorably with those reported in the patent literature.[8,9]

Anal. Calcd. for $C_5H_9O_3N$: C, 45.79; H, 6.92; N, 10.68; Hydroxyl value, 429. Found: C, 45.81; H, 6.89; N, 10.84; Hydroxyl value 428.7.

N-(2'-Chloroethyl)-2-Oxazolidone. A total of 238 g. (2.0 moles) thionyl chloride was gradually added to 262 g. (2.0 moles) *N*-(2'-hydroxyethyl)-2-oxazolidone in 200 ml. dry benzene over a 3-hr. period at 30 ± 5°. The use of an efficient Friedrichs condenser throughout the reaction period is strongly recommended since any thionyl chloride losses give an incomplete reaction and amplify isolation problems. The clear, amber-colored solution resulting from an originally cloudy dispersion was strongly acidic. Even though a slow stream of nitrogen was passed through the reaction mixture overnight, almost a full equivalent of sodium bicarbonate was required for complete neutralization (HCl complex with oxazolidone heterocycle?). The filtrate resulting from the products of this neutralization was combined with additional benzene washings of the sodium chloride salt, clarified with finely divided decolorizing carbon, and stripped of solvent to yield 241 g. (80.6%) of a light amber-colored liquid *N*-(2'-chloroethyl)-2-oxazolidone. This material was readily distilled, b.p. 100°/0.1 mm., n_D^{25} 1.4900.

Anal. Calcd. for $C_5H_8O_2NCl$: C, 40.15; H, 5.39; N, 9.37; Cl, 23.70. Found: C, 39.48; H, 5.45; N, 9.46; Cl, 24.65. Excess Cl equivalent to 1.39% (combined?) HCl.

N-Vinyl-2-oxazolidone. To a previously prepared solution of potassium *tert*-butoxide[10] in *tert*-butanol, made by reacting 40 g. (1.02 moles) potassium metal with 700 ml. dry *tert*-butanol, 150 g. (1.002 moles) *N*-(2'-chloroethyl)-oxazolidone was added slowly over a 2.5-hr. period. The initial exothermic reaction carried the temperature from 60° to 85° (reflux), and this latter temperature was maintained during most of the addition period. Reflux was then continued for an additional 20 hr. when a titration indicated the reaction to be 88% complete. The reaction slurry was then filtered and the solid potassium chloride thoroughly washed with additional solvent. Combined washings and filtrate were then treated with finely divided decolorizing carbon, and stripped of solvent to yield 90 g. (79.6%) of crude, amber-colored *N*-vinyl-2-oxazolidone. This liquid readily distilled at 70°/0.1 mm., n_D^{25} 1.4939. A cooling bath indicated the m.p. of this distilled product to be approximately −15°. An infrared curve showed strong absorption at 1620 cm.$^{-1}$ characteristic of the CH_2=CH— group.

Anal. Calcd. for $C_6H_7O_2N$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.54; H, 6.46; N, 12.42.

Homopolymerization of N-vinyl-2-oxazolidone. To a solution of 20 g. of *N*-vinyl-2-oxazolidone in 80 g. of xylene was added 0.60 g. (3% on weight of monomer) of α,α'-azobisisobutyronitrile (catalyst). The resulting clear solution was heated on a steam bath (95°) under a reflux condenser for 3 hr. The white solid polymer which precipitated from solution during the heating period was filtered and washed thoroughly with fresh xylene. After drying under reduced pressure, the poly(*N*-vinyl-2-oxazolidone) weighed 14.1 g. (70.5%). The dried material was found to be water soluble. The molecular weight of this polymer was about 1250 by microisopiestic measurements. Infrared confirmed the structure as that of poly(*N*-vinyl-2-oxazolidone).

Additional *N*-vinyl-2-oxazolidone polymerizations have indicated that homopolymers with molecular weights ranging from 450 to over 100,000 can be formed. All of the products were water soluble, white solids

Additional polymerization characteristics of N-vinyl-2-oxazolidone. Exposure of N-vinyl-2-oxazolidone monomer droplets to air gave clear, solid, orange-colored beads after several days' exposure. *N*-vinyl-2-oxazolidone when heated to 80° in the presence of benzoyl peroxide gave dark viscous liquids. Using the same conditions, α,α'-azobisisobutyronitrile gave clear, tough, orange-colored, water soluble glasses.

When a solution of one part *N*-vinyl-2-oxazolidone in four parts acrylonitrile was heated to 80° in the presence of α,α'-azobisisobutyronitrile, a vigorous evolution of heat resulted. The product, in part, was a rubbery, colorless, translucent mass which was water insoluble.

NEW PRODUCT DEVELOPMENT DEPARTMENT
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(8) J. R. Caldwell, U. S. Patent 2,656,328 Ex. 3 (1953); *Chem. Abstr.*, 48, 2415 (1954).

(9) J. B. Bell, and J. D. Malkemus, U. S. Patent 2,755,286 Ex. IV & V (1956).

(10) S. M. McElvain and A. N. Bolstad, *J. Am. Chem. Soc.*, 73, 1988 (1951).

Lithium Cleavages of Some Heterocycles in Tetrahydrofuran

HENRY GILMAN AND JOSEPH J. DIETRICH

Received December 13, 1956

Cleavages of heterocycles using various media and cleaving agents has often proved to be a valuable tool in synthesis and structure proof.

Using lithium in refluxing ether over a period of 22 hr., there were obtained excellent yields of 3,4-benzocoumarin from dibenzofuran when the reaction was terminated by carbonation. When refluxing dioxane was used as the solvent, only 2-hydroxybiphenyl was obtained upon hydrolysis or carbonation after 12 hr.[1]

Dibenzo-*p*-dioxin has been cleaved by lithium in refluxing ether after 24 hr. to yield upon carbonation 23% of 2-hydroxy-2'-carboxydiphenyl ether.[2] This molecule could presumably be cleaved in refluxing dioxane.

In refluxing ether lithium does not cause the cleavage of dibenzothiophene even after 36 hr. However, dibenzothiophene can be cleaved by lithium in refluxing dioxane over a period of 12 hr. to yield biphenyl and 2-mercaptobiphenyl

(1) H. Gilman and D. Esmay, *J. Am. Chem. Soc.*, 75, 2947 (1953).

(2) Unpublished studies.

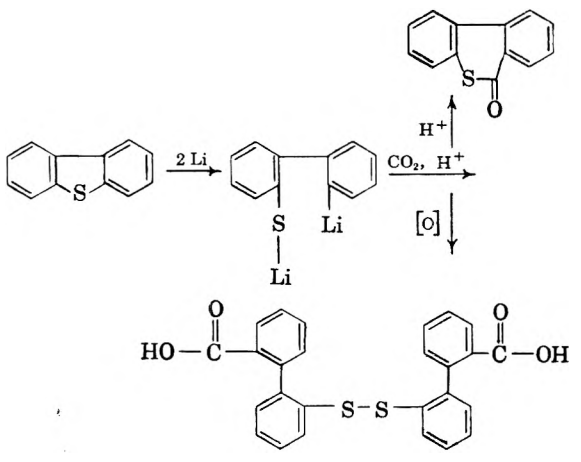
after hydrolysis or carbonation.[1] This again demonstrates the destructive nature of refluxing dioxane on organometallic compounds.

Attempts to cleave *N*-ethylcarbazole with lithium in refluxing dioxane have resulted in essentially quantitative recovery of starting material after 24 hr.[3] The cleavage was not attempted in ether, but a negative result may be a fairly safe assumption. Carbazole gave the same results under identical conditions.[3]

Using purified tetrahydrofuran all of the aforementioned compounds have undergone cleavage with significant ease. In all cases the reactions were exothermic giving rise to a dark blue-green color. Color Test I[4] was usually positive within 2 min. after the reactants were mixed. In many instances, the dark blue-green color gradually turned to a dark brown. For comparison purposes, the reactions were all run for 45 min. and then either hydrolyzed or carbonated.

Dibenzothiophene and dibenzo-*p*-dioxin reacted completely during the alloted time. Both reactions approached the reflux temperature of tetrahydrofuran if they were not controlled.

Dibenzo-*p*-dioxin gave the normal products upon carbonation in better yield than the corresponding diethyl ether cleavage, but dibenzothiophene produced 3,4-benzothiocoumarin and the disulfide of 2-mercapto-2′-carboxybiphenyl. These are probably formed from the 2-mercapto-2′-carboxybiphenyl during the work-up. A small amount of biphenyl was also obtained from the uncontrolled reactions of dibenzothiophene. A postulated reaction sequence for dibenzothiophene is as follows:[1]



A maximum yield of cleavage products was realized at 25° for dibenzothiophene and dibenzo-*p*-dioxin, using an ice bath to moderate the reactions.

In the case of dibenzofuran, it was best to use a higher temperature since a 75% recovery of starting material resulted at 25°. The uncontrolled reactions which warmed up to 40–50° gave a 20% yield of 3,4-benzocoumarin after carbonation.

Cleavage of thianthrene at 25° with lithium yielded no identifiable products, but most of the starting material was in the form of an unpleasant smelling, acidic oil after carbonation. This evidence plus the fact that Color Test I was positive can only be reconcilable with cleavage of this heterocycle. Using refluxing diethyl ether as the solvent, 72% of thianthrene was recovered even though Color Test I was positive after 1 hr.

No products have been identified from the lithium cleavage of *N*-ethylcarbazole in tetrahydrofuran. Some cleavage was certain though, since only 75% of the starting material was recovered after 45 min. of refluxing and Color Test I was positive. Some of the recovered oils showed an N—H band on their infrared spectra. Lithium in refluxing tetrahydrofuran for 45 min. failed to cleave carbazole, giving a 90% recovery of starting material.

It is interesting to note that while dibenzofuran cleaved rather easily in ether, dibenzothiophene resisted cleavage under these conditions. However, in tetrahydrofuran, dibenzothiophene gave the best yield of cleavage product at 25° whereas dibenzofuran was appreciably cleaved only at higher temperatures.

A noteworthy deviation from heterocycles was the cleavage of diphenyl ether to yield phenol, benzoic acid, and 2-carboxydiphenyl ether after carbonation. The last product may be accounted for by assuming metalation of the diphenyl ether by phenyllithium obtained by cleavage of the diphenyl ether.

EXPERIMENTAL[5]

The tetrahydrofuran used in all the experiments was purified by shaking with sodium hydroxide, drying over sodium metal, and finally distilling from lithium aluminum hydride prior to every reaction. A nitrogen atmosphere was always used.

Lithium cleavage of dibenzo-p-dioxin. Run I. To 50 ml. of tetrahydrofuran in a 500 ml. flask was added 9.2 g. (0.05 mole) of dibenzo-*p*-dioxin and 1 g. (0.15 g. atom) of lithium (1/8″ pieces of wire) at room temperature. A brown color immediately appeared and Color Test I was positive after 2 mins. The reaction was allowed to proceed without cooling for 45 min. at which time the reaction mixture was carbonated by pouring into a dry ice–ether slurry. Work-up resulted in 3.7 g. (32%) of 2-hydroxy-2′-carboxydiphenyl ether as white needles, m.p. 127–129° from petroleum ether–benzene; 0.4 g. of unidentified phenolic material, m.p. 192–195° from ethanol; and 0.5 g. of crude neutral material.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.82; H, 4.35; neut. equiv., 230. Found: C, 67.87, 67.86; H, 4.45, 4.46; neut. equiv., 228.

Run II. This time the temperature was controlled at 25°. Work-up, after carbonation, gave 6 g. (56%) of 2-hydroxy-2′-carboxydiphenyl ether and 0.5 g. of unidentified phenolic material.

(3) H. Gilman, J. B. Honeycutt, Jr., and R. Ingham, *J. Org. Chem.*, 22, 338 (1957).

(4) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, 47, 2002 (1925).

(5) All melting points are uncorrected. The petroleum ether used had b.p. 60–70°.

Lithium cleavage of dibenzothiophene. Several runs, all resulting in the same products, proved 25° to be a very effective temperature. If the temperature were allowed above 50° a small amount of biphenyl was found in the neutral ether layer.

In a 500 ml. flask was placed 50 ml. of tetrahydrofuran, 9.2 g. (0.05 mole) of dibenzothiophene, and 2 g. (0.3 g. atom) of lithium. The reaction started immediately but was kept at 25° for 45 min. and then carbonated. Subsequent work-up yielded a trace of biphenyl (identified by method of mixture melting point) from the neutral layer and 4.7 g. (48%) of 3,4-benzothiocoumarin as white needles from ethanol-water, m.p. 131–133°.

Anal. Calcd. for $C_{13}H_8OS$: S, 15.09. Found: S, 15.12. A small amount (0.4 g.) of the disulfide of 2-mercapto-2′-carboxybiphenyl was also obtained as white plates from ethanol, m.p. 264–266°.

Anal. Calcd. for $C_{26}H_{18}O_4S_2$: S, 13.97; neut. equiv., 229. Found: S, 13.97, 14.02; neut. equiv., 228.

Lithium cleavage of dibenzofuran. Fifty milliliters of tetrahydrofuran was added to 8.4 g. (0.05 mole) of dibenzofuran and 1 g. (0.15 g. atom) of lithium. The reaction was allowed to proceed for 45 min. without cooling and then carbonated to produce 1.5 g. (20%) of 3,4-benzocoumarin from methanol-water, m.p. 93.5–96° (reported[6] m.p. 94–95°).

The same reaction when terminated by hydrolysis yielded 2 g. (23%) of 2-hydroxybiphenyl (identified by method of mixture melting point) melting over the range of 54–58° from petroleum ether.

Lithium cleavage of thianthrene. This was carried out at 25° for 45 min. using 10.4 g. (0.05 mole) of thianthrene, 2 g. (0.3 g. atom) of lithium, and 50 ml. of tetrahydrofuran. The reaction was terminated by carbonation to produce 10 g. of unpleasant smelling, acidic oil which could not be identified. Only a trace of neutral material was recovered. An attempt to convert the acidic oil to a solid disulfide through a reaction with iodine in absolute ethanol was unsuccessful.

Lithium cleavage of N-ethylcarbazole. By refluxing 19.4 g. (0.1 mole) of *N*-ethylcarbazole, 2 g. (0.3 g. atom) of lithium, and 50 ml. of tetrahydrofuran for 1 hr., it was possible to obtain a positive Color Test I. However, carbonation, hydrolysis, or addition of this reaction mixture to benzophenone has not given an identifiable product. The usual recovery of starting material was about 75% with the remainder being presumably cleaved material.

Lithium cleavage of carbazole. The same conditions were used as with *N*-ethylcarbazole. No color change occurred and Color Test I was never positive. There was a 90% recovery of starting material.

Lithium cleavage of diphenyl ether. A mixture of 8.5 g. (0.05 mole) of diphenyl ether, 1 g. (0.15 g. atom) of lithium, and 50 ml. of tetrahydrofuran was allowed to react without cooling for 30 min. The reaction mixture gradually turned brown and Color Test I was positive after 10 min. After 30 min. the reaction mixture was carbonated. The products isolated consisted of phenol which was isolated as the 2,4,6-tribromophenol from ethanol, m.p. 93–96°; benzoic acid which was obtained by vacuum sublimation, m.p. 120–124°; and 2-carboxydiphenyl ether which remained as the residue after vacuum sublimation, m.p. 111–113°. All of the the products were verified by mixture melting points and infrared spectra.

Acknowledgment. The authors are indebted to E. M. Layton, Jr., of the Institute of Atomic Research for infrared spectra. This work was supported in part by the United States Atomic Energy Commission under Contract No. AT(11-1)-59.

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(6) R. Cahn, *J. Chem. Soc.*, 1400 (1933).

Chemistry of Unsaturated Lactones. I. Reaction of Oxazolones with Phenylmagnesium Bromide

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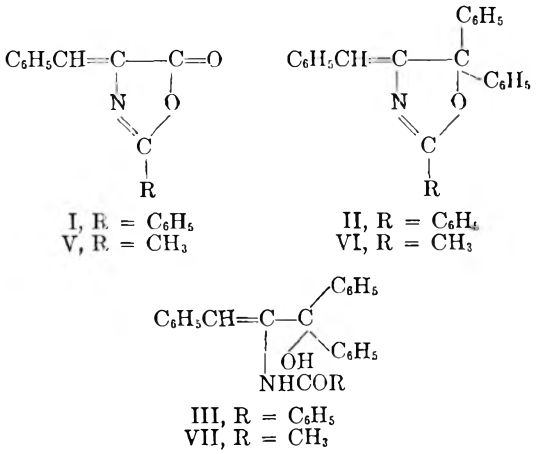
Received November 14, 1956

It has been shown[1] that 2-phenyl-4-methyl-5(4*H*)oxazolone reacts with excess phenylmagnesium bromide to form 1,1-diphenyl-2-benzamido-1-propanol. Recently, Pourrat[2] and Mustafa and Harhash[3] reported the reaction of unsaturated azlactones with this Grignard reagent. The results of these investigators differed in several instances. Thus Pourrat[2] found that 2-phenyl-4-benzylidene-5(4H)-oxazolone (I) reacted with excess phenylmagnesium bromide to give a mixture of 2,5,5-triphenyl-4-benzylidene-2-oxazoline (II) and 1,1-diphenyl-2-benzamidocinnamyl alcohol (III) in the ratio of 3:1.

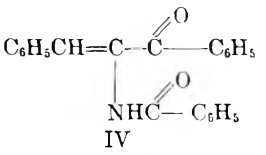


II and III were separated by means of elution chromatography on alumina. Mustafa and Harhash found, however, that III was the exclusive product of this reaction. III was converted by acetic acid-hydrochloric acid into a substance whose structure was tentatively assigned that of the oxazoline II. However the melting points of II and III differed markedly from those given by Pourrat. The structure proposed for II was based on elemental analysis and its yellow color, while the structure of III was inferred by its analysis and by the fact that it contained two active hydrogens.

We have studied this reaction in detail and have observed that the nature of the products is dependent upon the reaction conditions. When I was treated with phenylmagnesium bromide in a 1:1 molar ratio, using inverse addition, the reaction was very sluggish and most of the azlactone

(1) Cornforth in *The Chemistry of Penicillin*, Princeton University Press, Princeton, N. J., 1949, p. 738.
(2) Pourrat, *Bull. soc. chim. France*, 828 (1955).
(3) Mustafa and Harhash, *J. Org. Chem.*, 21, 575 (1956).

was recovered unchanged. However, a small amount of a colorless substance IV was isolated. IV is believed to be α-benzamidobenzalacetophenone. The structural assignment is based on elemental analysis, and its ultraviolet and infrared spectra.



IV

IV exhibits three maxima in the ultraviolet. The short wave length, high intensity K band of the conjugated system is found at 229 mμ (ε20,400), in close agreement with the value predicted by Woodward's rule.[4] The longest wave-length band at 296–299 mμ (ε15,700) may be attributed to the cinnamoyl system.[5a] The middle band maximum at 257 mμ (ε15,700) is probably due to the benzoyl or acrylophenone groups[5a] which behave as independent chromophores due to steric interference toward coplanarity brought about by the presence of the α-benzamido group. The styrylamine system may also make an important contribution.[5b] The infrared spectrum of IV shows absorption at 1660 cm.$^{-1}$ (probably due to C=O stretching in an α,β-unsaturated diaryl ketone),[6] 3250 cm.$^{-1}$ (due to —NH— stretching) and 1645 cm.$^{-1}$ and 1525 cm.$^{-1}$ (the amide I and II bands).[6] It is not possible with the available data definitely to assign the geometric configuration to IV. However, if based on the tentative assignment of configuration for the oxazolone,[7] the phenyl and benzoyl groups would be *trans* to each other.

When a suspension of I in ether or benzene was added to excess (3:1 molar ratio) phenylmagnesium bromide, the product isolated appeared to be primarily determined by a dilution factor. When we were unable to get consistent results and noted the conflicting reports of the other investigators, we examined the possibilities of temperature, solvent, and concentration factors. The course of the reaction was independent of the temperature or whether the azlactone was suspended in ether or benzene, but was markedly influenced by the total volume of solvent used. At relatively high dilution (as also used by Mustafa) the predominant product was III, in yields of 65 – 70%, m.p. 163–164°. This melting point is somewhat higher than that given by Mustafa (156°), but lower than the 174° reported by Pourrat. A small amount of gummy brown product was also isolated, but not identified. This may have been the oxazoline II. When the volume of solvent was considerably reduced, II, containing a small quantity of III, was obtained in over 80% yield. It was difficult to remove the last traces of III by fractional crystallization and elution chromatography on alumina was employed as mentioned earlier. The melting point was raised above that reported by Pourrat, but differed significantly from the product obtained by Mustafa and Harhash. We were unable to repeat their work, but we did obtain a mixture of II and III by heating II with acetic anhydride.

The favoring of an open chain compound at high dilution in the reaction of a Grignard reagent with a lactone has been previously described by Kohn.[8,9] Thus, α,γ-dihydroxy-α,γ-dimethylvaleric acid γ-lactone reacted with three equivalents of phenylmagnesium bromide to give the tetrahydrofuran derivative whereas the trihydroxy, open-chain product, was isolated at very high dilution.

The structure previously proposed for III is supported by its infrared spectrum which exhibited absorption at 1667 cm.$^{-1}$ and 1525 cm.$^{-1}$ (amide I and II bands), 3270 cm.$^{-1}$ (—NH— stretching) and 3475 cm.$^{-1}$ (OH stretching).[6] The conversion of III to a mixture of II and III also tends to favor this structure. There was no indication of the formation of a 1,4-addition product as might have been expected when one considers the normal preference of the reagent towards this mode of addition.[10,11a] Lutz[11a] has shown that phenylmagnesium bromide forms 1,4 addition products with both *cis* and *trans* α- phenylchalcones. The effect of an α-benzamido group on addition reactions to α,β-unsaturated systems has not been evaluated, though ethyl α-benzamido cinnamate reacted with the phenyl Grignard reagent to give only III.[3] While it is possible in the reaction we have studied that the geometric isomerism may be such as to offer steric resistance to 1,4-addition, a more important factor operating against such addition may be the electron-donating effect of the nitrogen atom.[11b]

The suggested structure for II is given support by the formation of a methochloride, by the presence of a medium intensity band at 1660 cm.$^{-1}$ (probably due to >C=N—)[6] and the absence of —OH, —NH, and amide absorptions, and by its ultraviolet spectrum. Two maxima were observed. The first, at 341 mμ (ε 15,200), may be attributed to the $C_6H_5CH{=}C{-}N{=}C$ chromophore.[12] The oxazolone I, which bears the same chromophore, exhibits a maximum at 361 mμ, but this bathochromic shift is enhanced by cross-

(4) Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941); **64**, 72, 76 (1942).

(5a) Black and Lutz, *J. Am. Chem. Soc.*, **77**, 5134 (1955).

(5b) The possible contribution of the styrylamine system was cited by one of the referees.

(6) Bellamy, *The Infrared Spectra of Complex Molecules*, J. Wiley and Sons, Inc., New York, N. Y. (1954).

(7) Buckles, Filler, and Hilfman, *J. Org. Chem.*, **17**, 233 (1952).

(8) Kohn, *Monatsh.*, **34**, 1729 (1913).

(9) Kohn and Ostersetzer, *Monatsh.*, **37**, 37 (1916).

(10) Kohler, *Am. Chem. J.*, **36**, 177, 511 (1906).

(11a) Lutz and Rinker, *J. Am. Chem. Soc.*, **77**, 366 (1955).

(11b) This suggestion was made by one of the referees.

conjugation, which is absent in I. The second maximum at 241 mμ (ε 22,800) may be due to partial chromophores such as $C_6H_5CH{=}C<$ and $C_6H_5C{=}N{-}$.[12]

We are unable at this time to resolve the differences between our results and those of Mustafa[3] with regard to II. Geometric isomerism may be involved. A number of such isomeric pairs in similar compounds[13–15] have been isolated. Further work toward elucidating the structures of these compounds is in progress.

2-methyl-4-benzylidene-5(4*H*)oxazolone (V) reacted with excess phenylmagnesium bromide to give the tertiary alcohol VII as previously reported by Pourrat,[2] though no structure proof was presented. However, we found that its infrared spectrum and its quantitative conversion by acetic anhydride to VI, substantiated this assignment. The structure of VI was inferred by its color, elemental analysis and infrared spectrum.

EXPERIMENTAL[16]

Reaction of 2-Phenyl-4-benzylidene-5(4H)-oxazolone with excess phenylmagnesium bromide. (a) High dilution. To 3.65 g. (0.15 g. atom) of magnesium turnings in 50 ml. anhydrous ether was added dropwise 23.6 g. (0.15 mole) of bromobenzene in 65 ml. of dry ether. To this Grignard reagent was added in portions over a period of 1 hr., 12.5 g. (0.05 mole) of 2-phenyl-4-benzylidene-5(4*H*)-oxazolone suspended in 250 ml. of ether. The reaction mixture was heated under reflux with stirring for an additional 1.5 hours and then decomposed with either a 10% solution of sulfuric acid or a saturated solution of ammonium chloride. The yellow-white product was insoluble in both ether and water and precipitated. The yellow-white product was insoluble in both ether and water and precipitated. The crude product was recrystallized twice from benzene to give 12.2 g. (66% yield) of small white needles, m.p. 163–164°. On evaporation of the ether layer about 5 g. of a brown amorphous material was obtained which could not be readily crystallized.

Anal. Calcd. for $C_{28}H_{23}NO_2$: C, 82.94; H, 5.72; N, 3.45. Found: C, 82.87; H, 5.60; N, 3.31.

When the material was heated with acetic anhydride and sodium acetate, a yellow-brown product, melting range 140–160°, was obtained.

(b) Lower dilution. When this Grignard reaction was carried out using a total solvent volume of about 150 ml., a bright yellow product was obtained, which was soluble in benzene and fairly soluble in ether. This material was crystallized from a 70–30 volume % mixture of ethanol and water to give small yellow plates, m.p. 141–144°. This melting point could not be raised by repeated crystallization. Elution chromatography on alumina using ether as eluant, raised the melting point of most of the crystals to 161–163° but some lower melting crystals were also obtained. The crude yield of oxazoline was 83%.

Anal. Calcd. for $C_{28}H_{21}NO$: C, 86.79; H, 5.46; N, 3.62. Found: C, 86.83; H, 5.73; N, 3.55.

Heating of the oxazoline with dimethyl sulfate and treatment of the resulting solution with 6*N* HCl yielded the *methochloride* as a gray precipitate which was crystallized from glacial acetic acid to give a white product, m.p. 108–111°.

Anal. Calcd. for $C_{29}H_{24}ClNO$: C, 79.53; H, 5.52. Found: C, 80.07; H, 5.30.

Reaction of the oxazolone with phenylmagnesium bromide in a 1:1 molar ratio using inverse addition. In a 500-ml., 3-necked flask was placed 12.5 g. (0.05 mole) of oxazolone suspended in 50 ml. dry ether. An ether solution of phenylmagnesium bromide, prepared from 1.22 g. (0.05 g. atom) magnesium turnings and 7.9 g. (0.05 mole) bromobenzene was then added dropwise with stirring. After addition was complete, the mixture was decomposed with dilute sulfuric acid. The ether was removed and the solid residue dissolved in hot ethanol. About 200 ml. of water was added and the oxazolone precipitated. The milky suspension was digested by heating and the product collected. After crystallization from benzene, about 1 g. of white product, m.p. 144–145°, was obtained.

Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23. Found: C, 80.45; H, 5.21.

2-Methyl-4-benzylidene-5(4H)oxazolone with excess phenylmagnesium bromide. Using a procedure similar to that described for the 2-phenyl analog at high dilution, a white product, m. 144–146°, was obtained.[17]

Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.39; H, 6.09; N, 4.09.

When this compound was heated with acetic anhydride and sodium acetate, light yellow needles, m.p. 95–96°, were isolated.

Anal. Calcd. for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 84.33; H, 5.70; N, 4.24.

Spectral measurements. The infrared spectra were obtained on a Baird Associates infrared double beam recording spectrophotometer equipped with a rock-salt prism. The samples were examined either as Nujol mulls or by use of a KBr disk.

The ultraviolet spectra were determined with a Beckman DU spectrophotometer. 95% ethanol was used as solvent.

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(12) Bassi, Doulofeu, and Ortega, *J. Am. Chem. Soc.*, **75**, 171 (1953).

(13) Carter and Risser, *J. Biol. Chem.*, **139**, 255 (1941).

(14) Larsen and Bernstein, *J. Am. Chem. Soc.*, **72**, 4447 (1950).

(15) Gagnon and Charette, *Can. J. Research*, **19B**, 275 (1941).

(16) All m.p.'s were determined on a Fisher-Johns block and are corrected.

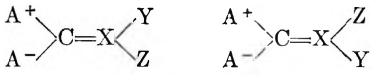
(17) Pourrat[2] reported m.p. 149° (uncorr.) for this compound.

Communications TO THE EDITOR

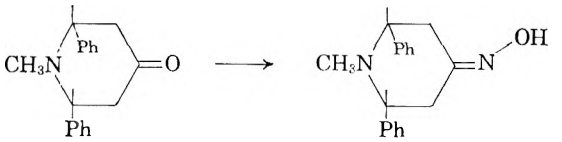
A Novel Type of Molecular Asymmetry

Sir:

Since the proposal by Van't Hoff and Le Bel in 1874 that the bonds of the quadricovalent carbon atoms form a perfect tetrahedron, the existence or absence of optical isomerism has been predicted for many unusual types of organic compounds.[1] Many of these predictions have been confirmed by the synthesis of and success or failure to resolve model compounds.[2] This communication describes the synthesis and resolution of enantiomorphs of an unsymmetrical molecule whose asymmetry is due to the *cis-trans* relationship of a substituent with respect to two similar asymmetrical carbon atoms having opposite configuration.[3]



Compounds which show geometrical enantiomorphic isomerism can be prepared by creating an unsymmetrically substituted double bond in a central location in a *meso* isomer. This was achieved by forming the oxime of the *meso* form of 2,6-diphenyl-1-methyl-4-piperidone (I).



I (meso) II (d or l)

2,6-Diphenyl-1-methyl-4-piperidone (I) was prepared by the condensation of dibenzylacetone with methylamine[4] and was obtained as a single modification. An attempt to resolve the ketone failed, and reduction of I with lithium aluminum hydride and catalytic hydrogenation led to two isomeric *meso* alcohols indicating that the ketone was the *meso* form. Catalytic hydrogenation of I produced α-2,6-diphenyl-1-methyl-4-piperidinol, m.p. 155–156.5° (calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92. Found: C, 80.86; H, 7.71). Reduction of I with lithium aluminum hydride led to β-2,6-diphenyl-1-methyl-4-piperidinol, m.p. 170–172.5° (calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92. Found C, 81.03; H, 8.02). A mixture of the two isomers melted 151–154°. Equilibration of the α-alcohol with sodium amyloxide gave a mixture containing both the α- and β-alcohols. Reduction of I with sodium in a solution of amyl and ethyl alcohols led to decomposition of the ketone by reversal of the aldol condensation.

The oxime (II)[5] of 2,6-diphenyl-1-methyl-4-piperidone, m.p. 194–196°, was converted to the *d*-10-camphor sulfonic acid salt (oxime salt: calcd. for $C_{28}H_{36}N_2O_5S$: C, 65.60; H, 7.08. Found: C, 65.67; H, 7.43). After three recrystallizations from methanol-ether, the more dextrorotatory isomer of the salt was obtained in pure form, m.p. 172–174° (dec.), $[\alpha]_D^{25}$ + 30.1° (calcd. for $C_{28}H_{36}N_2O_5S$: C, 65.60; H, 7.08. Found: C, 65.40; H, 7.33). The salt was converted to the oxime, m.p. 196–198°, $[\alpha]_D^{25}$ + 15.3°. Hydrolysis of the oxime with pyruvic acid in hydrochloric acid solution yielded the ketone, m.p. 148–151°, which showed no depression in melting point on mixture with an authentic sample and gave no rotation of plane polarized light.

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(1) R. Shriner, R. Adams, and C. Marvel, *Organic Chemistry*, 2nd Ed., John Wiley and Sons, New York, 1943, Vol. I, p. 214.

(2) G. E. McCasland and S. Proskow, *J. Am. Chem. Soc.*, 78, 5646 (1956); D. C. Iffland and H. Siegel, *J. Org. Chem.*, 21, 1059 (1956).

(3) The authors suggest the name "geometrical enantiomorphic isomerism" to describe this type of isomerism.

(4) J. D. Riedel, German Patent 269,429, July 18, 1913; *Beilstein's Handbuch der Organischen Chemie*, 4th Ed., Verlag von Julius Springer, Berlin, 1935, Vol. 21 I, p. 314.

(5) P. W. Neber, A. Burgard and W. Thier, *Ann.*, 526, 277 (1936).

(6) Abstracted from the thesis to be submitted by G. G. L. to the Graduate School of the University of New Hampshire in partial fulfillment of the requirements for the Ph.D. degree.

Paramagnetic Resonance Absorption and New Types of Group Translocations in the Reaction of Trialkyl Phosphites with Chloranil[1]

Sir:

We have observed[2] that the red solution obtained when chloranil (I) and *triphenylphosphine* (II, X = C_6H_5) are mixed in benzene exhibits strong paramagnetic resonance absorption.[2] The pale yellow 1:1 adduct which precipitates quantitatively from the solution was formulated[2] as V or as the ion pair (VII-VI). Water converted this adduct into tetrachlorohydroquinone and triphenylphosphine oxide.

We wish now to call attention to the generality

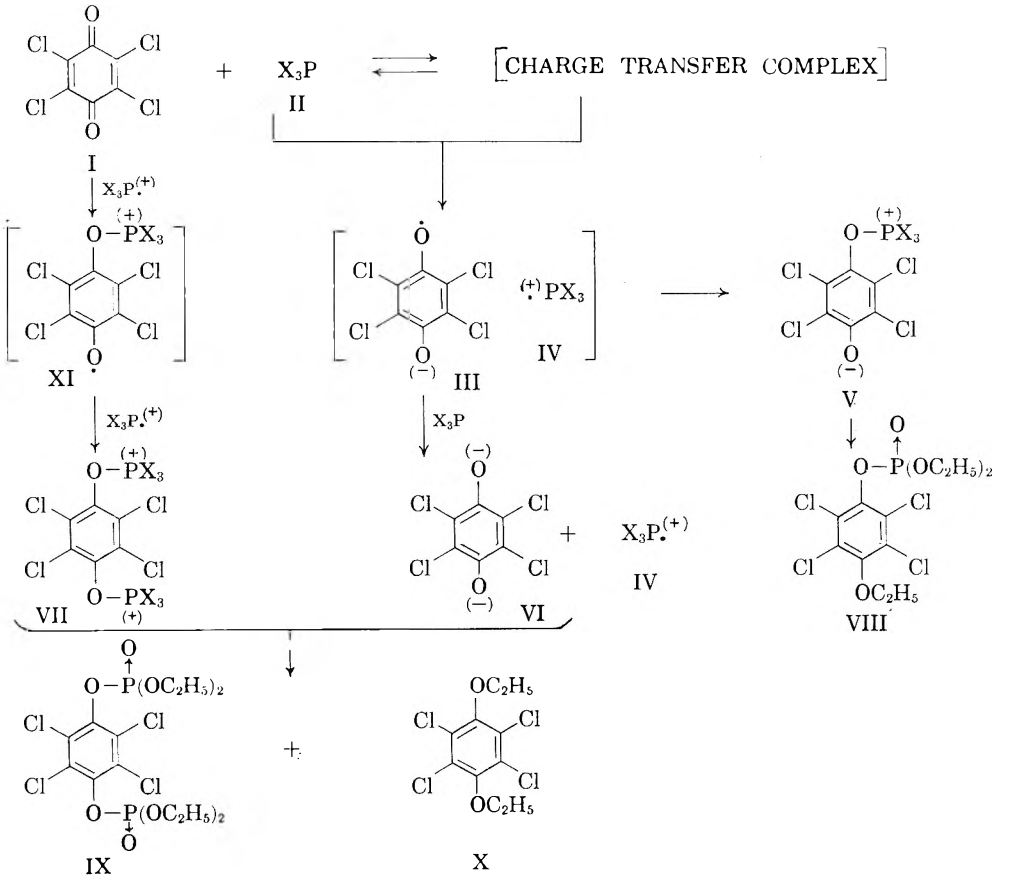
(1) The Structure of Quinone-Donor Adducts. Part II. We are grateful to the Eli Lilly Research Grants Committee for financial support.

(2) F. Ramirez and S. Dershowitz, *Chemistry & Industry*, 665 (1956); *J. Am. Chem. Soc.*, 78, 5614 (1956). We thank Drs. G. Fraenkel, B. Venkataraman, and B. Segal for the paramagnetic resonance absorption measurements.

of this phenomenon and to new types of group translocations among organophosphorus compounds. *Triethyl phosphite* (II, X = C_2H_5O) and chloranil(I) reacted at room temperature in benzene (or in dioxane) to give a deep red solution which *exhibited strong paramagnetic resonance absorption.* The color and the electronic paramagnetism slowly disappeared, but no precipitate was formed. The residue obtained upon removal of solvent at low temperature was not decomposed by water. This residue could be separated into three colorless crystalline substances: VIII [90% yield; m.p. 38–39°; calcd. for $C_{12}H_{15}Cl_4O_5P$: C, 35.0; H, 3.7; mol. wt. 412. Found: C, 34.7; H, 3.8; mol. wt. 349 (Rast); phosphate PO at 7.8μ]. IX (*ca.* 2% yield, m.p. 171–172°; calcd. for $C_{14}H_{20}Cl_4O_8P_2$: C, 32.3; H, 3.9. Found: C, 32.6; H, 3.9; phosphate PO at 7.8μ). X (*ca.* 1% yield) shown to be the diethyl ether of tetrachlorohydroquinone. Independent syntheses of VIII and IX confirmed their structures. The reaction of triethyl phosphite with chloranil in dioxane solution was reported[3] to afford ethyl chloride and diethyl trichloro-*p*-quinonephosphonate; we have been unable to substantiate this claim.

Triphenyl phosphite (II, X = C_6H_5O) did not react appreciably with chloranil at room temperature in benzene solution. However, when a suspension of chloranil in excess of triphenyl phosphite was illuminated at *ca.* 100°, a transient red color was observed resulting in a clear pale yellow solution. The residue obtained upon removal of excess phosphite was readily and quantitatively hydrolyzed to tetrachlorohydroquinone and triphenyl phosphate.

A possible interpretation of these observations is shown in Chart I. The 1:1 adduct V (or the ion pair VII-VI) undergoes no further change in the cases where X = C_6H_5 or C_6H_5O. A group translocation (presumably intermolecular) of the general type observed in the Arbuzov rearrangement, would produce the phosphate-ether VIII from the adduct V, when X = C_2H_5O. From the ion pair VII-VI, a similar group translocation would produce IX and X. If triethyl phosphite is added to a solution of chloranil in benzene containing some aqueous alcohol, a quantitative yield of tetrachlorohydroquinone and triethyl phosphate is obtained, presumably by hydrolysis of the intermediate V.



The paramagnetic resonance absorption spectrum of an equimolar solution of chloranil and triphenylphosphine in benzene consisted of two broad overlapping peaks, the spacing between the two peaks being 2.0 gauss and the *over-all* line width. 3.7 gauss; g = 2.0055. The spectrum of an equimolar solution of chloranil and triethyl phosphite in benzene was very similar, with somewhat better sepa-

(3) E. C. Ladd and M. R. Harvey, U. S. Patent 2,609,376, Sept. 2, 1952; *Chem. Abstr.*, **47**, P7540 (1953).

ration of the two peaks (2.2 gauss) and about the same over-all width (3.7 gauss).

We should like to call attention to the similarities between these novel oxidation reactions of organophosphorus compounds and the observations of Kainer, Bijl, Rose-Innes, and coworkers[4] involving the complex of *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine with chloranil. These authors[4] have described magnetic susceptibility, molar conductivity, and ultraviolet and infrared absorption measurements on this type of complex which they call "an ionic magnetically decompensated molecular compound." It would appear that all of these phenomena might be included in the category of "charge-transfer complexes."[5] On this basis, the species responsible for the color and for the electronic paramagnetism in the reaction of the organophosphorus compounds could perhaps be described in terms of the *ground state* $(\overset{-}{A}\text{–}\overset{+}{D})$ or the corresponding radical ion pair (III, IV) and of the *excited state* (A, D), where A and D stand for the electron acceptor and donor, respectively. In the more usual charge transfer complexes,[5] the situation is reversed and the color is due to the transition $(A, D)\rightarrow(\overset{-}{A}\text{–}\overset{+}{D})$. More information is being sought in a detailed spectrophotometric study now in progress.

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(4) H. Kainer and A. Überle, *Chem. Ber.*, **88**, 1147 (1955); H. Kainer and W. Otting, *Chem. Ber.*, **88**, 1921 (1955); H. Kainer, D. Bijl, and A. C. Rose-Innes, *Naturwissenschaften*, **41**, 303 (1954).

(5) (a) R. S. Mulliken, *Rec. trav. chim.*, **75**, 845 (1956) and references therein; (b) *cf.*, J. E. Wertz, *Chem. Revs.*, **55**, 922 (1955). We are grateful to Prof. Mulliken and Dr. Murrell (University of Chicago) for valuable theoretical suggestions.

The Direct *C*-Acylation of Pyridine

Sir:

We have succeeded in preparing pyridyl ketones by the reaction of pyridine and acid derivatives with amalgamated magnesium in 30–60% yields. Since the Friedel-Crafts and related reactions fail in the pyridine series, this new synthesis provides a means for obtaining directly a series of heterocyclic ketones heretofore available only through syntheses involving two or more steps.

The preparation of 2- and 4-benzoylpyridines was accomplished as follows: Magnesium, 24.3 g. (1.0 mole), was heated at 100° for 1 hr. with mercuric chloride, 46.0 g. (0.17 mole). The product (0.83 mole magnesium) was placed in a three-necked flask fitted with a stirrer, a reflux condenser, and a dropping funnel. A mixture of 25 g. each of pyridine and *N,N*-dimethylbenzamide was added and the materials heated to reflux. Within a few minutes a deep brown color appeared. The remainder of the pyridine, 250 g. (total 3.5 moles) was added slowly within 1 hr. Then the remainder of the amide, 273 g. (total 2.0 moles), was added over a period of 4 hr. maintaining the mixture at reflux throughout this period and until the magnesium disappeared (about 4 more hr.). The cooled reaction mixture was hydrolyzed with 100 g. of ammonium chloride in 500 cc. of water, filtered through Celite to remove insoluble salts, the upper layer of the filtrate extracted 5 times with 300-cc. portions of 6*N* HCl, the acid extracts made basic with 6*N* NaOH, the separated oil extracted with several 500-cc. portions of ether, the ether extracts dried and fractionally distilled, eventually under diminished pressure. The fraction b.p. 138–156° (2.8 mm.) was seeded with a crystal of 4-benzoylpyridine and was refrigerated in an ice box until no further product precipitated. Recrystallization of the solid from petroleum ether (90–100°) gave 8.2 g. (5.4% yield) of 4-benzoylpyridine, m.p. 72–73° (literature[1] 71.5–72.5°). The residual oil was redistilled and yielded 75.1 g. (50% theory) of 2-benzoylpyridine, b.p. 128–135° (1.0 mm.), literature[2] 133° (2 mm.). Total yield of benzoylpyridines based on gram atoms of magnesium reacted, 55.4%. A number of derivatives of each of the two isomers were prepared and found to correspond in properties with published values.

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(1) K. E. Crook and S. M. McElvain, *J. Am. Chem. Soc.*, **52**, 4006 (1930).

(2) E. H. Huntress and H. C. Walter, *J. Am. Chem. Soc.*, **70**, 3704 (1948).

Reaction of *N*-Nitrosodibenzylamines with Sodium Hydrosulfite. A New Reaction

Sir:

We wish to report the discovery of a new reaction. The powerful reducing action of sodium hydrosulfite ($Na_2S_2O_4$) toward C-nitro and C-nitroso groups in basic media has previously been reported.[1,2]

An attempt to reduce *N*-nitrosodibenzylamines to the corresponding 1,1-disubstituted hydrazines using sodium hydrosulfite at 60° in basic ethanolic

(1) C. T. Redemann and C. E. Redemann, *Org. Syntheses*, Coll. Vol. III, 69 (1955).

(2) J. B. Conant and B. B. Corson, *Org. Syntheses*, Coll. Vol. II, 33 (1943).

solution gave instead a theoretical nitrogen evolution and hydrocarbon products. From *N*-nitrosodibenzylamine (I), m.p. 60–61°,[3] there was obtained a theoretical evolution of nitrogen and 77% of bibenzyl, m. p. 53–54°; a mixture melting point with an authentic sample of bibenzyl melted at 53.5–54.5°; with *cis*-1-nitroso-2,6-diphenylpiperidine (II),[4] m.p. 67–69°, 56.8% of *cis*-1,2-diphenylcyclopentane,[5] m.p. 43.5–45.5°, 21.4% of 1,5-diphenyl-1-pentene and a theoretical evolution of nitrogen was obtained. A 2,4-dinitrobenzenesulfenyl chloride derivative of the 1,5-diphenyl-1-pentene melted at 113–115°, (113.5–115°),[4] mixture melting point with the 2,4-dinitrobenzenesulfenyl chloride derivative of authentic[6] 1,5-diphenyl-1-pentene undepressed. An infrared spectrum of the mixture of products was identical with a mixture of authentic 1,5-diphenyl-1-pentene and authentic[7] *cis*-1,2-diphenylcyclopentane, m.p. 46–47°.

Treatment of *trans*-1-nitroso-2,6-diphenylpiperidine (III),[4] m.p. 87–89.5°, with sodium hydrosulfite gave a 60.4% of a mixture of *trans*-1,2-diphenylcyclopentane and *cis*-1,2-diphenylcyclopentane, 19% of 1,5-diphenyl-1-pentene and a theoretical nitrogen evolution. The infrared spectrum of the mixture of products was identical with that of a mixture of authentic *cis*- and *trans*-1,2-diphenylcyclopentane, and 1,5-diphenyl-1-pentene.

Reaction of *N*-nitrosobenzylphenylamine (IV) with sodium hydrosulfite yielded no nitrogen but gave instead a 77% yield of 1-benzyl-1-phenylhydrazine, hydrochloric acid salt, m.p. 170–172° (m.p. 167–170°).[8] With *N*-nitrosodiphenylamine (V) an 80% yield of diphenylamine, m.p. 53.2–54.4°, (m.p. 53.9°)[8] was obtained, sulfuric acid salt, m.p. 124.5–126° (123–125°).[9] The formation of diphenylamine on reduction of V has previously been reported using other reducing agents.[10] Treatment of *cis*-1-nitroso-2,6-dimethylpiperidine[3] (VI) yielded *cis*-1-amino-2,6-dimethylpiperidine, picrate salt, m.p. 167.5–169° (m.p. 168–169),[3] a mixture with the picrate of authentic *cis*-1-amino-2,6-dimethylpiperidine, m.p. 167–168°, melted at 167–169°.

The products of the reaction of I, II, and III with sodium hydrosulfite are identical with those isolated in the mercuric oxide oxidation of the corresponding 1,1-disubstituted hydrazines,[4] suggesting a common intermediate for both reactions. Further work on the reaction of sodium hydrosulfite with *N*-nitrosodialkylamines is presently under investigation and will be reported at a later date.

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(3) C. G. Overberger, L. C. Palmer, B. S. Marks, and N. R. Byrd, *J. Am. Chem. Soc.*, **77**, 4100 (1955).

(4) C. G. Overberger, J. G. Lombardino, and R. G. Hiskey, *J. Am. Chem. Soc.*, **79**, 1510 (1957).

(5) H. A. Wiedlich, *Ber.*, **71B**, 1601 (1938).

(6) C. G. Overberger and J. J. Monagle, *J. Am. Chem. Soc.*, **78**, 4470 (1956).

(7) F. Japp and G. Lander, *J. Chem. Soc.*, **71**, 131 (1897).

(8) N. A. Lange, *Handbook of Chemistry*, 7th ed., Handbook Publishers, Inc., Sandusky, Ohio, 1949.

(9) I. Heilbron, *Dictionary of Organic Compounds*, Oxford University Press, N. Y., 1953.

(10) F. W. Schueler and C. Hanna, *J. Am. Chem. Soc.*, **63**, 4996 (1951).

Free-Radical Methylation of Simple Aromatic Hydrocarbons

Sir:

The free radical methylation of anthracenes,[1] trinitrotoluene,[2] and pyridines[3] has been reported[4a]. However, there appears to be no record[5] of substitution of methyl radicals on simple aromatics not activated by electron-withdrawing substituents; in fact, it has been suggested that such a reaction is energetically disfavored.[6]

We now wish to report that heating a *ca.* 1*M* solution of acetyl peroxide in toluene at the boiling point gives (in addition to bibenzyl and other dimeric or polymeric material) *o*-, *m*-, and *p*-xylene as well as ethylbenzene and an unidentified C_9 aromatic hydrocarbon fraction, the latter in very small amount. The over-all yield of C_8 aromatics isolated by careful fractional distillation is *ca.* 10% based on acetyl peroxide. The composition of this fraction, as determined by gas chromatography and ultraviolet analysis, is *o*-xylene, 44.5%, *m*-xylene, 21%, *p*-xylene, 13.5%, and ethylbenzene, 21%. Moreover, the reaction of benzene with acetyl peroxide yields (besides higher-boiling products[4b]) toluene, identified by boiling point, infrared spec-

(1) A. L. J. Beckwith and W. A. Waters, *J. Chem. Soc.*, 1108 (1956).

(2) L. F. Fieser, R. C. Clapp, and W. H. Daudt, *J. Am. Chem. Soc.*, **64**, 2052 (1942).

(3) St. Goldschmidt and M. Minsinger, *Ber.*, **87**, 956 (1954); St. Goldschmidt, *Angew. Chem.*, **69**, 132 (1957).

(4) *ADDED MAY 27, 1957:* (*a*) After this communication was submitted, we learned of the publication of A. L. J. Beckwith and W. A. Waters, *J. Chem. Soc.*, 1665 (1957) in which they describe the decomposition of di-*t*-butyl peroxide in chlorobenzene to give chlorotoluenes and 3,3′-dichloro-4,4′-dimethylbiphenyl. (*b*) We have identified 4,4′-dimethylbiphenyl as one of the products of the decomposition of acetyl peroxide in benzene.

(5) M. S. Kharasch, A. Fono, and W. Nudenberg [*J. Org. Chem.*, **16**, 111 (1951)] have stated that the decomposition of acetyl peroxide in benzene yields toluene and xylenes, but no experimental data are available.

(6) M. Szwarc, *Nature*, **161**, 890 (1948); see also F. R. Mayo, *Discussions Faraday Soc.*, 372 (1947); P. F. Nelson, *J. Chem. Ed.*, **32**, 606 (1955), and C. S. Rondestvedt and H. S. Blanchard, *J. Org. Chem.*, **21**, 229 (1956).

trum, and preparation of the dinitro substitution product.

We were encouraged to look for xylenes from the decomposition of acetyl peroxide in toluene after discovering[7] that the decomposition of a *ca.* 1*M* solution in ring-deuterated toluene gave rise to some methane-*d* (6–7% of the total methane evolved), the stoichiometric equation being[8]

$$(CH_3CO_2)_2 + C_6D_5CH_3 \longrightarrow C_6D_4(CH_3)_2 + CH_3D + 2CO_2 \quad (1)$$

This finding, incidentally, invalidates previous determinations[9] of isotope-effects from the CH_3D/CH_4 ratio in the reaction of acetyl peroxide (1*M* solution) with $C_6H_5CH_2D$, since evidently part of the CH_4 originates by abstraction of ring hydrogens.

Szwarc has shown[10,11] that in the reaction of acetyl peroxide with toluene, the ratio

$$\frac{CH_4 + 2C_2H_6}{CO_2}$$

is less than unity (0.71–0.87) indicating that some methyl radicals fail to be converted to either methane or ethane. He ascribed this "methyl loss" to addition of methyl radicals to the aromatic ring with the formation of cycloolefins.[10] The results summarized above suggest that "methyl loss" may also occur through substitution (Equation 1). Apparently such loss through substitution (*cf.* Equation 2, path A) occurs only at high

$$C_6H_5CH_3 + \cdot CH_3 \longrightarrow C_6H_5(CH_3)_2 \quad (2)$$

A: $C_6H_5(CH_3)_2 \cdot \longrightarrow C_6H_4(CH_3)_2 + CH_4$

B: $C_6H_5(CH_3)_2 \cdot \longrightarrow$ Cycloolefins (Dimers or Disproportionation Products)

acetyl peroxide concentrations, for we have been able to show that at the much lower concentrations (*ca.* 0.1*M*) used by Szwarc, ring-deuterated toluene gives little methane-*d*, in agreement with Equation 2, path B, which is similar to the reaction path postulated by Szwarc.[10]

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(7) Reported at the 130th Meeting of the American Chemical Society, Atlantic City, N. J., September, 1956. See E. L. Eliel, F. T. Fang, and S. H. Wilen, Division of Petroleum Chemistry Preprints, Vol. 1, No. 3, p. 135.

(8) In fact only partially deuterated substrate was used, but this does not affect the argument.

(9) F. B. Colton, Ph.D. dissertation, University of Chicago, 1950, p. 71; W. H. Urry. Abstracts of the Twelfth National Organic Chemistry Symposium, American Chemical Society, Denver, Colo., June, 1951, p. 30; data cited by K. B. Wiberg. *Chem. Revs.*, 55, 713 (1955) and by F. D. Greene, W. A. Remers, and J. W. Wilson, *J. Am. Chem. Soc.*, 79, 1416 (1957).

(10) M. Levy and M. Szwarc, *J. Am. Chem. Soc.*, 76, 5981 (1954); *J. Am. Chem. Soc.*, 77, 1949 (1955).

(11) R. P. Buckley, F. Leavitt, and M. Szwarc, *J. Am. Chem. Soc.*, 78, 5557 (1956).