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Infrared Spectra of Isotopically Labeled Compounds. I. Diisopropylketones

GERASIMOS JOHN KARABATSOS[1]

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The infrared spectra of isotopically labeled diisopropylketones were investigated. The 1712 cm.$^{-1}$ carbonyl frequency of diisopropylketone is shifted to 1675 cm.$^{-1}$ upon C^{13} substitution in the carbonyl group, and to 1681 cm.$^{-1}$ upon O^{18} substitution, indicating that it is composed of C=O and C—C stretches, in agreement with Halford's treatment of the carbonyl force constant for unconjugated ketones. The same carbonyl shift, 37 cm.$^{-1}$, is observed in the spectra of 2-methylpropionic-1-C^{13} and 2,2-dimethylpropionic-1-C^{13} acids. The 1024 cm.$^{-1}$ frequency of the ketone, shifted to 1004 cm.$^{-1}$ upon C^{13} substitution, and unaffected by either O^{18} or deuterium substitutions in the molecule, is assigned to an uncoupled C—C—C stretching vibration. The 1203 cm.$^{-1}$ frequency is assigned to C=O, C—C, and C—H coupled vibrations. Three other frequencies, 1129 cm.$^{-1}$, 983 cm.$^{-1}$, and 858 cm.$^{-1}$ are skeletal vibrations without any C—O contribution.

Studies of isotope shifts, caused by either C^{13} or C^{14}, in elucidating the infrared spectra of organic compounds are practically absent from the literature. Most of the studies published relate either to elements or to simple inorganic molecules.[2,3] Isotope shifts in simple organic compounds, caused by C^{13} of natural abundance, have been observed in the Raman spectra and quantitatively reported in the literature.[4,5]

The infrared spectrum of 2,4-dimethyl-3-pentanone-3-C^{13} exhibited certain pronounced differences from that of 2,4-dimethyl-3-pentanone. The data suggested that a study based on the infrared spectral frequencies of C^{13} labeled compounds, and some related deuterium and O^{18} derivatives, might be profitable in elucidating both the assigning of infrared frequencies and the degree to which various vibrations are coupled with others. Such information could help clarify certain regions of the spectrum, especially the 800–1500 cm.$^{-1}$ region where a great deal of controversy exists in the literature. As far as the degree to which various vibrations (in complex organic molecules) are coupled with others is concerned, a fairly good estimate could often be obtained from cases where the same molecule is isotopically labeled with either C^{13}, or O^{18}, or deuterium, in its various atoms. That such an estimate might not be too far off from values calculated by more rigorous methods is shown by the data regarding the carbonyl frequency of diisopropylketones.

RESULTS

This paper reports the results obtained from the investigation of the following diisopropylketones: 2,4 - dimethyl - 3 - pentanone, 2,4 - dimethyl-3-pentanone-3-C^{13}, 2,4-dimethyl-3-pentanone-O^{18}, 2,4-dimethyl-3-pentanone-2,4-d_2 and 2,4-dimethyl-3-pentanone-2,4-d_2-3-C^{13}. In addition, the carbonyl frequency of 2,2-dimethylpropionic-1-C^{13} acid is recorded. The infrared spectra were taken with a Perkin-Elmer double-beam Recording Infrared Spectrophotometer, Model 21. All frequencies reported in this paper were calculated from spectra taken in 4% and 12% (v./v.) solutions in carbon disulfide, except for those of the dimethylpropionic acids which were determined in 4% (v./v.) solutions in carbon tetrachloride. The purity of the samples used for the spectra was ascertained by vapor phase chromatography, a RECO Distillograph, Model D-2000, equipped with a 40% (w./w.) silicone oil on Celite column, being employed for that purpose. The composition of the

(1) Present address: Department of Chemistry, Michigan State University, East Lansing, Mich.

(2) A. H. Nielsen, *Phys. Rev.*, **53**, 983 (1938).

(3) A. H. Nielsen and R. T. Lagemann, *J. Chem. Phys.*, **22**, 36 (1954).

(4) G. Glockler and M. M. Renfrew, *J. Chem. Phys.*, **6**, 340 (1938).

(5) H. C. Cheng, C. F. Hsueh, and Ta-You Wu, *J. Chem. Phys.*, **6**, 8 (1938).

C^{13} labeled ketones consisted of about 62% labeled and 38% unlabeled, according to the isotopic purity of the carbon dioxide used in their synthesis. The composition of the O^{18} labeled ketone consisted of about 35% labeled and 65% unlabeled, according to the isotopic purity of O^{18} water.

The pertinent spectral frequencies, the experimental frequency differences ($\Delta\nu$), and certain calculated $\Delta\nu$ values of the investigated compounds are presented in Tables I–III. The infrared spectra of some of them are shown in Figs. 1-3.

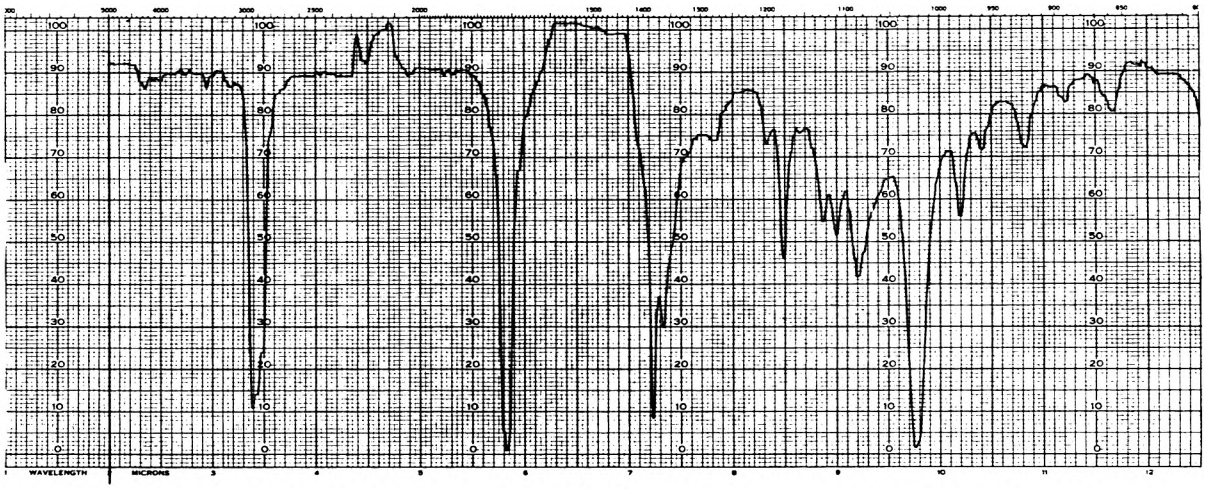

Fig. 1

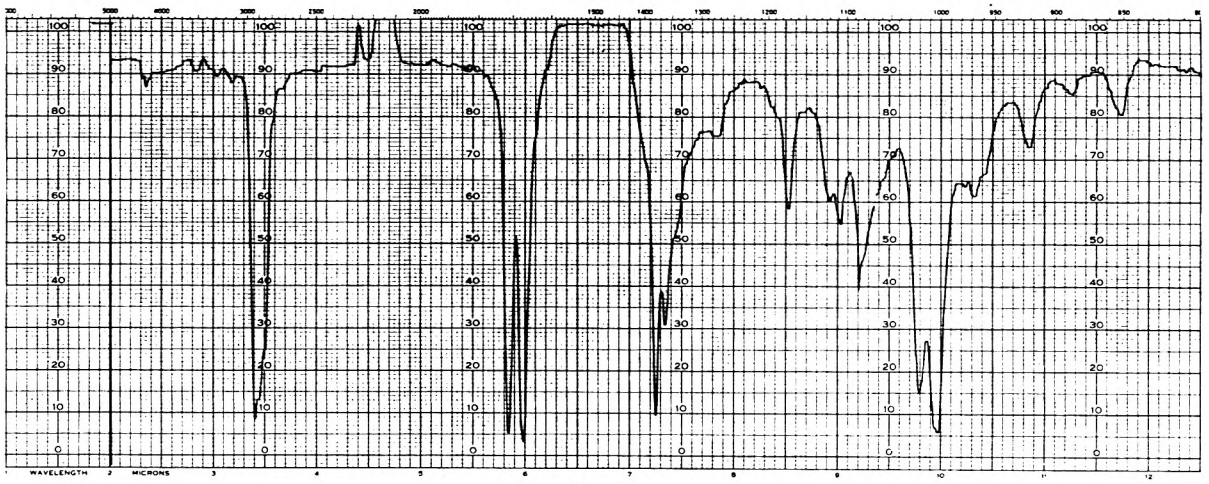

Fig. 2

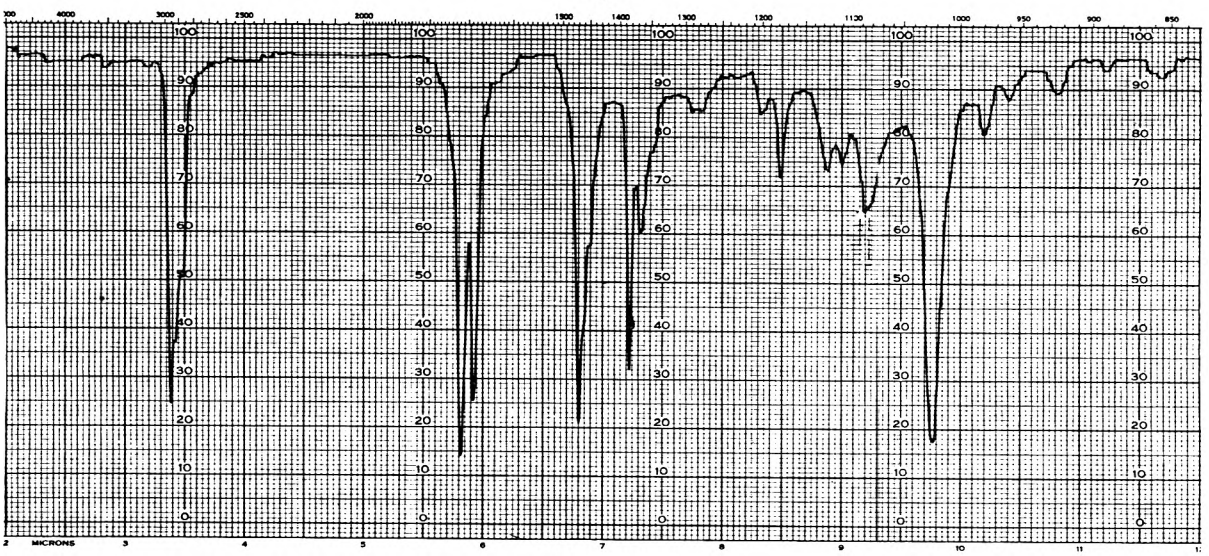

Fig. 3

TABLE I

INFRARED SPECTRAL FREQUENCIES OF DIISOPROPYLKETONES

Compound	Wave Number (cm.$^{-1}$)						$(\mu_2/\mu_1)^{1/2}$[a]
2,4-Dimethyl-3-pentanone	1712	1203	1129	1024	983	858	
2,4-Dimethyl-3-pentanone-3-C^{13}	1675	1190	1120	1004	972	853	
$\Delta\nu$ Experimental	37	13	9	20	11	5	
$\Delta\nu$ Calc. from ($\mu C{=}O$) and ($\mu C^{13}{=}O$)	38	27	25	23	22	19	1.0227
$\Delta\nu$ Calc. from ($\mu C{-}C$) and ($\mu C^{13}{-}C$)	34	24	22	20	19	17	1.020
$\Delta\nu$ Calc. from ($\mu CO{-}CH(CH_3)_2$) and ($\mu C^{13}O{-}CH(CH_3)_2$)	19	13	12	11	11	9	1.011

[a] μ_1 is the reduced mass calculated from the C^{12} compound and μ_2 the reduced mass calculated from the C^{13} compound.

TABLE II

INFRARED SPECTRAL FREQUENCIES OF 2,4-DIMETHYL-3-PENTANONE-O^{18}

Compound	Wave Number (cm.$^{-1}$)						$(\mu_2/\mu_1)^{1/2}$[a]
2,4-Dimethyl-3-pentanone	1712	1129	1203	1024	983	858	
2,4-Dimethyl-3-pentanone-O^{18}	1681	1129	1192	1024	983	858	
$\Delta\nu$ Experimental	31	0	11	0	0	0	
$\Delta\nu$ Calc. from ($\mu C{=}O$) and ($\mu C{=}O^{18}$)	42		29				1.025

[a] μ_1 is the reduced mass calculated from the unlabeled ketone and μ_2 is the reduced mass calculated from the O^{18} labeled ketone.

TABLE III

INFRARED SPECTRAL FREQUENCIES OF 2,4-DIMETHYL-3-PENTANONE-2,4-d_2 AND 2,4-DIMETHYL-3-PENTANONE-2,4-d_2-3-C^{13}

Compound	Wave Number (cm.$^{-1}$)							
2,4-Dimethyl-3-pentanone-2,4-d_2	2175	2140	1712	1203	1052	1024	867	838
2,4-Dimethyl-3-pentanone-2,4-d_2-3-C^{13}	2175	2140	1675	1190	1042	1004	860	835
$\Delta\nu$ Experimental	0	0	37	13	10	20	7	3
$\Delta\nu$ Calc. from ($\mu C{=}O$) and ($\mu C^{13}{=}O$)			38	27	23	23	19	19
$\Delta\nu$ Calc. from ($\mu C{-}C$) and ($\mu C^{13}{-}C$)			34	24	20	20	17	17
$\Delta\nu$ Calc. from ($\mu CO{-}CD(CH_3)_2$) and ($\mu C^{13}O{-}CD(CH_3)_2$)			19	13	11	11	9	9

DISCUSSION

The most striking differences in the spectra of 2,4-dimethyl-3-pentanone and 2,4-dimethyl-3-pentanone-3-C^{13}, Fig. 1 and Fig. 2, respectively, occur in the carbonyl and the 1024 cm.$^{-1}$ regions.[6] The 1712 cm.$^{-1}$ frequency (the well known carbonyl stretch) is lowered to 1675 cm.$^{-1}$ upon C^{13} substitution in the carbonyl group of diisopropylketone. The shift, 37 cm.$^{-1}$, is in good agreement with the 38 cm.$^{-1}$ frequency difference calculated from the reduced masses of the carbonyl groups without taking into account the mass of the rest of the molecule. The same shift, 37 cm.$^{-1}$, is observed in the spectra of 2-methylpropionic-1-C^{13} and 2,2-dimethylpropionic - 1 - C^{13} acids, *e.g.*, 1701 cm.$^{-1}$ and 1664 cm.$^{-1}$ for 2,2-dimethylpropionic and 2,2-dimethylpropionic-1-C^{13} acids respectively.

The good agreement between experimental shift and the one obtained from theoretical calculations does not necessarily indicate that the carbonyl frequency of diisopropylketone is a diatomic vibration[7] without any contribution from other vibrations. One could very well explain it by suggesting that it is composed of 75% C=O stretch and 25% C—C stretch. It is interesting to note that the carbonyl shifts obtained by Braude and Turner[8] on the O^{18} carbonyl labeled 1-phenylallyl-*p*-nitrobenzoate and by Halmann and Pinchas[9] on the O^{18} labeled benzophenone correspond only to 75% of the theoretical shift. Francis[10] suggests, from a normal coordinate treatment of the skeletal modes of the acetone molecule, that the 1720 cm.$^{-1}$ frequency of acetone includes about 80% of C=O stretching and about 20% of C—C stretching vibra-

(6) It might be interesting to report here the NMR spectrum of 2,4-dimethyl-3-pentanone-3-C^{13}. The coupling constant between the C^{13} and the methyl hydrogens (about 6 c.p.s.) is about twice as large as the coupling constant between the C^{13} and the tertiary hydrogens. The same coupling constants are observed with 2,4-dimethyl-3-pentanol-3-C^{13} and 2,4-dimethylpentane-3-C^{13}. Anomalies of this kind, involving either hydrogen-fluorine or hydrogen-mercury couplings, have been reported in the literature: M. Sharts and J. D. Roberts, *J. Am. Chem. Soc.*, **79**, 1008 (1957); H. H. Jaffe *et al.*, *J. Chem. Phys.*, **30**, 1422 (1959); P. T. Narasimhan and M. T. Rogers, *J. Am. Chem. Soc.*, **82**, 34 (1960).

(7) The term "diatomic vibration" is meant to indicate that the vibration is solely due to the motions of the two atoms involved, the rest of the atoms being treated as rigid.

(8) E. A. Braude and D. W. Turner, *Chem. & Ind.*, (*London*), 1223 (1955).

(9) M. Halmann and S. Pinchas, *J. Chem. Soc.*, 1703 (1958).

(10) S. A. Francis, *J. Chem. Phys.*, **19**, 942 (1951).

tions. Jones[11] has observed small carbonyl shifts, in the order of 1–5 cm.$^{-1}$, in some α-deuterated ketones in the steroid series, which again suggests that the carbonyl stretch in that series is not an uncoupled one. Halford's[12] treatment of the carbonyl force constant for unconjugated ketones clearly suggests that both the C=O and C—C stretchings are involved in the carbonyl frequency. In order to elucidate this point the infrared spectrum of 2,4-dimethyl-3-pentanone-O^{18} was examined. The carbonyl stretch was shifted by 31 cm.$^{-1}$, which corresponds to 74% of the calculated value. This finding is taken as an indication that the carbonyl frequency of diisopropylketone is a mixed one, composed of about 74% C=O stretch and 26% C—C stretch. The lack of evidence that any other vibrations are involved strongly supports Halford's treatment of the carbonyl force constant for unconjugated ketones.

The 1024 cm.$^{-1}$ frequency, a sharp strong band characteristic of many ketones, is shifted to 1004 cm.$^{-1}$ upon C^{13} carbonyl labeling, and is assigned here to an uncoupled C—C—C stretching between the carbon of the carbonyl group and the secondary carbons of the isopropyl groups. The experimental $\Delta\nu$ value, 20 cm.$^{-1}$, is in excellent agreement with the 20 cm.$^{-1}$ value calculated from the reduced masses of (C—C) and (C^{13}—C). The possibility that a C=O vibration might contribute is discounted by virtue of the data obtained from 2,4-dimethyl-3-pentanone-O^{13}, which show that the 1024 cm.$^{-1}$ frequency is unaffected. Likewise, the data of the dideuterated ketones reduce the contribution of any other vibration to insignificantly small proportions. The data, therefore, clearly point to the existence of an uncoupled vibration between three atoms which are deeply imbedded into the skeleton of a molecule. This, to the knowledge of this author, is the first case of this kind known.

The 1200 cm.$^{-1}$ frequency of ketones has been assigned by Kohlrausch[13] to the nonsymmetric C—C stretching vibration and by Francis[10] to the coupled vibrations[14] of C=O and C—C. Although the C^{13} data alone do not clearly differentiate between the two possibilities, when taken together with the results of 2,4-dimethyl-3-pentanone-O^{18} they support Francis' assignment. The 1129 cm.$^{-1}$, 983 cm.$^{-1}$, and 858 cm.$^{-1}$ frequencies are assigned to skeletal vibrations all of which possess a considerable contribution of C—H vibrations, since they are all shifted to 1052 cm.$^{-1}$, 867 cm.$^{-1}$, and 838 cm.$^{-1}$ respectively upon dideuteration. The fact that these frequencies are unaffected in the spectrum of 2,4-dimethyl-3-pentanone-O^{13} excludes any C=O contribution.

EXPERIMENTAL

2,4-Dimethyl-3-pentanone-3-C^{13}. Preparation of 2,4-dimethyl-3-pentanone-3-C^{13} will be described elsewhere.

2,4-Dimethyl-3-pentanone-O^{18}. 2,4-Dimethyl-3-pentanone (0.3 ml.) was shaken for 18 hr. with 41% atom excess O^{18} water (0.5 ml.) in the presence of a small drop of 70% perchloric acid. The organic layer was separated and vapor phase chromatographed.

2,4-Dimethyl-3-pentanone-2,4-D_2. A solution of 2,4-dimethyl-3-pentanone (0.2 g.) in anhydrous ether (5 ml.) was shaken for 16 hr. with heavy water (5 g.) and sodium hydroxide (0.02 g.). The ether layer was separated, dried over anhydrous sodium sulfate, the ether evaporated, and the residue vapor phase chromatographed. The same procedure was followed in the preparation of 2,4-dimethyl-3-pentanone-2,4-d_2-3-C^{13}.

Acknowledgments. The author is grateful to Professor Paul D. Bartlett for his great encouragement to pursue this work, despite the fact that it was incidental to the author's thesis, and for his helpful suggestions; to Professors W. A. Klemperer and E. L. Eliel for their valuable discussions and comments on this work, and to Dr. D. Samuel for generously providing the O^{18} labeled water. Also, he thanks the National Science Foundation for financial help.

East Lansing, Mich.

(11) R. N. Jones, A. R. H. Cole, and B. Nolin *J. Am. Chem. Soc.*, **74**, 5662 (1952).

(12) J. O. Halford, *J. Chem. Phys.*, **24**, 830 (1956).

(13) K. W. F. Kohlrausch, *Ramanspektren* (Akademische Verlagsgesellschaft Becker and Erler, Leipzig, 1943), p. 103.

(14) It seemed surprising that certain frequency shifts, especially those of 1203 cm.$^{-1}$ and 983 cm.$^{-1}$ frequencies, could be well correlated with calculations based upon the reduced masses of the carbonyl and isopropyl groups (corresponding to the assumption that the isopropyl group vibrates against the effective mass of the carbonyl group). However, the data (Table III) of the 2,4-dideuterated ketones suggest that such a correlation is more fortuitous than significant. The 1203 cm.$^{-1}$ frequency is unaffected by deuteration, while a shift of about 4 cm.$^{-1}$ is expected from theoretical calculations; the shifts of the 1129 cm.$^{-1}$, 983 cm.$^{-1}$, and 858 cm.$^{-1}$ frequencies are too large to substantiate such a hypothesis.

[CONTRIBUTION FROM SHELL DEVELOPMENT COMPANY]

Cyclic Acrolein Acetals

R. F. FISCHER AND C. W. SMITH

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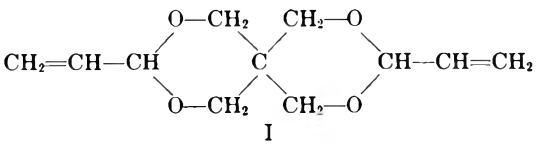
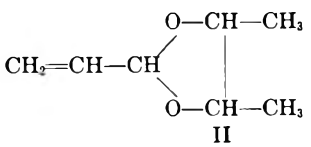
Acetals have been made in 70–98% yields by reaction of acrolein and various alcohols, largely 1,2- and 1,3-glycols. β-Chloro-, hydroxy-, cyano-, and α,β-epoxy-derivatives otherwise difficultly accessible are readily prepared from the acetals derived from 2-methyl-2,4-pentanediol or pentaerythritol.

Acrolein contains two highly reactive groups, an aldehyde and an ethylenic linkage. Numerous examples of addition to both the carbonylic and ethylenic functions are known.[1] Early attempts to form unsaturated acetals led to mixtures in which extensive addition to the double bond occurred.[2] Recently, however, a number of publications have indicated that in acidic media the carbonylic function is slightly more reactive toward alcohols than is the ethylenic group and in particular that substituted 1,2- and 1,3-glycols tend to form cyclic acetals. Schulz and Wagner[3] prepared 3,9-divinyl-2,4,8,10-tetroxaspiro-(5,5)-undecane (diallylidenepentaerythritol), I, from pentaerythritol and a large excess of acrolein,



I

while Neish and MacDonald[4] produced *l*-2-vinyl-4,5-dimethyl-1,3-dioxolane II

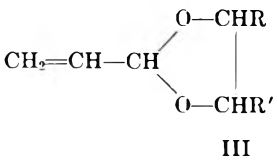


II

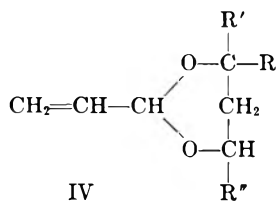
from *l*-2,3-butanediol. A recent patent[5] discloses that by means of very low catalyst concentrations (0.001 to 0.010 mole percent *p*-toluenesulfonic acid) and removal of water at temperatures below 50° for 24–36 hours, lower aliphatic acrolein acetals can be prepared in 50–80% yields.

We have found, however, that three factors can be controlled to maximize acetal formation while minimizing addition to the ethylenic link: 1) catalyst concentration should be reduced to the lowest value consistent with a practical rate while minimizing addition to the olefinic bond; 2) 1,2- or 1,3-glycols should be used, as they lead to the more stable cyclic acetals; 3) glycols substituted on the hydroxyl-bearing carbons are preferred, as such substitution favors ring formation while hindering addition to the ethylenic bond.

A number of representative acrolein cyclic acetals have been prepared in 70–98% yield. In most cases distillation without fractionation from the reaction mixture has given products with analyses in agreement with the theoretical values. The products from 1,2-glycols are 2-vinyl-1,3-dioxolanes. III, while from 1,3-glycols one obtains 2-vinyl-1,3-dioxanes, IV. Table I summarizes the products

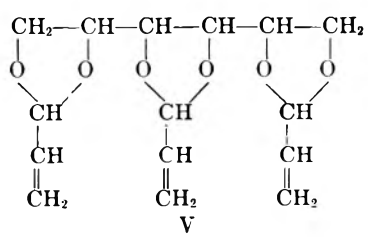


III



IV

obtained and reaction conditions employed for the best yields obtained from various alcohols. Many of the compounds in Table I have not been described in the literature (marked with an asterisk), and except for the pentaerythritol and 2,3-butanediol acetals, none has been prepared previously in good yield. For cyclic acetals two-five times as much catalyst as for noncyclic acetals could be used and the reaction temperature could be raised to 80°. This reduced the reaction time to as little as 50 minutes when using the efficient drying solvent, benzene. Under these conditions, the yield of I was increased to 80% while reducing the excess acrolein from 300%[2] to 20%. To illustrate the generality of the reaction, allyl alcohol and crotonaldehyde have also been included. The more complex polyol, sorbitol, however, gave only 33% yield of triallylidene sorbitol, probably V, in addition to much polymer.



V

(1) S. A. Ballard, H. de V. Finch, B. P. Geyer, G. W. Hearne, C. W. Smith, and R. R. Whetstone, "Chemicals from Acrolein," Proceedings of the Fourth World Petroleum Congress, Section IV C, Rome, Italy, 1955.

(2) *Org. Syntheses* II, **17**, 137 (1943).

(3) H. Schulz and H. Wagner, *Angew. Chem.* **62**, 105 (1950).

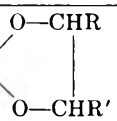
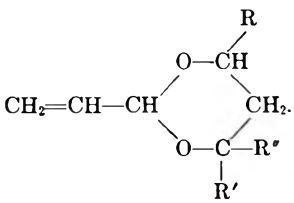
(4) A. C. Neish and F. J. MacDonald, *Can. J. Research* **25B**, 70 (1947).

(5) D. R. Myers, B. J. Magerlein, and G. W. Staffen, U. S. Patent **2,678,950** (1954) to Upjohn Co.

TABLE I

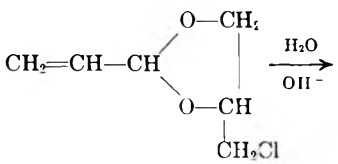
SYNTHESIS OF ACROLEIN ACETALS

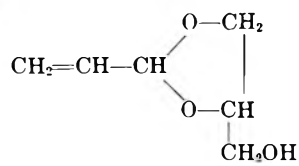
Alcohol	Product[a]	Conversion of Alcohol to Product	Yield on Alcohol	Excess Acrolein Present	Solvent	Mole % of Catalyst[b] Present	Reaction Time
Allyl alcohol	Acrolein diallyl acetal	72%	75%	None	Petroleum ether	0.0010	24 hr.
2,3-Butanediol	III, R=R′=CH_3	86%	86%	10%	Benzene	0.020	3 hr.
2-Methyl-2,4-pentanediol	IV, R=R′=R″=CH_3[c]	98.5%	98.5%	10%	Benzene	0.026	2.5 hr.
Glycerine	III, R=H, R′=CH_2OH	78.5%	88%	20%	Benzene	0.023	50 min.
1,2,6-Hexanetriol	III, R=H[c] R′=$CH_2CH_2CH_2CH_2OH$	88%	88%	50%	Benzene	0.020	50 min.
Glycerol α-monochlorohydrin	III, R=H, R′=CH_2Cl	75%	75%	None	Benzene	0.056	1.5 hr.
Trimethylene glycol	IV, R=R′=R″=H	78%	78%	None	67% Benzene 33% Ether	0.043	3 hr.
Ethylene glycol	III, R=R′=H[c]	58%	58%	10%	67% Benzene 33% Ether	0.025	9 hr.
Pentaerythritol	Diallylidenepentaerythritol, I	86%	86%	20%	Benzene	0.070	2.5 hr.
Sorbitol	Triallylidenesorbitol, V[c]	33%	33%	10%	Benzene	0.059	8 hr.
Pentaerythritol (with crotonaldehyde)	Dicrotonylidenepentaerythritol[c]	95%	95%	10%	Benzene	0.048	3 hr.

[a] "III" is the generalized 2-vinyl-1,3-dioxolane,  "IV" is the generalized 2-vinyl-1,3-dioxane,  [b] p-Toluenesulfonic acid. [c] Apparently new compounds.

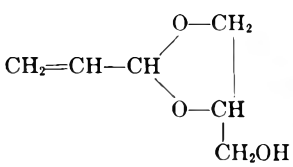
In two cases which gave relatively low yields under the usual conditions, catalysis with sulfuric acid adsorbed on silica gel has given marked improvements. Thus unsaturated acetals were prepared from ethylene glycol and glycerine in 70 and 83% yields. Corresponding yields with *p*-toluenesulfonic acid were 58 and 54% (for large runs).

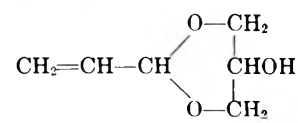
Although two structures are possible for the glycerine acetal, the isomer containing the five-membered ring predominates. Hibbert and Whelan,[6] who prepared an acetal (10% yield) by thermal reaction of glycerine and acrolein, methylated their product and then hydrolyzed it to the known glycerol α-methyl ether. The main product obtained by alkaline hydrolysis of the glycerol α-monochlorohydrin acetal has substantially the same infrared absorption spectrum as does the glycerine acetal obtained directly. The boiling range of the compound is generally taken as 65–70° (1 mm.), but there is usually a small forecut starting at 55°. As it was desired in one case to obtain a very pure sample, a large composite which had previously boiled in the range 65–70° (1 mm.) was fractionated through a 20-tray bubble plate, Oldershaw, column.





(The isomers may be in equilibrium, however.)





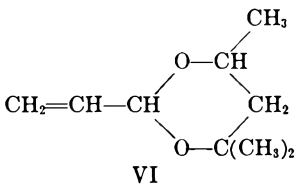
At a reflux ratio of 60:1, the head temperature remained at 54–55°, n_D^{20}, 1.4680. When 20% of the material had been taken overhead, the reflux ratio was changed to 20:1, whereupon the head temperature rose gradually to 65°. Here 33% of

(6) H. Hibbert and M. Whelan, *J. Am. Chem. Soc.* **51**, 3115 (1939).

the material was taken, b.p. 65–67° (1 mm.) n_D^{20} 1.4612. It is possible that under the very high reflux ratio, time was available for slow transformation of the common high-boiling isomer to a low-boiling one.

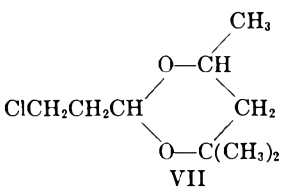
The acetal from glycerol α-monochlorohydrin, 2-vinyl-4-chloromethyl-1,3-dioxolane has also been obtained from acrolein and epichlorohydrin in the presence of stannic chloride. This is apparently the first unsaturated acetal obtained from acrolein and an epoxide.

The nearly quantitative yield of the acrolein acetal of 2-methyl-2,4-pentanediol is especially noteworthy and has led to the study of some of the reactions of the product, 4,4,6-trimethyl-2-vinyl-1,3-dioxane, VI.

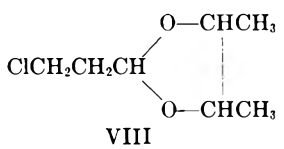


VI

Dry hydrogen chloride simultaneously adds to the double bond of acrolein and catalyzes acetal formation. From 2-methyl-2,4-pentanediol, 2-(2-chloroethyl)-4,4,6-trimethyl-1,3-dioxane, VII, was obtained in 94% yield, while 2,3-butanediol afforded 2-(2-chloroethyl)-4,5-dimethyl-1,3-dioxolane, VIII.



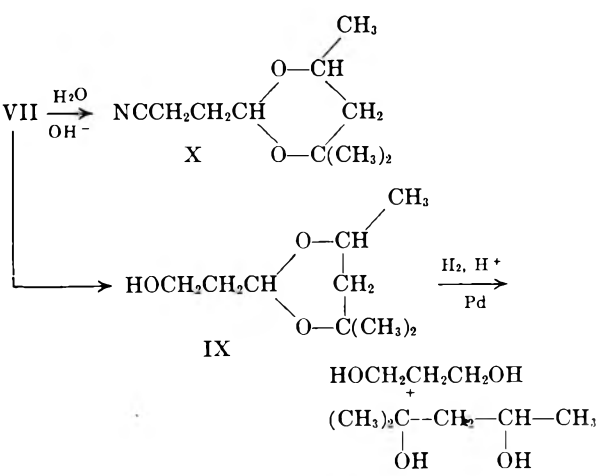
VII



VIII

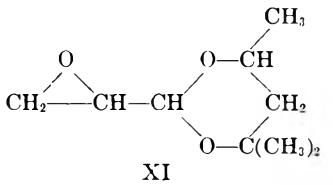
This general type of compound has been obtained previously only in poor yield.[7]

Reaction of the chloride, VII, with aqueous alkali at 160° gave the cyclic β-hydroxypropionaldehyde acetal, IX, (80% yield), and hydrogenolysis of this compound yielded trimethylene glycol in 50% yield. When VII is treated with sodium cyanide, the acetal of β-cyanopropionaldehyde, X, is obtained in 95% yield. The epoxide XI was prepared in fair purity



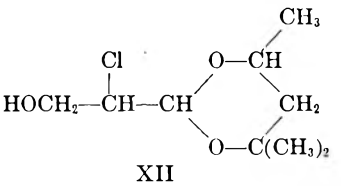
X

IX



XI

by epoxidation of VI with peracetic or peroxytrifluoroacetic acid, but preparation *via* chlorohydrination proved to be a better route. Two chlorohydration procedures were used; in one, carbon dioxide was passed into an emulsion of VI in aqueous calcium hypochlorite. The product probably consisted largely of 2-(1-chloro-2-hydroxyethyl)-4,4,6-trimethyl-1,3-dioxane, XII, but may have contained the 1-hydroxy-2-chloro isomer.

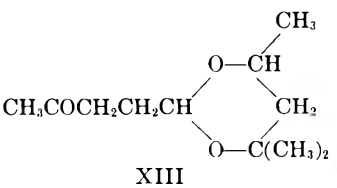


XII

Dehydrochlorination of the chlorohydrin gave XI in 90% purity in good yield. Overall yields from acrolein were 55%. The chlorohydrin was acetylated, but failed to react with ammonia or potassium phthalimide.

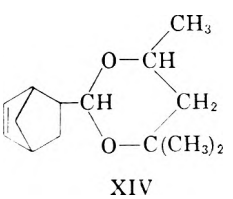
When chlorohydrin samples were prepared from hypochlorous acid generated from chlorine and sodium hydroxide the epoxide ultimately obtained was persistently contaminated with unidentified chlorine-containing impurities.

Mondon[8] has described the peroxide-catalyzed reaction of aldehydes with simple acrolein acetals, and we have found that VI reacts similarly to give the cyclic levulinic aldehyde acetal.

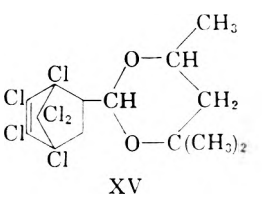


XIII

The acetal VI has also given adducts with cyclopentadiene and hexachlorocyclopentadiene.



XIV



XV

(7) M. Bergmann, A. Miekeley, and E. V. Sippmann, *Ber.* **62B**, 1467 (1929).

(8) A. Mondon, *Angew. Chem.* **64**, 224 (1952).

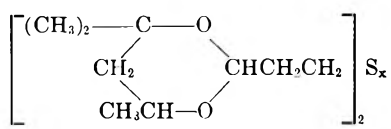
TABLE II

PROPERTIES OF ACROLEIN ACETALS

Starting Alcohol	Product[a]	B.P.	n_D^{20}	Analyses, %
Allyl alcohol	Acrolein diallyl acetal	75°/28 mm.	1.4380	Calcd.: C, 70.2; H, 9.2; Br_2 No., 312 g./100 g. Found: C, 70.0; H, 9.2; Br_2 No., 315 g./100 g.
2,3-Butanediol	III. R=R′=CH_3	56–58°/42 mm.	1.4282	Calcd.: C, 65.6; H, 9.4; Br_2 No., 124 g./100 g. Found: C, 65.4; H, 9.5; Br_2 No., 118 g./100 g.
2-Methyl-2,4-pentanediol	IV. R=R′=R″=CH_3	62–64°/18 mm.	1.4381	Calcd.: C, 69.2; H, 10.2; Br_2 No., 102 g./100 g. Found: C, 69.1; H, 10.3; Br_2 No., 100 g./100 g.
Glycerine	III. R=H R′=CH_2OH	70–72°/2 mm.	1.4647	Calcd.: C, 55.4; H, 7.7; OH value, 0.77 eq./100 g. Found: C, 55.4; H, 8.0; OH value, 0.76 eq./100 g.
1,2,6-Hexanetriol	III, R=H R′=$CH_2CH_2CH_2CH_2OH$	95–105°/0.2 mm.	1.4641	Calcd.: C, 62.7; H, 9.4; OH value, 0.58 eq./100 g. Found: C, 62.3; H, 9.4; OH value, 0.63 eq./100 g.
Glycerol α-monochlorohydrin	III. R=H R′=CH_2Cl	60°/9 mm.	1.4611	Calcd.: C, 48.5; H, 6.1; Cl, 23.9 Found: C, 48.6; H, 6.3; Cl, 24.2
Trimethylene glycol	IV, R=R′=R″=H	65–66°/44 mm.	1.4438	Calcd.: C, 63.1; H, 8.8 Found: C, 62.9; H, 8.8
Ethylene glycol	III, R=R′=H	114–116°/ atm.	1.4327	Calcd.: C, 60.0; H, 8.0 Found: C, 60.6; H, 8.1
Pentaerythritol	Diallylidenepentaerythritol I	93–4°/1 mm.	M.P. 42°	Lit.,[3] 43°
Pentaerythritol-crotonaldehyde	Dicrotonylidene pentaerythritol	130–132°/ 0.5 mm.	M.P. 50–52°	Calcd.: C, 65.1; H, 8.3; Br_2 No., 133 g./100 g. Found: C, 64.9; H, 8.4; Br_2 No., 131 g./100 g.
Sorbitol	Triallylidene sorbitol V	149–151°/ 0.9 mm.	1.4865	Calcd.: C, 60.8; H, 6.8; Br_2 No., 162 g./100 g. Found: C, 60.9; H, 6.9; Br_2 No., 158 g./100 g.

[a] "III" is the generalized 2-vinyl-1,3-dioxolane, $CH_2{=}CH{-}CH{-}O{-}CHR$ with $O{-}CHR'$; "IV" is the generalized 2-vinyl-1,3-dioxane, $CH_2{=}CH{-}CH{-}O{-}CHR$ with $O{-}C(R')(R'){-}CH_2$.

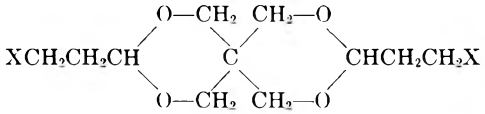
Attempts to add hydrogen sulfide to VI in the presence of cobalt polysulfide[9] led largely to the disulfide (XVI,x = 2) and trisulfide (XVI,x = 3). The disulfide may have arisen from the thiol



XVI

during the workup but was also obtained from β-chloropropionaldehyde acetal and sodium sulfide.

The diacetal I from pentaerythritol and acrolein has served as the precursor of a series of bifunctional derivatives. Addition of hydrogen chloride gave the bis(β-chloropropionaldehyde acetal) XVIIa in 80% yield, and reaction of XVIIa with sodium cyanide has given the dinitrile XVIIb in 50% yield.



XVII a. X = Cl b. X = CN

Epoxidation of I with peracetic acid gave mainly monoepoxide, along with small amounts of diepoxide.

(9) A. M. Alvarado, U. S. Patent 2,402,586 (to E. I. du Pont de Nemours and Co.) (1946).

EXPERIMENTAL[10]

Acrolein Acetals. General. Benzene soluble glycols were mixed with a small excess of acrolein, 1–3 volumes of an azeotroping solvent (usually benzene) and a small quantity of *p*-toluenesulfonic acid and then refluxed vigorously under a phase separating head until water evolution had ceased. After excess acrolein and some benzene had been removed through the head, the residue was cooled and an excess of calcium oxide was stirred into the solution. After filtration (sometimes omitted) the solvent was removed and the residue was distilled at reduced pressure. When benzene-insoluble glycols were used, a stirred three-necked flask was employed. Conditions were listed in Table I and the products are described in Table II.

2-Vinyl-4-hydroxymethyl-1,3-dioxolane. Solid Catalyst. In a 2-l., three-necked flask equipped with stirrer and phase-separating head were placed 228 ml. (3.2 mol.) of 96% acrolein, 276 g. (3.0 mol.) of glycerine, 600 ml. of benzene and 0.15×10^{-4} mol. of sulfuric acid adsorbed on 0.3 g. silica gel.[11] After 3 hr. under reflux, 62 ml. of water layer had been removed. The clear solution was decanted and the solvent removed at reduced pressure. Distillation from a Claisen flask gave 327 g. (83%) of crude 2-vinyl-4-hydroxymethyl-1,3-dioxolane b.p. 70–125° (2 mm.) (90% between 75° and 85°). The residue weighed 56 g.

Several such preparations were combined and distilled through a 20-tray bubble plate column at reflux ratios varying from 20:1 to 60:1. The following fractions were taken at 1 mm.

(10) Melting points corrected; boiling points not corrected.

(11) Prepared by addition of 40 ml. of water containing 0.5 g. of sulfuric acid to 100 g. of dry silica gel (Davison, grade 9–12, 28–200 mesh), followed by stirring on a hot plate until the silica is free-flowing. We are indebted to Dr. L. C. Fetterly of these laboratories for this material.

Fraction	B.P.°	Weight, g.	n_D^{20}	Yield, %
1	54–58	224	1.4680	26
2	58–65	106	1.4639	12
3	65–67	338	1.4612	39
4	67–75	101	1.4620	12
5	75–78	43	1.4650	5
residue	—	64	—	6

Fractions 1 and 3 may be respectively the isomeric dioxane and dioxolane. Fractions 4 and 5 are probably merely less pure dioxolane. Numerous earlier fractionations had shown only a very small low-boiling fraction, and it is therefore possible that conversion was occurring during the distillation.

Several attempts to prepare large amounts of this acetal with *p*-toluenesulfonic acid catalysis gave relatively poor yields. For example, from 3.1 mol. of glycerine, 4.15 mol. of acrolein and 0.2 g. of *p*-toluene-sulfonic acid, only 1.7 mol. (54%) of crude monomer was obtained. On redistillation through a 2-foot helices-packed column an analytically pure sample was taken as 2-vinyl-4-hydroxymethyl-1,3-dioxolane, b.p. 67° (0.6 mm.).

Anal. Calcd. for $C_6H_{10}O_3$: C, 55.4 H, 7.7; OH, 0.77 eq./100 g.; Br_2No., 123 g./100 g. Found: C, 55.1; H, 7.9; OH, 0.78 eq./100 g.; Br_2No., 123 g./100 g.

Several redistillations of the high boiling residue gave 36 g. (32 ml.) of pure material, b.p. 129° (0.10 mm.), n_D^{20} 1.4733. Its analysis was in agreement with a linear dimer of the acrolein–glycerine acetal from addition of the hydroxyl group of one molecule to the ethylenic linkage of another.

Anal. Calcd. for $C_{12}H_{20}O_6$: C, 55.4; H, 7.7; OH, 0.38 eq./100 g., Br_2No., 61.5 g./100 g., acetal-bound acrolein, 21.6%;[12]) (acetal + ether) bound acrolein, 43.1%.[13] Found: C, 55.5; H, 7.7; OH, 0.40 eq./100 g., Br_2No., 61 g./100 g.; acetal-bound acrolein, 23%; (acetal + ether) bound acrolein 45%.

Reaction of Acrolein and Epichlorohydrin. A solution of 156 ml. (2.2 mol.) of acrolein and 189 g. (2.0 moles) of epichlorohydrin in 500 ml. of benzene was dried by refluxing under a phase separating head. The solution was cooled to 20° and 1.4 g. of stannic chloride in 20 ml. of benzene was added with stirring. The temperature was held at 35° (ice cooling) for 1.5 hr., then 0.7 g. of stannic chloride in benzene was added, and the mixture was allowed to stand overnight.

Five grams of calcium oxide was added with stirring, after which the benzene and excess acrolein were removed at reduced pressure. The residue was distilled (Claisen still). After 8 g. of forcut b.p. 45–53° (10 mm.), probably largely recovered epichlorohydrin, the bulk of the product boiled in the range 55–67° (10 mm.) n_D^{20} 1.4603; yield 210 g. (71%, based on epichlorohydrin used).

2-(2-Chloroethyl)-4,4,6-trimethyl-1,3 dioxane (VII). Dry hydrogen chloride was bubbled with stirring into a solution of 236 g. (2.0 mole) of 2-methyl-2,4-pentanediol and 142 ml. (2.0 mole) of 96% acrolein in 350 ml. of chloroform at −15° to −10°. When hydrogen chloride was no longer absorbed, the aqueous layer which had formed was separated, the organic layer was washed with water and bicarbonate solution, dried, filtered, and relieved of solvent in vacuo. Distillation of the residue from a Claisen flask gave 360 g. (94% yield) of product, b.p. 69–77° (5 mm.). A center cut b.p. 71° (5 mm.) gave analyses in agreement with 2-(2-chloroethyl)-4,4,6-trimethyl-1,3-dioxane.

Anal. Calcd. for $C_8H_{17}O_2Cl$: C, 56.2; H, 8.8; Cl, 18.4. Found: C, 56.1; H, 8.9; Cl, 18.5.

(12) *p*-Phenylenediamine method.

(13) Dinitrophenylhydrazine – potassium hydroxide method. Both methods developed by Analytical Research Groups, Shell Development Company, and performed under the supervision of Mr. J. L. Jungnickel.

2-(2-Chloroethyl)-4,5-dimethyl-1,3-dioxolane (VIII). This was prepared similarly from acrolein, 2,3-butanediol, and hydrogen chloride gas. The product, b.p. 72–88° (20 mm.) was obtained in 77% yield; a heart cut, b.p. 85° (20 mm.) n_D^{20} 1.4419 was analyzed.

Anal. Calcd. for $C_7H_{13}O_2Cl$: C, 51.1; H, 8.0; Cl, 21.5. Found: C, 51.0; H, 8.0; Cl, 22.0.

2-(2-Hydroxyethyl)-4,4,6-trimethyl-1,3-dioxane (IX). A mixture of 112 g. (0.5 mole) of the cyclic β-chloropropionaldehyde acetal VII, 300 ml. of water, and 16 g. of sodium carbonate were placed in a stirred 1–1 autoclave. No apparent reaction occured at 140°, but at 160° 27% sodium hydroxide had to be pumped into the autoclave to maintain the *p*H at 8–9. In 6 hr., 61 ml. (94% of theory) was consumed, after which no further reaction occurred. The cooled product was taken up in ether, dried, filtered, and relieved of solvent. Distillation of the residue (Claisen) gave 82 g. (82% yield), b.p. 82–92° (3 mm.). Redistillation through a 2-foot helices-packed column gave a complete recovery; b.p. 69° (1 mm.), n_D^{20} 1.4485.

Anal. Calcd. for $C_9H_{18}O_3$: C, 62.1; H, 10.4; OH value, 0.58 eq./100 g. Found: C, 62.1; H, 10.4; OH value, 0.58 eq./100 g.

Hydrogenolysis of 2-(2-hydroxyethyl)4,4,6-trimethyl-1,3-dioxane. A solution of 55 g. (0.316 mole) of the acetal (IX) in 100 ml. of 20% acetic acid was hydrogenated at 100° and 1000 p.s.i.g. in a stainless steel vessel over 5 g. of 10% palladium on charcoal. After filtration the water and acetic acid were removed in vacuo, leaving 58 g. of residue. Twenty-six grams (45%) of this residue was distilled in a Piros-Glover spinning band column. There was obtained a 94% recovery of 2-methyl-2,4-pentanediol, b.p. 114.5° (35 mm.), n_D^{20} 1.4274, and 4.7 g. (48% yield) of trimethylene glycol, b.p. 130° (35 mm.) n_D^{20} 1.4388.

Anal. Calcd. for $C_3H_8O_2$: C, 47.4; H, 10.6; OH value, 2.63 eq./100 g. Found: C, 46.9; H, 10.6; OH value, 2.63 eq./100 g.

The actual yield of trimethyl glycol was doubtless higher, as the kettle and still drainings amounted to 3 g. probably largely trimethylene glycol.

2-(2-Cyanoethyl)-4,4,6-trimethyl-1,3-dioxane (X). A mixture of 95 g. (0.5 mole) of 2-(2-chloroethyl)4,4,6-trimethyl-1,3-dioxane and 26.5 g. (0.52 mole) of sodium cyanide was refluxed with stirring in 300 ml. of methyl cellosolve for 19 hr. After cooling, 1.5 g. of water was added and the mixture was extracted four times with chloroform. The extracts were washed with water, dried, filtered, and freed of solvent. Distillation from a flask equipped with a Claisen head gave 87 g. (95% yield) of the nitrile, b.p. 85–7° (2 mm.).

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.5; H, 9.4; N, 7.6. Found: C, 65.3; H, 9.4; N, 7.2.

2-(1,2-Epoxyethyl)-4,4,6-trimethyl-1,3-dioxane (XI). *With peracetic acid.* Forty-nine grams of 45% peracetic acid was added with stirring to 39 g. (0.25 mole) of VI in 150 ml. of chloroform. The temperature rose to 27°, whereupon cooling water was applied. After standing overnight, titration indicated no more peracetic acid was present. The solution was washed with water and bicarbonate, dried, and relieved of solvent. Distillation and redistillation through a 2-foot helices-packed column gave 18 g. of starting acetal, b.p. 65–70°C. (17 mm.), n_D^{20} 1.4355, and 12 g. of 2-(1,2-epoxyethyl)-4,4,6-trimethyl-1,3-dioxane, b.p. 96–99° (15 mm.), n_D^{20} 1.4461.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.8; H, 9.4; epoxide value, 0.58 eq./100 g Found: C, 63.3; H, 9.3; epoxide value, 0.60 eq./100 g.

2-(3-Ketobutyl)-4,4,6-trimethyl-1,3-dioxane (XIII). A mixture of 78 g. (0.5 mole) of VI, 66 g. (1.5 mole) of acetaldehyde and 4 g. of azobisisobutyronitrile was held at 80° for 40 hr. in a Hastelloy vessel. After removal of excess acetaldehyde the product was distilled from a Claisen flask and then through a 2-foot helices-packed column. There was obtained 10 g. of VI b.p. 39° (1 mm.) and 41 g. (40% conversion, 47% yield of the desired aldehyde acetal, b.p. 99° (1 mm.), n_D^{20}, 1.4430.

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 66.0; H, 10.0; carbonyl value, 0.50 eq./100 g. Found: C, 65.7; H, 10.0; carbonyl value, 0.50 eq./100 g.

Reaction of VI *with Hexachlorocyclopentadiene.* A mixture of 30 g. (0.1 mole) of hexachlorocyclopentadiene (Hooker Electrochemical Co.) and 16 g. (0.1 mole) of VI was heated to 180°, whereupon an exothermic reaction set in. Distillation of the partly charred product gave 12 g. of recovered diene, b.p. 57–60° (1 mm.), followed by 29 g. (60%) of viscous yellow products, b.p. 160–168° (0.5 mm.). Redistillation gave 21 g. of a product, analyses of which indicate that it may contain 2,3,4,5,7,7-hexachloro-1,2,5,6-tetrahydro-2,5-methanobenzaldehyde, 2-methyl-2,4-pentanediol acetal, b.p. 157–160° (0.5 mm.).

Anal. Calcd. for $C_{14}H_{26}Cl_6O_2$: C, 39.2; H, 3.8; Cl, 49.5. Found: C, 40.3; H, 3.8; Cl, 49.9.

Reaction of VI *with Cyclopentadiene.* Twenty-one grams (0.32 mole) of freshly distilled cyclopentadiene and 18 g. (0.12 mole) of VI were heated for 4 hr. at 180° in a stainless steel vessel. Distillation and redistillation through a 2-foot helices-packed column gave 12 g. of recovered VI, b.p. 60–70° (3 mm.), and 19 g. (50% conversion, 70% yield based on VI of 1,2,5,6-tetrahydro-2,5-methanobenzaldehyde, 2-methyl-2,4-pentanediol acetal, b.p. 93–4° (3 mm.), n_D^{20} 1.4747.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.8; H, 10.0. Found: C, 75.7; H, 10.0.

3,9-Bis(2-chloroethyl)-2,4,8,10-tetroxaspiro[5.5]undecane. Dry hydrogen chloride was passed into a stirred solution of 278 g. (1.3 mole) of I in 350 ml. of chloroform at −15° to −10°. When hydrogen chloride was no longer absorbed the solution was stirred for 1 hr. with solid sodium carbonate. After filtration and removal of solvent, the residue was distilled from a flask equipped with a Claisen head. The first cut, b.p. 113–144° (0.6 mm.), 31 g., was redistilled, b.p. 118–122° (1 mm.) and gave analyses in agreement with 3(2-chloroethyl)-9-vinyl-2,4,8,10-tetroxaspiro[5.5]undecane.

Anal. Calcd. for $C_{11}H_{17}ClO_4$: C, 53.2; H, 6.9; Cl, 14.3. Found: C, 53.3; H, 7.2; Cl 14.1.

Analyses indicate that the main cut, b.p. 140–150° (0.2 mm.), contains 3,9-bis(2-chloroethyl)-2,4,8,10-tetroxaspiro[5.5]undecane, XVIIa, apparently contaminated with the mono-chloro derivative.

Anal. Calcd. for $C_{11}H_{18}Cl_2O_4$: C, 46.5; H, 6.3; Cl, 24.8. Found: C, 47.3; H, 6.5; Cl, 24.0.

3,9-Bis(2-cyanoethyl)-2,4,8,10-tetroxaspiro[5.5]undecane. This was prepared from 0.5 mole of crude XVIIa in the manner described above. Simple distillation of the product gave a large (62 g.) unidentified forecut, b.p. 46–178° (0.14 mm.) and 65 g. (49%) of dinitrile, b.p. 187–199° (0.14 mm.). Redistillation gave a product, b.p. 180–181° (0.2 mm.), with analyses in agreement with 3,9-bis(2-cyanoethyl)-2,4,8,10-tetroxaspiro[5.5]undecane.

Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.2; H, 6.8; N, 10.1. Found: C, 58.5; H, 7.0; N, 10.1.

Epoxidation of (*I*).[14] A mixture of 53 g. (0.25 mole) of the bisacetal, 150 ml. of chloroform, and 92 g. (0.56 mole) of freshly prepared peracetic acid was stirred gently at room temperature. Titration after 16 hr. showed 57% consumption of active oxygen, and after 40 hr., 90% consumption. The solution was stirred with sodium bicarbonate solution, dried over magnesium sulfate, filtered, and relieved of solvent.

The 55 g. of residue was distilled and redistilled from a Claisen still, giving 10 g. of recovered acetal, b.p. 102–110° (2 mm.), and 10 g. of a fraction containing mainly the mono epoxide, b.p. 133° (1 mm.).

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.9; H, 7.1; epoxide value, 0.44 eq./100 g. Found: C, 58.0; H, 7.1; epoxide value, 0.37 eq./100 g.

A third fraction contained the bisacetal of glycidaldehyde, b.p. 176° (1 mm.) 11 g.

Anal. Calcd. for $C_{11}H_{16}O_6$: C, 54.2; H, 6.6; epoxide value 0.82 eq./100 g. Found: C, 55.1; H, 6.7; epoxide value, 0.67 eq./100 g.

EMERYVILLE, CALIF.

(14) Fischer, R. F., U. S. Patent 2,895,962 (1959) to Shell Development Co.

[CONTRIBUTION NO. 1051 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Reaction of Benzyne With An Allylic Olefin

EDWARD M. ARNETT

Received August 31, 1959

An attempted Diels-Alder condensation of benzyne with 2,5-dimethyl-2,4-hexadiene produced 2,5-dimethyl-3-phenyl-1,4-hexadiene (II), the first example, to our knowledge, of alkylation by an olefin through the benzyne intermediate. It is suggested that the reaction follows the mechanism that has been well established for the addition of allylic olefins to other dienophiles at high temperatures. At this point the reaction we have observed appears to offer little promise of having general synthetic value.

In the past several years considerable interest[1–4] has developed in the synthesis of the unknown hydrocarbon *o*-di-*t*-butylbenzene and varying estimates have been made of its strain energy. An attractive path to its synthesis that would avoid the difficult step of forcing two bulky groups into *ortho*- positions through substitution on the benzene nucleus would be through the Diels-Alder condensation of the benzyne intermediate[5] with 2,5-dimethyl-2,4-hexadiene to give the unknown 1,1,4,4-tetramethylnaphthalene (I) which could then be oxidized to *o*-phenylenebis(α-isobutyric acid)[6] and hence by suitable reduction to the desired hydrocarbon.

(1) H. C. Brown, D. Gintis, and L. Domash, *J. Am. Chem. Soc.*, **78**, 5390 (1956).

(2) R. B. Turner, D. E. Nettleton, Jr., and M. Perelman, *J. Am. Chem. Soc.*, **80**, 1430 (1958).

(3) M. S. Newman and G. R. Kahle, *J. Org. Chem.*, **23**, 666 (1958).

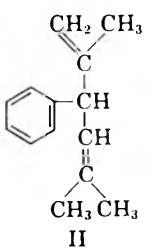
(4) W. H. Puterbaugh and M. S. Newman, *J. Am. Chem. Soc.*, **81**, 1611 (1959).

(5) G. Wittig, *Angew. Chem.*, **69**, 245 (1957).

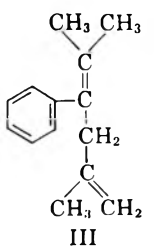
This reaction was attempted using carefully purified 2,5-dimethyl-2,4-hexadiene and *o*-fluorobromobenzene with magnesium in tetrahydrofuran as a source of benzyne, following Wittig's work. The only isolable product gave an analysis consistent with the formula for I, decolorized bromine in carbon tetrachloride, gave a positive test for unsaturation with tetranitromethane, and showed an infrared spectrum generally permissive of this formula except for a strong band at 895 cm.$^{-1}$

The NMR spectrum[7] did not show the expected ratio of 2:4:12 for the ethylenic:aromatic:aliphatic protons but gave instead 3:5:10 with one aliphatic hydrogen slightly removed from the others. This suggested that we were dealing with an isomer of I in which a side chain had become attached to the benzene ring at only one point leaving five aromatic hydrogens on the ring. Although some difficulty was encountered in oxidizing the product cleanly, the use of potassium permanganate in acetone with pyridine at room temperature gave a high yield of benzoic acid, supporting the belief that only monosubstitution of the benzene ring had occurred.

Structure II suggested by the NMR study[7] explained all of the facts so far observed including the infrared band at 895 cm.$^{-1}$ which is typical of a terminal methylene group.[8] This was confirmed further by catalytic hydrogenation and ozonization. Using palladium on charcoal as catalyst, the product absorbed two moles of hydrogen; the first rapidly, presumably saturating the terminal ethylene group; and the second mole much more slowly as it added to the more sterically hindered double bond. Exactly two moles of ozone were absorbed and formaldehyde and acetone were isolated from the products. Although it is possible to write another structure III for the product which will fit most of the evidence, we reject it as being incompatible with the NMR results (it would show a 2:5:11 ratio), because no conjugation is apparent from the infrared or ultraviolet spectra and because we can see no convenient mechanistic path for the formation of III whereas an easily available one with good precedent can be proposed for the formation of II.



II

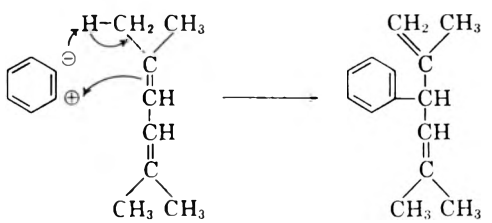


III

We are somewhat puzzled as to why II is not isomerized to 2,5-dimethyl-3-phenyl-2,4-hexadiene during the reaction. It may be that the magnesium fluorobromide which could catalyze isomerization also catalyzes polymerization of the 2,4-diene much more easily than the 1,4-diene isolated. If this were so, any isomerization would result in products that we would not isolate by distillation.

DISCUSSION

We have observed the reaction of an allylic olefin with a dienophile to give a product in which the multiplicity of the reactive bond in the dienophile is reduced by one and in which the double bond in the olefin has migrated to a new position allylic to the point of attack by the dienophile. Ample precedent for this type of reaction may be found in the work of Alder,[9-11] Arnold,[12,13] Rondestvedt,[14,15] and others[16] on the high temperature reaction of strong dienophiles with allylic olefins. Several elegant experiments by Arnold's group[12,13] give clear evidence that the reaction proceeds through a concerted ionic mechanism involving a six-membered ring transition state and this suggestion is supported by Rondestvedt's[14,15] results. It is proposed that the reaction described above follows the same course.



Although abundant examples of the high temperature reaction are to be found in the references above, to our knowledge none of them presents a case where the high temperature addition takes

(6) While we were attempting to prepare the diacid by the unsuccessful method described here, its synthesis by a different route was described by H. A. Bruson, F. W. Grant, and E. Bobko, *J. Am. Chem. Soc.*, **80**, 3633 (1958). To our knowledge this is the first *o*-di-*t*-butylbenzene derivative to be described in the literature.

(7) This spectrum was determined and interpreted by Dr. Aksel Bothner-By of Mellon Institute who suggested the correct structure on the basis of this result. We wish to express our gratitude to him for this experimental work and for his many helpful suggestions in the course of this study.

(8) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., John Wiley and Sons, New York, N. Y., 1958, p. 51.

(9) K. Alder, F. Pascher, and A. Schmitz, *Ber.*, **76**, 27 (1943).

(10) K. Alder and T. Noble, *Ber.*, **76**, 54 (1943).

(11) K. Alder and C. Schmidt, *Ber.*, **76**, 183 (1943).

(12) R. T. Arnold and J. F. Dowdall, *J. Am. Chem. Soc.*, **70**, 2590 (1948).

(13) R. T. Arnold and J. S. Showell, *J. Am. Chem. Soc.*, **79**, 419 (1957).

(14) C. Rondestvedt and B. Wark, *J. Org. Chem.*, **20**, 368 (1955).

(15) C. Rondestvedt and A. Filbey, *J. Org. Chem.*, **19**, 548 (1954).

(16) For further references to the work of these and other authors in this field, see a recent review by R. D. Gilliom in M.I.T. Seminar Reports, 1956–57, 456.

place with a diene in preference to a Diels-Alder condensation as we have observed. The reason for this unusual behavior of 2,5-dimethyl-2,4-hexadiene is apparent from a model of the molecule which shows that it cannot be forced into the conformation required for ring closure but that the two isobutylene groups assume a position *trans* to each other and one of them is in the proper position for the addition to the dipolar bond in benzyne. The fact that the reaction occurs at room temperature attests to the reactivity of benzyne.

The discovery of this reaction for 2,5-dimethyl-2,4-hexadiene at once suggested that a general synthetic alkylation procedure using other allylic olefins might be developed. We are currently investigating this possibility but must report that at present the results are not at all promising; so far we have not found another case. (Using isobutylene as olefin we have obtained a 2% yield of an oil with the correct boiling point, infrared and NMR for 2-methyl-3-phenyl-propene-1 but with very poor analysis and refractive index.) Although allylbenzene gives particularly high yields in the thermal reaction with maleic anhydride, we have been unable to isolate 1,3-diphenylpropene from its reaction with benzyne under our conditions. Also reaction of cyclohexene with benzyne formed either from *o*-fluorobromobenzene and magnesium or from the reaction of bromobenzene and sodium amide in liquid ammonia failed to produce 3-phenylcyclohexene. Perhaps the reason that we cannot isolate simple adducts in these cases involving relatively favorable olefins but can find a simple product in the apparently less favorable case of 2,5-dimethyl-2,4-hexadiene is that the product of such a reaction is always another allylic olefin which if sufficiently reactive can continue to add to more benzyne molecules. If these following reactions are rapid enough in the cases of allylbenzene and cyclohexene, the main products will remain in the pot with the polymer that is always formed in the reaction and may not be separated by distillation.

EXPERIMENTAL

o-Fluorobromobenzene was prepared through pyrolysis of *o*-bromobenzenediazonium fluoroborate following directions of Bartlett and Giddings[17] based on a method of Schieman and Winkelmüller.[18] *2,5-Dimethyl-2,4-hexadiene* was purchased from Matheson, Coleman, and Bell. Since distillation failed to give adequate purification, the material was repeatedly frozen and the liquid phase decanted. This gave a product melting at 14.5° in agreement with the highest literature melting point[19] but with n_D^{20} = 1.4769 instead of 1.4796. Further purification failed to improve this value. The well known[20] proclivity of this diene to polymerize explains the difficulty in purifying it.

Other reagents and solvents were commercially available and were purified until physical constants agreed with literature values.

Preparation of 2,5-dimethyl-3-phenyl-1,4-hexadiene (II). In a flame dried 100-ml. three necked flask with stirrer, condenser and addition funnel were placed 5.0 g. (0.207 mol.) of Grignard-grade magnesium turnings covered with 12 ml. of dry tetrahydrofuran. In the addition funnel was placed a solution of 20 ml. (0.200 mol.) of *o* fluorobromobenzene and 28.3 ml. (0.200 mol.) of 2,5-dimethyl-2,4-hexadiene in 93 ml. of dry tetrahydrofuran. In cases where the reaction did not begin spontaneously within 5 min. after the addition of 5–10 ml. of solution from the funnel, it could be initiated easily by scratching the magnesium, addition of a crystal of iodine or local heating with a match. The reaction was maintained at reflux by the addition of reactants, which required about an hour. Further refluxing with stirring on the steam bath consumed most of the remaining magnesium and produced a clear brown, viscous solution. After stripping off the solvent with water pump and steam bath, the residue was hydrolyzed with saturated ammonium chloride and 5% hydrochloric acid was added until two clear layers formed. The system was extracted with three successive portions of ether. After treatment with 5% sodium carbonate solution until no more carbon dioxide was evolved, the ether layer was washed with three portions of distilled water and the ether stripped off.

Distillation at 0.2 mm. began at 45° and between 65–67° a clear main fraction was obtained. Raising the temperature did not remove any other well defined fractions, the major portion of the product remaining in the pot as an intractible polymer. The 65–67° cut was not homogeneous but contained crystals that had apparently sublimed with the liquid phase. These were precipitated by adding ligroin and after recrystallization from carbon tetrachloride melted at 198°. This material was identified as triphenylene, a common by-product when benzyne is generated from *o*-fluorobromobenzene[6]; the melting point was undepressed by mixture with authentic triphenylene purchased from K and K Laboratories.

Anal. Calcd. for $C_{18}H_{12}$: C, 94.69; H, 5.31. Found: C, 94.06; H, 5.51 (Schwarzkopf).

After removal of the ligroin, 4.29 g. (11.9% yield) of clear oil remained. This distilled completely at 83–86°, 0.45 mm., but very serious foaming, which could not be suppressed, interfered with all attempts to purify the product by distillation. The product decolorized bromine in carbon tetrachloride instantly, and showed unsaturation with tetranitromethane and potassium permanganate. The ultraviolet curve (using Beckman DU and 95% ethanol) showed gradual loss of optical density from 220–300 mμ and no aromatic fine structure. This may be attributed to masking by end absorption from the double bonds. The infrared spectrum was obtained with a Perkin-Elmer Model 21 Spectrophotometer (purchased on a grant from the National Science Foundation) with carbon tetrachloride as solvent.

Anal. Calcd. for $C_{14}H_{18}$: C, 90.26; H, 9.73. Found: C, 89.83; H, 9.96 (Microanalytical Laboratory of Mellon Institute).

Oxidation of the product. The product (0.637 g.) was dissolved in 100 ml. of acetone containing 5 ml. of pyridine and 4.0 g. of potassium permanganate. It was stirred rapidly at room temperature for 72 hr., rendered slightly acid with dilute sulfuric acid, and then treated with sodium bisulfite until the manganese dioxide disappeared. The solution was extracted with three 100-ml. portions of chloroform and the combined chloroform solutions dried over sodium sulfate and then Drierite. Evaporation of the chloroform left light green crystals corresponding in weight to a quantitative yield (0.424 g.) of benzoic acid. Recrystallization from water

(17) P. D. Bartlett and W. Giddings, private communication.

(18) G. Schiemann and W. Winkelmüller, *Org. Syntheses*, Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 299.

(19) Heilbron, *Dictionary of Organic Compounds*, Vol. II, Oxford University Press, New York, N. Y., 1953, p. 311.

(20) M. C. Kloetzel, *Org. Reactions*, 4, 13 (1948).

gave white crystals melting at 121° (undepressed upon admixture with authentic benzoic acid).

Hydrogenation. Hydrogenation of 0.195 g. (1.05 mmol.) of product was performed in ethyl alcohol using palladium on charcoal in the usual way[21] at room temperature. The first molar equivalent of hydrogen was absorbed within 15 min. while 24 hr. was required for the second mole.

Ozonization. To a 0.8409-g. sample dissolved in 100 ml. of anhydrous methanol as participating solvent was added ozone at −40° from a Welsbach T 23 ozonizer at a flow rate of 17 l. per hr. and an ozone concentration of 66.5 mg. per l.; oxygen pressure was eight p.s.i. and potential was 90.[22] It was estimated that at this rate 23.2 min. would be required for complete ozonization of two double bonds. After 20 min. the first traces of ozone broke through to the ozone meter and the reaction was stopped at 23 min. Now 2 g. of zinc dust was added and after warming to room temperature, 10 ml. of 5% sulfuric acid was added to destroy remaining peroxides. The solution was steam distilled until the distillate tested negative with 2,4-dinitrophenylhydrazine, the volume at this point being nearly 3 l. The first 1500-ml. portion of distillate was made just acid and 3 g. of dimedone in 50 ml. of 50% aqueous ethanol added.[23] A fluffy precipitate formed slowly which when dried gave the proper melting point for the formaldehyde-dimedone adduct, 196° (hot stage), and was not lowered by mixing with authentic adduct.

The filtrate from the dimedone reaction was steam distilled and 2,4-dinitrophenylhydrazine added. The mixed derivatives were collected by filtration, dried, dissolved in chloroform and chromatographed first on Fisher alumina and then on Woelm alumina using chloroform as eluent in both cases. The wide range of melting points for acetone-2,4-dinitrophenylhydrazone that may be found in the literature attests to the difficulty in its purification. Several recrystallizations of the twice chromatographed product failed to raise the melting point from 123° to the desired 126°.[24] However, chromatography on Florosil with benzene eluent raised the melting point to the desired temperature and the identification was completed by mixed melting point and comparison of the infrared spectrum (Nujol mull)[25] with an authentic sample.

NMR spectrum.[7] This was obtained using a Varian Dual-Purpose 60-mc. NMR Spectrometer coupled to a Varian 60-mc. magnet with flux stabilizer. In addition to the gross features of the spectrum described above it was noticed that the hydrogens in the olefinic region consisted of a non-equivalence quartet and one sharp peak of intensity two. The quartet implies the presence of two lone hydrogens on adjacent carbons and the single spike the presence of two equivalent hydrogens on a carbon adjacent to another carbon bearing no hydrogens (*i.e.*, the methylene hydrogen on carbon-1). The lower of the nonequivalent lone hydrogens is that on carbon-4 of the 1,4-hexadiene chain and the higher one is presumably on carbon-3 and is shifted to its low position by its proximity to two trigonal carbons.

Acknowledgment. The writer is glad to express his appreciation to Professor Robert Levine of this Department and Dr. Bothner-By of Mellon Institute for critical readings of this manuscript.

PITTSBURGH 13, PA.

(21) K. G. Stone, *Determination of Organic Compounds*, McGraw-Hill, New York, N. Y., 1956, p. 21.

(22) These conditions were chosen by Dr. R. H. Callighan of Mellon Institute who performed the ozonization for us. We are grateful for this help from him.

(23) R. P. Linstead, J. A. Elvidge, and M. Whalley, *A Course in Modern Techniques of Organic Chemistry*, Butterworths, London, 1955, Chapter 20.

(24) Shriner, Fuson, and Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley and Sons, New York, N. Y., 1956, p. 316.

(25) J. H. Ross, *Anal. Chem.*, 25, 1288 (1953).

[CONTRIBUTION FROM THE AGRICULTURAL RESEARCH DIVISION, SHELL DEVELOPMENT COMPANY AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

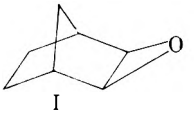
Bridged Polycyclic Compounds. XI. Epoxidation of Norbornene and of *exo*-Dihydrodicyclopentadiene[1]

S. B. SOLOWAY AND STANLEY J. CRISTOL

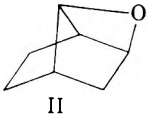
Received September 23, 1959

Epoxidation of norbornene has been shown to give 2,3-epoxynorbornane and epoxidation of *exo*-dihydrodicyclopentadiene (*exo*-5,6-cyclopentano-2-norbornene) has been shown to give *exo*-2,3-epoxy-*exo*-5,6-cyclopentanonorbornane. Thus both epoxidations occur without rearrangement and by *exo* addition to the bicycloheptene ring.

The epoxidations of norbornene (bicyclo(2,2,1)-heptene-2) with monoperoxyacetic acid[2] and monoperoxyphthalic acid[3] have been reported. The structure of the oxide was formulated as *exo*-2,3-epoxynorbornane (I) in view of its reduction by lithium aluminum hydride to *exo*-2-norborneol[2] and its ring opening to a 2,7-dihydroxynorbornane.[2,3] This formulation of the epoxide as the 2,3-isomer suggests that Wagner-Meerwein rearrangement has occurred in the ring-opening step, but the facts available in the literature are also consistent with the formulation of the epoxide as the 2,7- isomer, if the assumption is made that reduction by lithium aluminum hydride involves attack at the bridge carbon atom. We had pre-



I



II

(1) Previous paper in series: S. J. Cristol, W. K. Seifert, and S. B. Soloway, *J. Am. Chem. Soc.*, in press (1960).

(2) H. M. Walborsky and D. F. Loncrini, *J. Am. Chem. Soc.*, **76**, 5396 (1954).

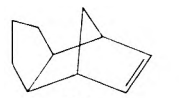
(3) H. Kwart and W. B. Vosburgh, *J. Am. Chem. Soc.*, **76**, 5400 (1954).

pared this epoxide from norbornene and peroxybenzoic acid, and had found properties and reactions similar to those reported in the other preparations.

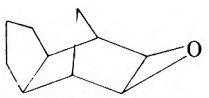
Barrow and Searles[4] have shown that, while 1,2-epoxides have strong infrared absorption bands at about 11.9μ,[5] trimethylene oxides have bands at about 10.3 μ and tetrahydrofurans at about 9.2μ. Accordingly, structure I should have a strong band at about 11.9μ, and structure II, which may be classified as having both four- and five-membered oxide rings, should have a strong absorption peak or peaks in the range 9.1 to 10.3μ.

An infrared spectral analysis showed the position of a strong band at 11.85μ for the epoxide of norbornene and this result, coupled with the lithium aluminum hydride reduction to *exo*-2-norborneol confirms the structure *exo*-2,3-epoxynorbornane (I).[2,3]

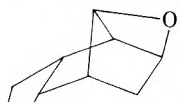
We felt it worthwhile to study a system in which a *chemical* proof could be added to the infrared analysis result. Accordingly, epoxidation of *exo*-5,6-cyclopentano-2-norbornene (III) was carried out, using peroxybenzoic acid in chloroform.



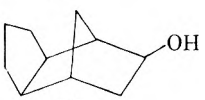
III



IV



V



VI

If the epoxidation occurred without rearrangement, product IV would result, and lithium aluminum hydride reduction would give *exo*-5,6-cyclopentano-*exo*-2-norborneol (VI). On the other hand, addition with rearrangement would give V, which on reduction would give an alcohol related to *endo*-5,6-cyclopentanonorbornane.

The epoxide product was an oil, which had a strong absorption band at 11.84μ; it was reduced by lithium aluminum hydride in refluxing tetrahydrofuran very slowly to give slightly impure *exo*-5,6-cyclopentano-*exo*-2-norborneol[6] m.p. 37–46° (lit.[1,7] m.p. 53–54°). The alcohol was converted to the *p*-nitrobenzoate and acid phthalate esters, and melting point and mixed melting-point determinations with esters prepared from authentic alcohol confirmed the identity of the alcohol as VI.

Thus, addition of an oxygen atom to the olefinic bond in norbornene and one of its derivatives involves *exo* addition without rearrangement.

EXPERIMENTAL

exo-2,3-Epoxynorbornane, I. A chloroform solution, 1340 ml., containing 104 g. (0.75 mole) of peroxybenzoic acid[8] was added slowly to 65.8 g. (0.7 mole) of solid norbornene,[9] producing a strongly exothermic reaction. The addition was completed with cooling, and the resulting solution was kept in a refrigerator for 4 days; at this time, titration with sodium thiosulfate showed the consumption of 96.2 g. of peroxybenzoic acid (theory 96.6 g.). The chloroform solution was washed with alkali and water, dried over anhydrous sodium sulfate, and distilled through a modified Claisen flask at atmospheric pressure (630 mm.). After the chloroform was removed there was obtained a forerun of 3 g., b.p. 142–146° (m.p. 121–122°) and 59 g. of product, b.p. 146–148°, which solidified in the receiver as fern-like crystals, m.p. 121–125° (total yield 80%). Recrystallization of a specimen from cold hexane gave I as needle-like crystals, m.p. 125.5–126.5° (lit. m.p. 125–127°;[2] 118–119°[3]).

Anal. Calcd. for $C_7H_{10}O$: C, 76.3; H, 9.15. Found: C, 76.7; H, 9.24.

The compound smelled like camphor and sublimed readily at room temperature. It did not react with potassium permanganate in acetone, nor with bromine in carbon tetrachloride. Its infrared spectrum had a strong peak at 11.85 μ characteristic of 1,2-epoxides.[10]

This epoxide could be reduced to *exo*-2-norborneol by heating at reflux with a solution of lithium aluminum hydride in tetrohydrofuran for seven days. A similar reduction, using *N*-ethylmorpholine as solvent, has already been reported.[2]

exo-2-syn-7-Norbornanediol diacetate. A solution of 5.5 g. (0.05 mole) of I, and 4.9 g. (0.05 mole) of potassium acetate in 100 ml. of acetic acid was heated at reflux for 48 hr. The product was isolated by diluting with water and extracting with pentane. The oil remaining after evaporation of the pentane was distilled; 5.2 g. (49%), b.p. 134–135° (15 mm.), n_D^{20} 1.4657, was obtained.

Anal. Calcd. for $C_{11}H_{16}C_4$: C, 62.2; H, 7.60; sapon. equiv., 106. Found: C, 62.0; H, 7.60; sapon. equiv., 109.

exo-2-syn-7-Norbornanediol. A solution of 24.5 g. (0.115 mole) of the diacetate in 75 ml. of dry ether was added slowly with stirring to 11.9 g. (0.345 mole) of lithium aluminum hydride in 600 ml. of ether, and the mixture was stirred for 24 hr. The excess lithium aluminum hydride was destroyed with 35 ml. of ethyl acetate, the complex was decomposed, and the inorganic hydroxides were coagulated by the addition of 125 ml. of water. The ether solution was then filtered through a plug of dry cotton. Evaporation of the solvents at reduced pressure gave 13.8 g. (93% yield) of a crystalline residue, m.p. 177–181°. Recrystallization from nitromethane gave 5.5 g. (37%) of pure *exo*-2-*syn*-7-norbornanediol as fern-like crystals, m.p. 191–192° (lit. m.p. 179–181°;[2] 174–176°[3]).

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.6; H, 9.44. Found: C, 65.6; H, 9.56.

The water-soluble diol gave a negative test for a vicinal diol with periodic acid.

exo-2,3-Epoxy-exo-5,6-cyclopentanonorbornane (*exo-5,6-epoxyoctahydro-exo-4,7-methanoindene*, IV). A chloroform solution, 250 ml., containing 15.2 g. (0.11 mole) of peroxybenzoic acid was added slowly to 13.4 g. (0.10 mole) of *exo*-dihydrodicyclopentadiene (III),[1] with cooling to moderate the exothermic reaction. After the reaction solution was kept in a refrigerator overnight, titration with sodium thiosulfate showed that all of the peracid had been consumed.

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(10) The infrared spectrum is given in the Ph.D. thesis of S. B. Soloway, University of Colorado, January 1955.

Additional chloroform solution, 110 ml., containing 6.6 g. (0.048 mole) of peroxybenzoic acid was added. After 4 hr. at room temperature, 0.044 mole of peracid was still present. The chloroform solution was then washed repeatedly with sodium carbonate solution and dried over anhydrous sodium sulfate. The chloroform was removed at atmospheric pressure and the residual oil was distilled to yield 12.0 g. (80%) of IV as a colorless oil, b.p. 50–51.5° (0.7 mm.), n_D^{28} 1.5031.

Anal. Calcd. for $C_{10}H_{14}O$: C, 80.0; H, 9.39. Found: C, 80.0; H, 9.50.

The infrared spectrum of IV showed a characteristic 1,2-epoxide peak at 11.84 μ.[10]

exo-5,6-Cyclopentano-exo-2-norborneol (octahydro-exo-4,7-methanoinden-exo-5-ol, VI). Lithium aluminum hydride, 3.8 g. (0.1 mole) was dispersed in 50 ml. of tetrahydrofuran by refluxing with stirring, 5.0 g. (0.033 mole) of epoxide IV was added, and the reaction mixture was heated at reflux for 5 days. The excess lithium aluminum hydride was destroyed with 10 ml. of ethyl acetate and the complex was decomposed with 100 ml. of water. Extraction of both the solid and liquid phases with pentane, drying and evaporation of the solvents, and, finally, distillation yielded 1.15 g. of a forerun, b.p. 50–73° (0.5 mm.), which was about 65% epoxide by infrared analysis, and 3.14 g. (62%) of impure alcohol VI, b.p. 75–79° (0.7 mm.), which solidified, m.p. 37–46°.

The *acid phthalate* derivative was prepared by heating 1.0 g. (6.6 mmoles) of the reduction product with 1.27 g. (8.6 mmoles) of phthalic anhydride in 15 ml. of pyridine on the steam bath. Water and 6*N* hydrochloric acid were added and the precipitated oil was taken up in ether. The ethereal solution was dried over anhydrous sodium sulfate and the solvent was evaporated to yield 1.9 g. (96%) of product, m.p. 151–153.5°. Crystallization from acetone gave 0.81 g. of pure acid phthalate, m.p. 157.5–158°; mixed m.p., 157.5–158°, with the acid phthalate of authentic VI.[1,6,7]

Treatment of 0.5 g. (3.3 mmoles) of the alcohol with 0.73 g. (3.9 mmoles) of *p*-nitrobenzoyl chloride in 5 ml. of pyridine yielded 0.6 g. (60%) of crude product, m.p. 86–90°. Two crystallizations from hexane gave 0.25 g. of *p*-nitrobenzoate, m.p. 91.5–93°; mixed m.p. 93.5–94° with the *p*-nitrobenzoate of authentic VI[1,6] (m.p. 94–94.5°).

Acknowledgments. The authors are indebted to Paul Saliman for elemental analyses and to Glen Pollard for infrared spectra.

BOULDER, COLO.

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICAL SCIENCE, KANSAS STATE COLLEGE]

Condensation Reactions of Carbon Monoxide with Aluminum Chloride and Aromatic Systems

ELBERT W. CRANDALL, C. H. SMITH,[1] AND R. C. HORN[2]

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Carbon monoxide reacts with aromatic hydrocarbons in the presence of molar quantities of aluminum chloride at 60° and a pressure of 50 p.s.i. to give substituted anthracenes. Toluene gives a dimethylanthracene, diphenylmethane gives a dibenzylanthracene, and *p*-xylene yields 1,4,5,8-tetramethylanthracene. Diphenyl ether forms xanthydrol at 80°.

Aromatic aldehydes, benzyl alcohol, and benzhydrol are cleaved in the presence of excess aluminum chloride to give carbon monoxide. If an aryl hydrocarbon is present, polynuclear systems are formed.[3–7] Carbon monoxide should then react with aromatic hydrocarbons to form derivatives of anthracene.

In the present investigation, carbon monoxide under 50 p.s.i. pressure was shaken with various aromatic hydrocarbons and diphenyl ether in the presence of aluminum chloride over a period of 12–18 hours. Pressure drops of 5–15 pounds were noted in most cases.

At 60°, toluene reacts with carbon monoxide to form a mixture of dimethylanthracenes which is regarded as a eutectic mixture of the 2,6- and 2,7-isomers.[8] Diphenylmethane gives a dibenzylanthracene, while *p*-xylene gives a tetramethylanthracene, probably the 1,4,5,8 isomer.[4]

The dimethyl and dibenzylanthracenes were analytically and spectroscopically identical with the products obtained from the reactions of benzaldehyde with toluene and diphenylmethane.[3,4,6] Each is regarded as a mixture of the 2,6- and 2,7-isomers[8].

The reaction is temperature dependent. At 30°, toluene reacts to give some *p*-tolualdehyde along with dimethylanthracene. At 40°, only a trace of aldehyde is observed. The yield of dimethylanthracene increases to a maximum at 60° (Table I). A comparison of this reaction with the Gattermann-Koch reaction was carried out.[9] Toluene, saturated with dry hydrogen chloride, failed to give increased yields of dimethylanthracene at 60°.

Diphenyl ether is unique in that the carbon monoxide bridges the *ortho*- positions to give xanthydrol.

(1) In part from the master's thesis of C. H. Smith, Kansas State College, Pittsburg, Kan.

(2) From the master's thesis of R. C. Horn, Kansas State College, Pittsburg, Kan.

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(7) H. E. Ungnade, E. F. Cline, and E. W. Crandall, *J. Am. Chem. Soc.*, **75**, 3333 (1953).

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TABLE I

EFFECT OF TEMPERATURE ON YIELD OF DIMETHYLANTHRACENE[a]

Temperature, °C.	*p*-Tolualdehyde, g.	Dimethylanthracene, g.
30	3.86	0.7
40	0.10	2.1
50	0.10	2.7
60	0.10	3.0

[a] 60 ml. toluene; 12 hours.

Anal. Calcd. for $C_{28}H_{22}$: C, 93.85; H, 6.15. Found: C, 93.61; H, 6.00.

Dibenzoylanthraquinone. Oxidation of 1 g. of the dibenzylanthracene with 4 g. of chromic anhydride, 28 ml. of glacial acetic acid, and 4 ml. of water gave 1.09 g. (98.1%) of dibenzoylanthraquinone which melted at 241–242° (from 95% ethanol).

Anal. Calcd. for $C_{28}H_{16}O_4$: C, 80.70; H, 3.85. Found: C, 80.47; H, 3.61.

The reaction of toluene with carbon monoxide and hydrogen chloride in the presence of aluminum chloride at 60°. Toluene (60 ml.) was saturated for 1 hr. with dry hydrogen chloride gas. This toluene and 25 g. of aluminum chloride were treated with carbon monoxide at 50 p.s.i. and 60°. The mixture was agitated for 12 hr. The reaction mixture was worked up in the usual way and gave no aldehyde. The solid material weighed 4.7 g. from which 1.10 g. of dimethylanthracene were obtained.

TABLE II

ULTRAVIOLET DATA

	λ_{max}	log ϵ	λ_{max}	log ϵ	λ_{max}	log ϵ	λ_{max}	log ϵ	λ_{max}	log ϵ
Anthracene	252	5.30	322	3.50	338	3.80	355	4.00	375	3.90
Dimethylanthracene	257	5.10			340	3.60	359	3.71	378	3.60
Tetramethylanthracene	259	5.38			343	3.69	359	3.79	380	3.69
Dibenzylanthracene	253	5.46	324	3.75	339	4.06	356	4.24	375	4.20
Xanthydrol	249	3.75	284	3.33						

Diphenyl ether has been reported[7] previously to react with benzaldehyde and aluminum chloride to give 9-phenylxanthydrol.

As evidence that the anthracenes are substituted on the benzenoid positions, the dimethyl- and dibenzylanthracenes were oxidized to the corresponding anthraquinones. In each case the disubstituted anthraquinone was obtained, indicating that the groups could not be on the 9 or 10 position.

EXPERIMENTAL

The reaction of toluene and carbon monoxide in the presence of aluminum chloride. Toluene (60 ml., 0.65 mol.) and 25 g. (0.2 mol.) of aluminum chloride were placed in the reaction flask of a Parr hydrogenation apparatus. The system was filled with carbon monoxide to 50 p.s.i. The reaction mixture was agitated and allowed to react for 12 hr. at 60°. The reaction mixture was then decomposed with ice and hydrochloric acid and steam distilled.

The solid residue from the steam distillation was removed by filtration and dried by azeotroping with benzene and sublimed under vacuum (1 mm.). Crystallization of this product from ligroin (b.p. 60–90°) gave 2.1 g. of a dimethylanthracene which melted at 223–225°.

Anal. Calcd. for $C_{16}H_{14}$: C, 93.10; H, 6.80. Found: C, 92.87; H, 6.69.

Dimethylanthraquinone. Dimethylanthracene (0.45 g.), dissolved in 7 ml. of glacial acetic acid, was refluxed gently over a low flame. A solution of 2.0 g. of chromic anhydride in 2.0 ml. of water and 8 ml. of acetic acid was added during 1 hr. The solution was cooled, diluted with 200 ml. of water, and filtered. The crude green solid was washed with water, dilute aqueous sodium hydroxide, and again with water. Crystallization from 95% ethanol gave yellow needles of dimethylanthraquinone (0.41 g., 79%) which melted at 154–155°.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.30; H, 5.08. Found: C, 81.04; H, 4.89.

The reaction of diphenylmethane and carbon monoxide with aluminum chloride. Diphenylmethane (60 ml.) and aluminum chloride (25 g.) when shaken with carbon monoxide at 50 p.s.i. for a period of 12 hr. at 60° gave, after decomposition, 10 g. of solid which was vacuum sublimed (1 mm.). Crystallization from ligroin (b.p. 60–90°) gave 3 g. of a dibenzylanthracene which melted at 191–192°.

The reaction of toluene with carbon monoxide in the presence of aluminum chloride at 30°. Toluene (60 ml.) and 25 g. of aluminum chloride were treated with carbon monoxide as previously described. The reaction mixture was agitated for 12 hr. at 30°. The distillate from the steam distillation was positive to the Schiff reagent. The organic layer was separated and treated with saturated aqueous sodium bisulfite. The solid formed was removed by filtration, dried, and decomposed with concentrated hydrochloric acid. *p*-Tolualdehyde (3.86 g., 0.032 mol.) was recovered. The 2,4-dinitrophenylhydrazone melted at 233–235°, lit.[10] m.p. 232–234°.

The solid from the steam distillation was removed by filtration, dried, and sublimed under vacuum (1 mm.). Crystallization from ligroin gave 0.7 g. of dimethylanthracene, m.p. 223–225°.

The same reaction carried out at 40° gave 0.1 g. of *p*-tolualdehyde and 2.1 g. of dimethylanthracene. At 50°, 0.1 g. of aldehyde and 2.7 g. of dimethylanthracene were obtained.

The reaction of diphenyl ether and carbon monoxide with aluminum chloride. Diphenyl ether (60 ml.) and aluminum chloride (25 g.) were shaken at 80° for 16 hr. with carbon monoxide at 50 p.s.i. Steam distillation gave first unchanged diphenyl ether and later white crystals of xanthydrol. The xanthydrol was removed by filtration and weighed 2.1 g. It melted at 120–122°, lit.[10] m.p. 121°. The dixanthyl urea derivative melted at 260–261°, lit.[10] m.p. 260°.

The reaction of p-xylene and carbon monoxide with aluminum chloride. p-Xylene (60 ml.) and aluminum chloride (25 g.) were shaken at 60° for 16 hr. with carbon monoxide at 50 p.s.i. The solid remaining after steam distillation weighed 16.00 g. Vacuum sublimation gave 8.5 g. of a tetramethylanthracene which melted at 268–269° (from ligroin b.p. 60–90°). Ellison and Hey[4] have prepared 1,4,5,8-tetramethylanthracene, m.p. 270°.

Anal. Calcd. for $C_{18}H_{18}$: C, 92.37; H, 7.63. Found C, 92.16; H, 7.45.

Absorption spectra. The ultraviolet absorption spectra

(10) E. H Huntress and S. P. Mulliken, *Identification of Pure Organic Compounds*, John Wiley & Sons, New York (1946), p. 65.

were carried out in spectra grade cyclohexane with a Beckmann Model DU spectrophotometer.

The values for maxima and minima of the anthracenes are in good agreement with the proposed effects of groups.[11] The dimethyl and tetramethylanthracenes show a bathochromic effect with some loss of fine structure, with respect to anthracene. Dibenzylanthracene shows a fine structure effect, with a hyperchromic shift, no loss in fine structure and no bathochromic shift.

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PITTSBURG, KAN.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE PAINT DIVISION OF THE PITTSBURGH PLATE GLASS COMPANY]

N-Alkylation of Nitriles with Benzyl Alcohol, Related Alcohols, and Glycols[1]

CHESTER L. PARRIS AND ROGER M. CHRISTENSON

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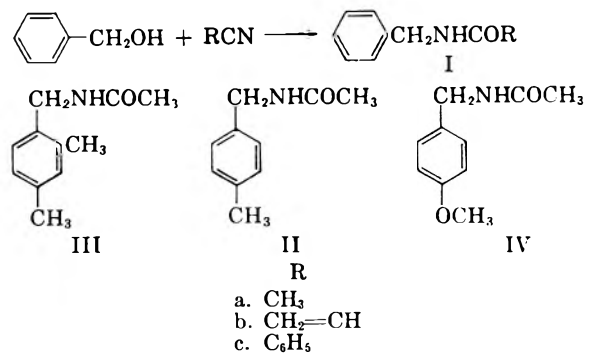
Nitriles are readily *N*-alkylated under mild conditions with primary alcohols related to benzyl alcohol and with glycols of the di(hydroxymethyl)benzene type to give good yields of *N*-aralkylamides and *N*,*N*'-bisaralkylamides, respectively.

In the reaction of nitriles with olefins and alcohols,[2,3] ethers,[4] esters,[5] and halides,[6] the alkylating compound is ordinarily restricted to those which can form a secondary or tertiary carbonium ion in an acidic medium.[7] An exception may be noted in the case of the primary halides which are known to form *N*-substituted nitrilium complexes with nitriles in the presence of Lewis acids.[8] Recently, Lora-Tamayo, Madronero, and Munoz reported that nitriles may be alkylated with β-phenylethyl chloride in the presence of stannic chloride to give derivatives of dihydroisoquinoline.[9] However, it has been asserted that primary alcohols are unreactive toward nitriles notwithstanding recourse to prolonged reaction times, elevated temperatures, and the use of fuming sulfuric acid as catalyst.[3c]

It was therefore noteworthy to observe in this laboratory that primary alcohols and glycols of the aralkyl type were condensed smoothly with nitriles under mild conditions to give *N*-aralklyamides and *N*,*N*'-bisaralkylamides in good yields. Thus, careful addition of benzyl alcohol to a large excess of acetonitrile containing substantial proportions of sulfuric acid resulted in a spontaneous reaction at 5–30° which afforded *N*-benzylacetamide[10] (Ia) in good yield. *N*-Benzylacrylamide[11] (Ib) was prepared from acrylonitrile, and, in similar manner, *N*-(4-methylbenzyl)acetamide[12] (II), *N*-(2,4-dimethylbenzyl)acetamide[13] (III), and *N*-(4-(methoxybenzyl)acetamide[14] (IV) were prepared



from the corresponding alcohols (Table I). The reaction was readily extended to glycols of the arenedimethanol type to produce several new difunctional amides. The reaction of 4,6-dimethyl-1,3-di(hydroxymethyl)-benzene with excess acetonitrile afforded *N*,*N*'-diacetyl-4,6-dimethyl-1,3-di(amino-

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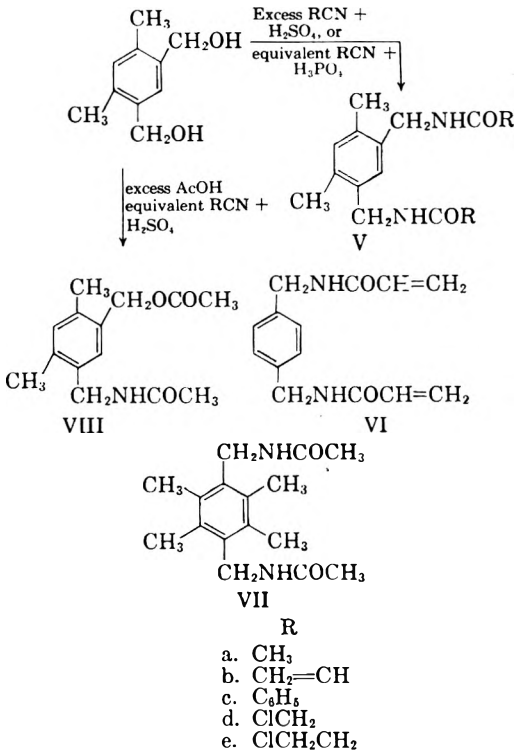
TABLE I

N-ARALKYLAMIDES FROM BENZYL-TYPE ALCOHOLS WITH NITRILES AND SULFURIC ACID

Compound	Formula	Yield, %	Melting Point °C.	Melting Point Lit., °C. (ref.)		Analyses C	Analyses H	Analyses N
Ia	$C_9H_{11}NO$	48	64.5–66.5	69–61[a]	Calcd.	72.45	7.43	9.40
				60.4–61.4[b]	Found	72.30	7.64	9.35
						72.52	7.64	
Ib	$C_{10}H_{11}NO$	50	70–72	69[c]	Calcd.	74.50	6.88	8.70
					Found	74.86	6.81	8.60
						74.69	6.84	
II	$C_{11}H_{15}NO$	40	110.5–111.5	109[d]	Calcd.	74.54	8.53	7.90
					Found	74.81	8.53	7.77
						74.90	8.55	
III	$C_{10}H_{13}NO$	87	111–112	106.5[e]	Calcd.	73.59	8.03	8.58
				107–108[f]	Found	73.61	7.70	8.76
						73.57	7.79	
IV	$C_{10}H_{13}NO_2$	60	94.5–96	96[g]	Calcd.	67.02	7.31	7.82
				97[h]	Found	67.30	7.16	7.68
						67.28	7.09	

[a] Ref. (10) (c). [b] Ref. (10) (d). [c] Ref. (11). [d] Ref. (13). [e] Ref. (12) (a). [f] Ref. (12) (b). [g] Ref. (14) (a). [h] Ref. (14) (b).

methyl)-benzene (Va) in 62% yield. A variation in technique consisted in treating the glycol with a slight molar excess of nitrile in a large volume of sirupy phosphoric acid. In similar manner the diamides Vb–e, VI, and VII were prepared from the corresponding glycols. The properties of these compounds are summarized in Table II.



When the reaction was carried out in the presence of acetic acid both alkylation and esterification occurred in some instances. Thus 2,4-dimethylbenzyl alcohol with acetonitrile in acetic and sulfuric acids afforded 28% of 2,4-dimethylbenzyl acetate together with 33% of the amide III. Under the same conditions 4,6-dimethyl-*m*-xylene-α,α'-diol afforded only an 8% yield of the diamide Va. The main product, melting at 114–115°, displayed both ester and monosubstituted amide bands in the infrared spectrum, and had the correct analysis for the mixed ester-amide VIII.

EXPERIMENTAL[15]

Benzyl alcohol and 4-methoxybenzyl alcohol were obtained from commercial sources and used without further purification. p-Xylene-α,α'-diol, m.p. 117.3–118.5°, was obtained from the Columbia-Southern Chemical Company. 2,3,5,6-Tetramethyl-*p*-xylene-α,α'-diol, m.p. 250–251°, was obtained from the Shell Development Company. 4-Methylbenzyl alcohol, m.p. 57.5–59°, was prepared from the corresponding bromide.[16] 2,4-Dimethylbenzyl alcohol, b.p. 108–110° (5 mm.) and 4,6-dimethyl-*m*-xylene-α,α'-diol, m.p. 152–154°, were prepared similarly from the corresponding chlorides.[17] Commercial acetonitrile and acrylonitrile were redistilled before use; other nitriles were not purified further.

Reactions in excess of nitrile. Preparation of N-benzylacrylamide (Ib). To 200 g. (3.8 mole) of freshly distilled acrylonitrile contained in a 1 l. three-necked flask equipped with a Hershberg stirrer, thermometer, and dropping funnel was added dropwise 75 ml. concentrated sulfuric acid at 0–10° over a period of 1 hr. A clean dropping funnel was substituted and then 108.0 g. (1 mole) benzyl alcohol was added slowly at the same temperature in 1 hr. After 2 hr. longer the yellow solution was allowed to warm slowly to 25–30°, then stirred for 2 days. The mixture was poured into ice water and the resulting oil was separated. The aqueous phase was extracted with three 200-ml. portions of ethyl acetate. The combined organic phases were washed successively with three 200-ml. portions of saturated salt solution, saturated sodium bicarbonate solution, and again with salt solution. The neutral extract was concentrated and the oily residue was distilled. The product was a light yellow

(15) All melting and boiling points are uncorrected. Kjeldahl analyses by Dr. James B. Lear and staff of these laboratories. Infrared spectra by Miss Ruth M. Johnston. Carbon and hydrogen analyses by Galbraith Laboratories, Knoxville, Tenn.

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TABLE II

N,N'-BISARALKYLAMIDES PREPARED FROM ARENEDIMETHANOLS AND NITRILES

Nitrile, mol/mol of Glycol, Acid[a]	Product	Formula	Melting Point, °C.	Yield, %		Analyses C	H	N
CH_3CN, 29/1, S	VII	$C_{18}H_{24}N_2O_2$	over 300	88	Calcd.	69.53	8.75	10.14
					Found	69.45	8.69	10.07
CH_2=CHCN, 23/1, S	VI	$C_{14}H_{16}N_2O_2$	polym. 230	65	Calcd.	68.83	6.60	11.47
					Found	68.93	6.44	11.25
						68.71	6.45	
CH_3CN, 30/1, S	Va	$C_{14}H_{20}N_2O_2$	245–246.5	62	Calcd.	67.71	8.12	11.28
					Found	67.70	8.01	11.16
						67.46	8.06	
CH_3CN, 1.1/1, P	Va		244–245.5	74				
CH_2=CHCN, 1.1/1, P	Vb	$C_{16}H_{20}N_2O_2$	polym. 250	98	Calcd.	70.56	7.40	10.29
					Found	70.79	7.50	10.32
						70.70	7.41	
C_6H_5CN, 1.1/1, P	Vc	$C_{24}H_{24}N_2O_2$	263.5–264.5	98	Calcd.	77.18	6.48	7.50
					Found	76.96	6.60	7.45
						77.17	6.55	
$ClCH_2CN$, 1.1/1, P	Vd	$C_{14}H_{18}Cl_2N_2O_2$	231–232	98	Calcd.	53.01	5.72	8.83
					Found	53.21	5.51	8.61
						53.39	5.60	
$ClCH_2CH_2CN$, 1.1/1, P	Ve	$C_{16}H_{22}Cl_2N_2O_2$	206 (dec.)	98	Calcd.	55.65	6.42	8.11
					Found	55.49	6.63	8.29
						55.45	6.62	

[a] S, concentrated sulfuric acid; P, sirupy phosphoric acid.

oil, b.p. 120–124° (0.02 mm.), that crystallized in the cold receiver. The yield of solid distillate was 97–99 g. (60–61%). The product was dissolved in a mixture of 50 ml. benzene and an equal volume of Skellysolve B on the steam bath. The solution was transferred quantitatively to a 500-ml. erlenmeyer flask with the aid of a little more benzene and was then concentrated to about two thirds of its volume. The product crystallized upon refrigeration. After filtration and drying there was recovered 95–98 g. of amide, m.p. 65–67.5°. The analytical sample melted at 70–72° after repeated recrystallization from benzene. The compounds reported in Table I were prepared in similar fashion from the corresponding alcohols and nitriles.

Preparation of N,N'-diacrylyl-1,4-di(aminomethyl)benzene (VI). To a cold solution of 75 ml. sulfuric acid in 600 g. (11.3 mole) acrylonitrile was added 69.0 g. (0.5 mole) *p*-xylene-α,α'-diol in small portions at 0–10°. After 2 hr. the temperature was allowed to rise slowly to 30° and the resulting two-phase mixture was then stirred overnight. The upper layer was decanted and discarded. The residue formed a voluminous precipitate upon neutralization with dilute ammonium hydroxide. After filtration and drying there was obtained 80 g. (64%) of diamide which polymerized at about 230°. The analytical sample was prepared by three recrystallizations from methanol. The diamides Va and VII were prepared similarly (Table II).

Reactions in 85% phosphoric acid. Preparation of N,N'-diacetyl-4,6-dimethyl-1,3-di(aminomethyl)benzene (Va). To a mixture of 16.6 g. (0.1 mole) of 4,6-dimethyl-*m*-xylene-α,α'-diol and 9.1 g. (0.22 mole) of acetonitrile was added 100 ml. sirupy phosphoric acid. The temperature was allowed to rise spontaneously to 55° accompanied by changes in color from pink to yellow. After 18 hr. the mixture was poured into ice water. The resulting granular solid was filtered, washed, and dried to give 19 g. (72%) of crude diamide, m.p. 225–240°. The analytical sample was prepared by three recrystallizations from methanol. In similar manner the diamides Vb–e (Table II) were prepared from the corresponding glycols and nitriles.

Reactions in acetic acid–sulfuric acid mixture. Reaction of 2,4-dimethylbenzyl alcohol. From the reaction of 13.6 g. (0.1 mole) of 2,4-dimethylbenzyl alcohol and 4.5 g. (0.11 mole) of acetonitrile in 175 ml. acetic acid with 5.5 ml. of sulfuric acid there were obtained two products. The first fraction consisted of 5.0 g. (28%) of colorless oil, b.p. 65–72° (0.1 mm.), $n^{25}D$ 1.5040, identified by the infrared spectrum as 2,4-dimethylbenzyl acetate. A fraction obtained at 130–140° (0.1 mm.) weighed 6.1 g. and solidified in the receiver. After recrystallization from a mixture of benzene and hexane the melting point was 112–113° and did not depress the melting point of *N*-(2,4-dimethylbenzyl)acetamide (III) prepared by the method of Nightingale and Shanholzer,[13] m.p. 110–112°.

Reaction of 4,6-dimethyl-1,3-di(hydroxymethyl)benzene. To a mixture of 16.6 g. (0.1 mole) of glycol and 9.1 g. (0.22 mole) of acetonitrile was added a cold solution of 15 ml. sulfuric acid in 175 ml. acetic acid with cooling below 30°. After 18 hr. at room temperature the mixture was treated with water and dilute ammonium hydroxide. The resulting oily semi-solid weighed 18 g. and melted at 80–130°. Recrystallization from a mixture of benzene and hexane gave 2.0 g. of solid, m.p. 197–237°. The mother liquor was retained. A second recrystallization of the solid raised the melting point to 244–247°. By mixture melting point and infrared spectrum this fraction was shown to be the diacetyl derivative of 4,6-dimethyl-*m*-xylene-α,α'-diamine (Va) described above.

Concentration of the original mother liquors gave 10 g. of solid, m.p. 106–110°. Recrystallization from benzene, distillation, and another recrystallization from benzene-hexane raised the melting point to 114–115°. The infrared spectrum showed a typical strong ester band at 5.8 μ and the usual bands at 6.1 μ and 6.5 μ characteristic of a monosubstituted amide,[18] suggesting the structure to be the ester-amide VIII.

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.21, 67.20; H, 7.50, 7.60; N, 5.82.

(18) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., Methuen and Co., Ltd., London, 1958, pp. 179, 211.

Acknowledgment. The authors wish to thank Drs. Howard L. Gerhart and Stewart W. Gloyer for their encouragement of this work and for permission to present it for publication. Many stimulating discussions with Prof. Charles G. Overberger, Brooklyn Polytechnic Institute, and Prof. Charles D. Hurd, Northwestern University, are acknowledged with gratitude. The authors are indebted to Messrs. Joseph A. Muir and Raymond F. Cornuet for invaluable technical assistance.

SPRINGDALE, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

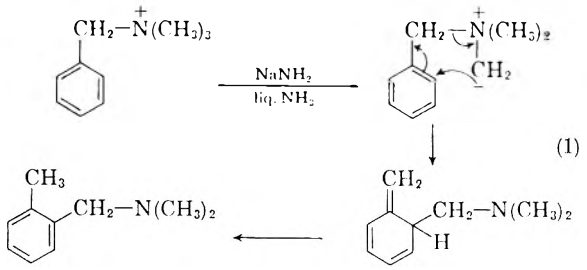
Consecutive Ortho Substitution Rearrangements Starting with 2- and 4-Substituted Benzyltrimethylammonium Ions[1]

WILLIAM Q. BEARD, JR.,[2] AND CHARLES R. HAUSER

Received October 22, 1959

Ortho substitution rearrangements of 2-substituted benzyltrimethylammonium ions and of the methiodides of the products were found to take place not only when the substituent was methyl or ethyl as reported previously, but also when the substituent was methoxy or chlorine. Similar consecutive rearrangements were realized starting with 4-substituted benzyltrimethylammonium ions where the substituent was methyl, isopropyl, methoxy, or chlorine, but not when the substituent was cyano. The yields were generally good to excellent, but they were very low in the second rearrangement when the substituent was chlorine. The structures of the rearranged amines were established in several ways. These results extend considerably the usefulness of the ortho substitution rearrangement in synthesis. Infrared data for a number of benzyldimethylamines are presented.

It has previously been shown that the benzyltrimethylammonium ion undergoes the ortho substitution rearrangement with sodium amide in liquid ammonia to form 2-methylbenzyldimethylamine in 96% yield[3,4] The mechanism has been represented by Equation 1.[3] The methiodide of the



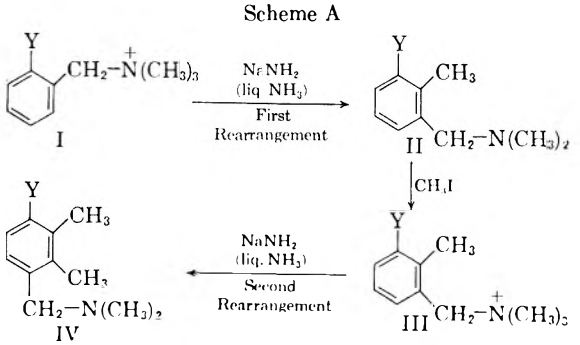
product was further rearranged, and the process was repeated until the aromatic ring was completely substituted.[3]

The α-methylbenzyltrimethylammonium ion also has been rearranged and the resulting 2-ethylbenzyldimethylamine rearranged through its methiodide.[5] This process was repeated once more.[5]

In the present investigation a study was made of the generality of this type of rearrangement starting with 2- and 4-substituted benzyltrimethylammonium ions.

Results with 2 - substituted benzyltrimethylammonium ions. The general reactions for two consecutive rearrangements starting with quaternary ammonium ions of this type may be represented by Scheme A.

Scheme A



Y = CH_3, C_2H_5, CH_3O, Cl

As indicated above, these two consecutive rearrangements have previously been observed when Y is methyl and ethyl. They have now been realized when Y is methoxy and chlorine. The yields, including those from the earlier examples for comparison, are summarized in Table I. The yields for the methylations of type II amines to form type III quaternary ions, which are not included in this table, were almost quantitative.

The structures of the two new amines IIc and IId from the first rearrangement in Scheme A were established by oxidations to known acids and anhydrides (Scheme B).

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(1) Supported in part by the National Science Foundation.

(2) Union Carbide Chemicals Co. Fellow, 1956–58.

(3) S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, **73**, 4122 (1951).

(4) W. R. Brasen and C. R. Hauser, *Org. Syntheses*, 63–4, *Note 8* (*1954*).

(5) C. R. Hauser and A. J. Weinheimer, *J. Am. Chem. Soc.*, **76**, 1264 (1954).

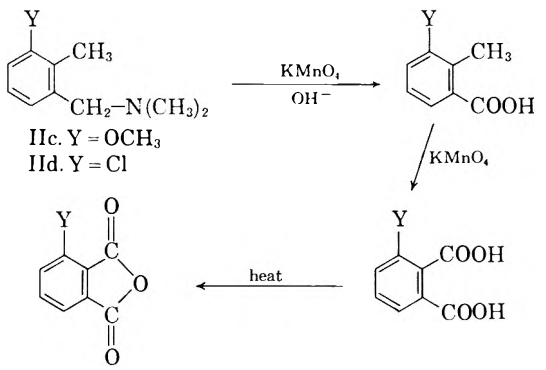
TABLE I

YIELDS OF REARRANGED AMINES II AND IV FROM QUATERNARY IONS I AND III WITH SODIUM AMIDE IN LIQUID AMMONIA

Quat. Ion	Y	Rearranged Amine No.	Rearranged Amine Yield, %	Quat. Ion	Rearranged Amine No.	Rearranged Amine Yield, %
Ia	CH_3	IIa	60–70[a]	IIIa	IVa	43[b]
Ib	C_2H_5	IIb	90[c]	IIIb	IVb	46[c]
Ic	OCH_3	IIc	84	IIIc	IVc	59
Id	Cl	IId	18(37)[d]	IIId	IVd	2

[a] Refs. 3 and 4. [b] Ref. 3. [c] Ref. 5. [d] Potassium amide was employed in ether at room temperature (25–30°).

Scheme B



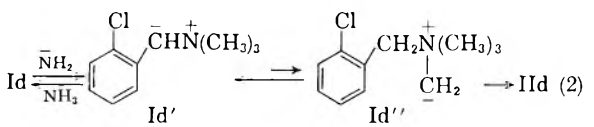
The structures of the two new amines IVc and IVd from the second rearrangement in Scheme A were supported by their infrared spectra, each of which showed a band in the 850–800 cm.$^{-1}$ region. These bands are attributed to the out-of-plane deformation frequency of the two adjacent hydrogens on the aromatic ring,[6] since the three vicinal hydrogens on the aromatic ring in amines IIc and IId absorbed in the 800–750 cm.$^{-1}$ region.[6] The structures of the amines IVc and IVd were further established by mild oxidations to the corresponding monocarboxylic acids, which gave satisfactory analyses.

It can be seen from Table I that the yields of the rearranged amines of type II from the first rearrangement in Scheme A were good to excellent not only when Y was methyl[3,4] or ethyl[5] but also when Y was methoxy (IIc, 84%). However, the yield of rearranged amine IId where Y was chlorine was only 18% in the usual medium, liquid ammonia, and 37% with potassium amide in ether at room temperature (25–30°).

Whereas the 2-ethyl and 2-methoxy quaternary ions (Ib and Ic) gave relatively little residual by-product, the 2-methyl quaternary ion Ia produced, besides the good yield of rearranged amine IIa, a considerable amount of neutral and basic dimeric and trimeric by-products, one of which was 2,2′-dimethylstilbene.[7]

The 2-chloro quaternary ion Id gave relatively little residual material with an equivalent of sodium amide in liquid ammonia even after 13 hours, which is much longer than the usual 1–2 hour reaction period. Yet the rearranged amine IId was obtained in only 18% yield, and 59% of the quaternary salt Id was recovered unchanged. When this quaternary ion was treated with two equivalents of sodium amide in liquid ammonia for 5 hours, essentially none of the rearranged amine IId was isolated. Instead, considerable amine residue was obtained, and 61% of the quaternary salt Id was recovered. Apparently this amine residue arose from further reaction of the rearranged amine IId with excess amide ion, since a similar amine residue was produced in a blank experiment with the amine IId and the reagent. The two samples of residue gave positive diazonium tests for primary aromatic amines and infrared bands at 3470 cm.$^{-1}$ and 3390 cm.$^{-1}$ for the N—H bond in primary amines.[8] Evidently these residues were formed by the benzyne type of reaction involving the chlorine atom of amine IId and the amide ion.[9] Incidentally, the quaternary ion Id did not appear to undergo appreciable benzyne reaction.[10]

These results indicate that the 2-chloro quaternary ion Id rearranged much more slowly than quaternary ions Ia–c. This might be due partly to a more unfavorable equilibrium than usual between the predominant benzyl carbanion Id′[11] and the methyl carbanion Id″, which presumably is the reactive intermediate in the rearrangement (Equation 2).[12]



It is possible that in the experiment in ether at a higher temperature (25–30°) the *ortho*- substitution rearrangement of quaternary ion Id was accompanied by some of the Stevens type of 1,2-

(6) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd. ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 78

(7) It was reported previously (ref. 3) and confirmed in the present work that yields of approximately 6–8% each of dimeric and trimeric neutral and basic by-products, totaling 25–30%, are produced.

(8) Ref. 6, p. 249.

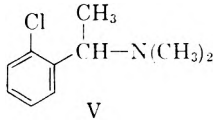
(9) J. D. Roberts, H. Simmons, Jr., L. Carlsmith, and C. Vaughan, *J. Am. Chem. Soc.*, **75**, 3290 (1953).

(10) The crude recovered salts gave an infrared spectrum identical with that of the pure starting quaternary salt, except for two additional bands from the ammonium chloride used in the neutralization of the reaction mixture.

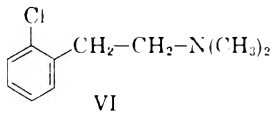
(11) Because of the inductive effect of the *o*-chlorine atom the benzyl carbanion Id′ might be expected to be a considerably weaker base than the corresponding benzyl carbanions of quaternary ions Ia–c.

(12) Although some precipitate was present in the reaction mixture, it was no more noticeable than those observed with the quaternary ions that readily underwent the rearrangement.

shift, since the latter reaction is known to be favored at the expense of the former by an elevation of temperature.[13] The 1,2- shift of a methyl group within carbanion Id′ would form tertiary amine V and that of the 2-chlorobenzyl group within carbanion Id″, tertiary amine VI.



V

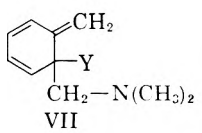


VI

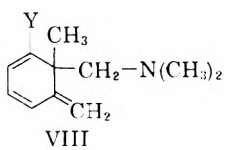
However, the amine isolated in 37% yield must have consisted at least largely of the *ortho*- substitution rearrangement product IId, since it produced on oxidation the acids and the anhydride shown in Scheme B. Apparently this oxidation process yielded no *o*-chlorobenzoic acid, which should have been formed had amines V or VI been present.

It can further be seen from Table I that the yields of amines of type IV from the second rearrangement in Scheme A were fairly good (43–59%) when Y was methyl, ethyl, or methoxy. However, the yield of amine IVd where Y was chlorine was only 2% even when quaternary ion IIId was treated with an equivalent of sodium amide in liquid ammonia employing the inverse addition procedure. Apparently the rearranged amine IVd was not formed in appreciably higher yield and then destroyed through the benzyne reaction, since most of the product consisted of amorphous neutral material.

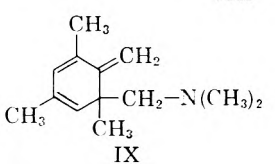
It should be pointed out that the first and second rearrangements in Scheme A might have been accompanied by some reaction at the substituted *ortho*- position to form *exo*-methyleneamines of types VII and VIII, since the 2,4,6-trimethylbenzyltrimethylammonium ion rearranges to give the *exo*-methyleneamine IX in 70% yield.[14]



VII



VIII



IX

Since *exo*-methyleneamine IX was shown to be decomposed readily by acid to form isodurene, the *exo*-methyleneamines VII and VIII presumably would have been converted to corresponding neutral compounds on acidification of the reaction mixtures.

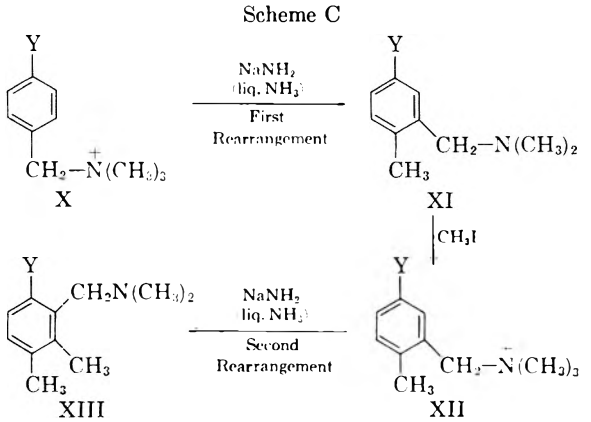
(13) C. R. Hauser, R. M. Manyik, W. R. Brasen, and P. L. Bayless, *J. Org. Chem.*, 20, 1119 (1955); G. Wittig and H. Strieb, *Ann.*, 584, 1 (1953).

(14) C. R. Hauser and D. N. Van Eenam, *J. Am. Chem. Soc.*, 76, 1264 (1954).

Actually small amounts of compounds VII and VIII (Y = CH_3) must have been formed in the original relatively large scale experiments with quaternary ions Ia and IIIa, since *o*-xylene and hemillitene were isolated in yields of 1% and 3%, respectively. Small amounts of such products might have been produced in the present work, but they were not isolated.

Results with 4-substituted benzyltrimethylammonium ions. The general reactions for two consecutive rearrangements starting with quaternary ammonium ions of this type may be represented by Scheme C.

Scheme C



Y = CH_3, $(CH_3)_2CH$, CH_3O, Cl

These two consecutive rearrangements were realized when Y was methyl, isopropyl, methoxy, and chlorine, but not when Y was cyanide. The yields are summarized in Table II. The yields for the methylations of amines of type XI to form quaternary ions of type XII (Scheme C) were almost quantitative.

TABLE II

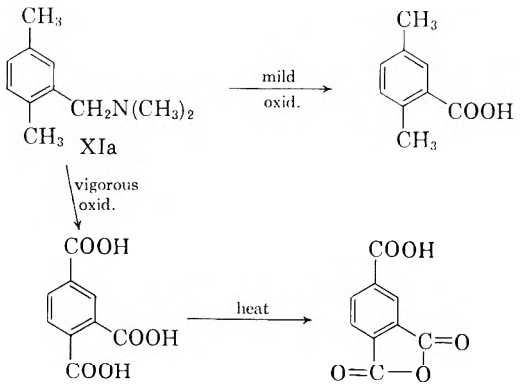
YIELDS OF REARRANGED AMINES VII AND IX FROM QUATERNARY IONS VI AND VIII WITH SODIUM AMIDE IN LIQUID AMMONIA

		Rearranged Amine			Rearranged Amine	
Quat. Ion	Y	No.	Yield, %	Quat. Ion	No.	Yield, %
Xa	CH_3	XIa	53–63	XIIa	XIIIa	84
Xb	$CH(CH_3)_2$	XIb	92	XIIb	XIIIb	68
Xc	OCH_3	XIc	93	XIIc	XIIIc	78
Xd	Cl	XId	54–60	XIId	XIIId	8
Xe	CN	XIe	0	—	—	—

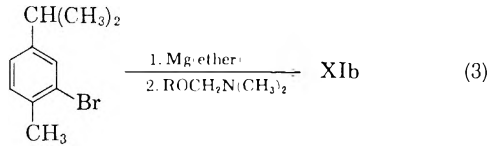
The structures of the rearranged amines of type XI from the first rearrangement in Scheme C were established in several ways. That of amine XIa was determined by mild and vigorous oxidations to form the corresponding mono- and tricarboxylic acids, respectively. The latter acid was dehydrated to give the anhydride (Scheme D).

Rearranged amine XIb was independently synthesized from the Grignard reagent of 2-bromo-*p*-

Scheme D



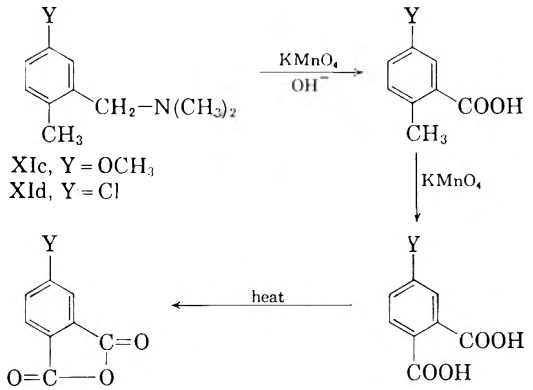
cymene and dimethylaminomethyl isobutyl ether (Equation 3, R = isobutyl).[15]



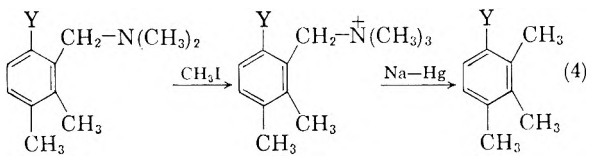
(3)

Rearranged amines XIc–d were oxidized to the corresponding monocarboyxlic acids and dicarboxylic acids, the latter compounds being dehydrated to form anhydrides (Scheme E).

Scheme E



The structures of the rearranged amines of type XIII from the second rearrangement in Scheme C were established by reductions or oxidations. Amines XIIIa–b were converted to their methiodides, which were reduced by the Emde method (Equation 4).



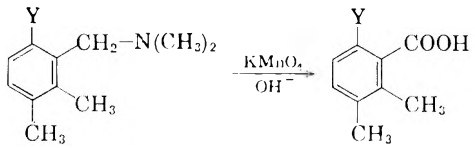
(4)

XIIIa, Y = CH_3
XIIIb, Y = $(CH_3)_2CH$

(15) Similar reactions of Grignard reagents with dimethylaminomethyl alkyl ethers have been reported by G. M. Robinson and R. Robinson, *J. Chem. Soc.*, 532 (1923).

The prehnitene from amine XIIIa exhibited an infrared spectrum identical with that of an authentic sample of this hydrocarbon. The 4-isopropyl-1,2,3-trimethylbenzene from amine XIIIb gave, besides a satisfactory analysis, an infrared spectrum showing the same type of aromatic substitution as prehnitene.

Rearranged amines XIIIc–d were oxidized to the corresponding monocarboxylic acids, both of which gave satisfactory analyses (Equation 5).



(5)

XIIIc, Y = OCH_3
XIIId, Y = Cl

In further support for structures XIIIc–d, the infrared spectra of the amines lacked a band in the 900–860 cm.$^{-1}$ region which was present in the spectra of amines XIc–d. This band is attributed to an isolated hydrogen atom situated between two substituents on the aromatic ring.[16]

It can be seen from Table II that the yields of the rearranged amines of type XI from the first rearrangement in Scheme C were excellent (92–93%) when Y was isopropyl or methoxy, and good (53–63%) when Y was methyl or chlorine. The similarities and differences of these results compared to those from the 2-substituted quaternary ions are considered below.

Similar to the 2-methyl quaternary ion Ia, the 4-methyl quaternary ion Xa gave, besides the rearranged amine XIa, a considerable amount of neutral residual material from which the dimer 4,4′-dimethylstilbene was isolated in 8–10% yields. Also, a small amount of basic residue was obtained. However, this ratio of neutral to basic residual by-products was considerably higher than that obtained from quaternary ion Ia, with which the ratio was approximately 1:1.[3,7] Moreover, the yield of the rearranged amine appeared to be influenced by reaction conditions much less with quaternary ion Xa than with Ia.[17]

Like the 2-ethyl and 2-methoxy quaternary ions Ib and Ic, the 4-isopropyl and 4-methoxy quaternary ions Xb and Xc produced excellent yields of the rearranged amines with very little residual material. Incidentally, the 93% yield of the rearranged amine XIc given in Table II was obtained with two equivalents of sodium amide in liquid ammonia on stopping the reaction after only 5 minutes. The yields listed for certain of the other

(16) Ref. 6, p. 79.

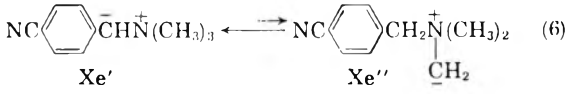
(17) Whereas the yields of 53–63% of amine XIa were obtained on varying the amount of ammonia used and the rate of addition of quaternary ammonium ion Xa, the 60–70% yield of amine IIa was lowered to 30% when quaternary ion Ia was added rapidly to the reagent in a relatively small amount of ammonia (ref. 3).

rearranged amines could probably also be obtained in much shorter time than the usual 1 to 2 hours allowed.

Whereas the 2-chloro quaternary ion Id produced only an 18% yield of the rearranged amine after 13 hours, the 4-chloro quaternary ion Xd gave 54–60% yields with an equivalent of sodium amide in liquid ammonia within 30 minutes to 1 hour. The inverse addition procedure was employed for the best yield, but the rapid addition of the quaternary salt Xd to the reagent gave almost as good yield.

Similar to the 2-chloro quaternary ion Id, the 4-chloro quaternary ion Xd gave considerable amine residue with two equivalents of the reagent, although some of the rearranged amine XId was isolated. This residue, the amount of which increased with the length of the reaction period, apparently arose from further reaction of the rearranged amine XId with excess reagent, since it gave a positive diazonium test and infrared bands for the N–H bond.

The failure of the 4-cyano quaternary ion Xe to rearrange with an equivalent of sodium amide liquid ammonia cannot be ascribed to side reactions, since 93% of the essentially pure quaternary salt was recovered after 3 hours. However, when two equivalents of the reagent were employed the recovered quaternary salt was quite impure.[18] Since color was produced, carbanions Xe′ and/or Xe″ were evidently produced. The failure of the latter to rearrange under the conditions employed might possibly be due to its relatively low concentration in equilibrium with the more weakly basic resonating carbanion Xe′ (Equation 6).

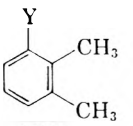


(6)

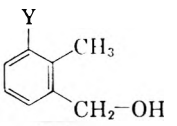
It can further be seen from Table II that the yields of tertiary amines of type XIII from the second rearrangement in Scheme C were good to excellent (68–84%) when Y was methyl, isopropyl, or methoxy. The larger size of the isopropyl group compared to the methyl group evidently had relatively little effect on the rearrangement. However, the yield was only 8% when Y was chlorine, and 57% of the quaternary salt XIIa was recovered.

The fact that the second rearrangement in Scheme C as well as that in Scheme A was realized in better yield when Y was alkyl or methoxy than when Y was chlorine was not anticipated on the basis of the current aromatic nucleophilic mechanism (see Equation 1). While this mechanism has been useful for correlating previous results, the present results suggest that it may need modification. A further study of the mechanism is now in progress.

Synthetic considerations. The ortho substitution rearrangements represented in Equation 1 and Scheme A (Y = CH_3) have previously been employed for the synthesis of not only the rearranged amines, but also of certain vicinal methyl derivatives. For examples, the methiodide of rearranged amine IIa has been converted by an Emde reduction to hemimellitene (XIV, Y = CH_3) in reproducible yields of 85–90%.[19] Also the ethobromide derivative of IIa has been converted by a displacement reaction with sodium acetate in acetic acid followed by saponification to 2,3-dimethylbenzyl alcohol (XV, Y = OCH_3) in reproducible over-all yields of 84–88%.[20]

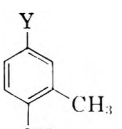


XIV

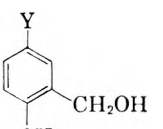


XV

The present results extend considerably the synthetic possibilities of the rearrangement. The reactions mentioned above should be applicable not only to other quaternary ions of Type II where Y is alkyl or methoxy. producing compounds of types XIV and XV, but also to those of rearranged amines of type IV (see Scheme A) or even to further rearranged amines, yielding higher substitution products. Moreover, such reactions should be feasible with quaternary ions of the rearranged amines of types XI and XIII (see Scheme C) to form compounds of types XVI and XVII and the corresponding higher substitution products in which Y is alkyl or methoxy.



XVI



XVII

Examples of the Emde reduction of the methiodides of type XIII rearranged amines are illustrated in Equation 4, in which the higher substitution products where Y is isopropyl or methyl are obtained in 66% and 75% yields, respectively.

Besides the types of compounds indicated above, certain carboxylic acids may be prepared conveniently through the *ortho*- substitution rearrangement. For example, the oxidation of rearranged amines IIc and XIc has produced 3-methoxy-2-methylbenzoic and 5 - methoxy - 2 - methylbenzoic acids in yields of 80% and 83%, respectively.

(18) Although the excess amide ion might be expected to attack the nitrile group to form an amidine, an infrared spectrum of the crude recovered quaternary salt failed to show bands for the N—H bond.

(19) W. R. Brasen and C. R. Hauser, *Org. Syntheses*, **34**, 56 (1954).

(20) W. R. Brasen and C. R. Hauser, *Org. Syntheses*, **34**, 58 (1954).

Infrared absorption spectra of benzyldimethylamines. All of the substituted benzyldimethylamines obtained in the present investigation and those others which were also examined exhibited a single moderate to strong band in their infrared spectra within the narrow range of 837–853 cm.$^{-1}$ This band appears to be specific for benzyldimethylamines and seems not to have been described previously. Table III summarizes the amines the spectra of which have been recorded and their characteristic absorption wave lengths in this region.

TABLE III

Amine	Infrared Absorption Frequency,[a] Cm.$^{-1}$
Benzyldimethylamine	849
2,3-Dimethylbenzyldimethylamine	847
2,5-Dimethylbenzyldimethylamine	848
3-Methoxy-2-methylbenzyldimethylamine	844
5-Methoxy-2-methylbenzyldimethylamine	837
3-Chloro-2-methylbenzyldimethylamine	847
5-Chloro-2-methylbenzyldimethylamine	838
5-Isopropyl-2-methylbenzyldimethylamine	842
2,3-Dimethyl-4-methoxybenzyldimethylamine	850
2,3-Dimethyl-6-methoxybenzyldimethylamine	850[b]
2,3-Dimethyl-6-isopropylbenzyldimethylamine	847
6-Chloro-2,3-dimethylbenzyldimethylamine	849[b]
4-Chloro-2,3-dimethylbenzyldimethylamine	853
2,3,6-Trimethylbenzyldimethylamine	849[b]

[a] All spectra run on a Perkin-Elmer Model 21 Infrared Spectrophotometer unless otherwise designated. [b] Spectra run on Perkin-Elmer Infracord.

It is interesting to note that the methiodides of these amines do not absorb in this region. The dimethylaminomethyl group alone is probably not responsible for the absorption, since several substituted β-phenylethyldimethylamines were found to show no absorption within this range. The band is also weak or absent in many α-substituted benzyldimethylamines which have been prepared in this laboratory.

EXPERIMENTAL[21]

2-Methoxybenzyltrimethylammonium bromide (Ic). 2-Methoxybenzoic acid (76 g., 0.5 mole) was reduced with 25 g. (0.6 mole) of 95% lithium aluminum hydride in 1000 ml. of anhydrous ether by the method used for the reduction of 3,5-dimethoxybenzoic acid[22] to give 59.5 g. (86%) of 2-methoxybenzyl alcohol, b.p. 125–127° at 13 mm., lit.,[23] b.p. 125–127° at 13 mm.

This alcohol (59.5 g., 0.43 mole) was treated with 58.0 g. (0.215 mole) of phosphorus tribromide in 750 ml. of ether and allowed to stand overnight. The excess phosphorus tribromide was hydrolyzed with ice and the layers separated. The ether layer was washed with water and sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Distillation yielded 73.0 g. (85%) of 2-methoxybenzyl bromide, b.p. 114.5–116° at 10 mm., lit.,[24] b.p. 115° at 10 mm. This bromide polymerized unless used within a few hours.

A solution of the freshly prepared bromide (73 g., 0.36 mole) in 350 ml. of acetonitrile cooled in an ice bath was treated with an excess (29 g., 43 ml., 0.5 mole) of liquid trimethylamine. After 1 hr., 1500 ml. of ether was added gradually with stirring to precipitate the 2-methoxybenzyltrimethylammonium bromide (Ic), which was collected on a suction funnel, washed with ether, and dried in a vacuum desiccator. Yield, 89 g. (94%), m.p. 188.5–189.5°. Since it was somewhat hygroscopic, its picrate was prepared for analysis. After three recrystallizations from 95% ethanol it melted at 152.5–153°.

Anal. Calcd. for $C_{17}H_{20}N_4O_8$: C, 50.00; H, 4.94; N, 13.72. Found: C, 49.96; H, 5.15; N, 13.71.

Rearrangement of quaternary salt Ic to form amine IIc. To a stirred suspension of 0.20 mole of sodium amide in 300 ml. of liquid ammonia[25] was added during 10 min. 26.0 g. (0.1 mole) of 2-methoxybenzyltrimethylammonium bromide (Ic). The color of the reaction mixture was reddish purple, which soon faded to gray. After 1 hr. 10.7 g. (0.2 mole) of solid ammonium chloride was added, and the liquid ammonia was evaporated as an approximately equal volume of ether was added. The resulting ethereal suspension was filtered (to remove the salts) and extracted with three 100-ml. portions of 2*N* hydrochloric acid.[26] The ether solution was dried over magnesium sulfate and evaporated, leaving no appreciable residue. The combined acid extract was carefully made strongly basic with solid sodium hydroxide, cooled with ice, and extracted with two 100-ml. portions of ether. This ethereal solution of the amine was dried over magnesium sulfate and distilled, yielding 15.10 g. (84%) of 3-methoxy-2-methylbenzyldimethylamine (IIc), b.p. 111–113° at 9.5 mm., n_D^{25} 1.5176, and leaving 0.90 g. of acid-soluble pot residue.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.91. Found: C, 73.86; H, 9.74; N, 7.97.

The picrate, recrystallized twice from 95% ethanol, melted at 125–125.5°.

Anal. Calcd. for $C_{17}H_{20}N_4O_8$: C, 50.00; H, 4.94; N, 13.72. Found: C, 50.03; H, 4.84; N, 13.74.

Oxidation of a 2.0 g. sample of amine IIc was effected at room temperature with 6.0 g. of potassium permanganate in 100 ml. of 0.5*N* sodium hydroxide solution. A 3.0-g. portion of the potassium permanganate was added at first, and three 1.0-g. portions were each added after the color of the preceding portion had disappeared. After filtration through a Supercel mat the filtrate was acidified and the product collected. After one recrystallization from aqueous ethanol the yield was 1.48 g. (80%) of 3-methoxy-2-methylbenzoic acid, m.p. 145–146°, lit.,[27] m.p. 145–146°.

Further oxidation of the above monoacid was effected by heating a 0.5-g. sample with 0.95 g. of potassium permanganate in 100 ml. of 0.05*N* sodium hydroxide solution until the purple color had disappeared (about 15 min.). The manganese dioxide was removed by filtration through a Supercel mat, and the filtrate was acidified and filtered again to remove a small amount of the starting monoacid. The solution was saturated with sodium sulfate and extracted with ether, which was then dried over magnesium

(21) Analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Melting points were determined on a Fisher melting point block and are corrected. Infrared spectra were produced on either a Perkin-Elmer Model 21 spectrophotometer or a Perkin-Elmer Infracord.

(22) R. Adams, M. Harfienst, and S. Leowe, *J. Am. Chem. Soc.*, **71**, 1624 (1949).

(23) M. G. Vavon, *Compt. rend.*, **154**, 359 (1912).

(24) E. Späth, *Monatsh.*, **34**, 1996 (1913).

(25) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, 122 (1954).

(26) The acid extraction was omitted in subsequent experiments, since no neutral material was obtained.

(27) L. F. Fieser and W. C. Lothrop, *J. Am. Chem. Soc.*, **58**, 749 (1936).

sulfate and evaporated to give 0.17 g. of 3-methoxyphthalic acid. After two recrystallizations from ethanol and hexane the product melted at 169.5–170.5° dec., lit.,[28] m.p. 173–174° dec.

A small sample of this dicarboxylic acid was boiled in a test tube to give 3-methoxyphthalic anhydride, m.p. 158–158.5°, lit.,[28] m.p. 160–161°.[28]

3-Methoxy-2-methylbenzyltrimethylammonium iodide (IIIc). To a stirred, cooled solution of 28.64 g. (0.16 mole) of 3-methoxy-2-methylbenzyldimethylamine (IIc) in 150 ml. of acetonitrile was added 43.0 g. (0.30 mole) of methyl iodide. Crystallization began within a few minutes. After 1 hr. the precipitation was completed by the addition of 500 ml. of dry ether while the mixture was stirred vigorously. The salt was collected on a suction filter, washed with dry ether, and dried in a vacuum desiccator. The yield was 50.9 g. (97%) of 3-methoxy-2-methylbenzyltrimethylammonium iodide (IIIc), m.p. 225° dec. A sample recrystallized from a mixture of ethanol and acetonitrile melted at 227° dec.

Anal. Calcd. for $C_{12}H_{20}INO$: C, 44.73; H, 6.25; N, 4.35. Found C, 44.88; H, 6.34; N, 4.34.

Rearrangement of IIIc *to 2,3-dimethyl-4-methoxybenzyldimethylamine* (IVc). This reaction was carried out with 30.1 g. (0.094 mole) of 3-methoxy-2-methylbenzyltrimethylammonium iodide (IIIc) and 0.112 mole of sodium amide in 300 ml. of liquid ammonia as described for Ic. The color, which was blue-black during the addition, became a light purple shortly after the addition was complete.

From the neutral fraction 1.67 g. of light brown amorphous material was obtained. Distillation of the basic fraction yielded 0.58 g. of forerun, b.p. 120–126° at 9 mm., n_D^{25} 1.5195, and 10.72 g. (59%) of 2,3-dimethyl-4-methoxybenzyldimethylamine (IVc), b.p. 126–127.5° at 9 mm., n_D^{25} 1.5204, and 1.96 g. of pot residue.

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.76; H, 9.71; N, 7.24.

The methiodide of a 2.0 g. sample of amine IVc was prepared with excess methyl iodide in 15 ml. of acetonitrile. After the mixture had stood for 30 min., it was heated to boiling and the methiodide slowly precipitated by the careful addition of anhydrous ether. A yield of 3.15 g. (91%), m.p. 232–233°, was obtained. The melting point was not raised by further recrystallization.

Anal. Calcd. for $C_{13}H_{22}INO$: C, 46.58; H, 6.62; N, 4.18. Found: C, 46.34; H, 6.55; N, 4.07.

Oxidation of 2.0 g. of amine IVc with 5.2 g. of potassium permanganate as described for amine IIc yielded after one recrystallization from aqueous ethanol 0.80 g. (42%) of 2,3-dimethyl-4-methoxybenzoic acid, m.p. 204–205°.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.36; H, 6.71.

2-Chlorobenzyltrimethylammonium chloride (Id). This quaternary salt was prepared in 96% yield from 161 g. (1 mole) of 2-chlorobenzyl chloride and 118 g. (2 moles) of liquid trimethylamine as described for Ic. Its melting point was 208–209°.

The picrate, after one recrystallization from 95% ethanol, melted at 166.5–167.5°.

Anal. Calcd. for $C_{16}H_{17}N_4ClO_7$: C, 45.00; H, 4.02; N, 13.12. Found: C, 45.17; H, 4.16; N, 13.23.

Rearrangement of quaternary salt Id *to amine* IId. (A) *In liquid ammonia.* To a suspension of 0.15 mole of sodium amide in 500 ml. of liquid ammonia was added through Gooch tubing as rapidly as possible 33.0 g. (0.15 mole) of 2-chlorobenzyltrimethylammonium chloride (Id). The mixture was allowed to stir under a Dry Ice reflux condenser for 13 hr. The initial bright green color gradually changed to yellow and then to tan. Ammonium chloride 8.02 g., 0.15 mole was added for neutralization, and the ammonia was replaced by ether as it was evaporated. The salts were removed by filtration and the ether evaporated from the filtrate. Distillation of the residue yielded 4.59 g. (18%) of 3-chloro-2-methylbenzyldimethylamine (IId), b.p. 103–106.5° at 9.5 mm., n_D^{25} 1.5248, and 1.68 g. of acid-soluble pot residue.

The ether-insoluble salts mentioned above were triturated with 250 ml. of hot acetonitrile and filtered. Dilution of the filtrate with ether precipitated 19.5 g. (59%) of recovered 2-chlorobenzyltrimethylammonium chloride (Id), m.p. 204–206°, mixed m.p. 205–207°.

Recovery of 92–93% of the starting material was observed with 1–2 equivalents of amide ion within 45 min.

(B) *With potassium amide in ether.* To a solution of 0.20 mole of potassium amide in liquid ammonia[29] was added rapidly 55 g. (0.2 mole) of 2-chlorobenzyltrimethylammonium chloride (Id). After 10 min., 400 ml. of dry ether was added, the ammonia being allowed to evaporate while the mixture was stirred for 22 hr. Hydrolysis was carried out carefully with 100 ml. of water, then 250 ml. of 2*N* hydrochloric acid. The layers were separated, and the aqueous phase was carefully made strongly basic by the addition of solid sodium hydroxide. Ice was added and the mixture extracted with three 100-ml. portions of ether. The ether solution was dried over magnesium sulfate and the solvent evaporated. The residue was distilled to give 14.82 g. of a fraction boiling at 105–109° at 10.1 mm. and 5.04 g. of undistillable tar. Redistillation of the distillable fraction yielded 13.36 g. (37%) of 3-chloro-2-methylbenzyldimethylamine (IId), b.p. 105.5–108° at 10 mm., n_D^{25} 1.5246.

Anal. Calcd. for $C_{10}H_{14}ClN$: C, 65.40; H, 7.68; N, 7.63. Found: C, 65.52; H, 7.63; N, 7.66.

The picrate, recrystallized three times from 95% ethanol, melted at 140–140.5°.

Anal. Calcd. for $C_{16}H_{17}ClN_4O_7$: C, 46.56; H, 4.14; N, 13.56. Found: C, 46.49; H, 4.04; N, 13.57.

Almost the same yield (33%) of amine IId was obtained when quaternary ion Id was treated with two equivalents of potassium amide in ether for 24 hr. However, more basic tar was obtained.

Mild oxidation of 2.0 g. of amine IId as described for IIc gave 1.0 g. (53%) of 3-chloro-2-methylbenzoic acid, m.p., 157.5–158.5°, lit.,[30] m.p. 159°.

Further oxidation of a 0.2 g. sample of the above monoacid was effected with 0.39 g. of potassium permanganate to give 0.20 g. of 3-chlorophthalic acid, m.p. 182–184°, lit.,[31] m.p. 186°.

A small sample of the acid was boiled in a test tube, yielding 3-chlorophthalic anhydride, m.p. 120–121.5°, lit.,[31] m.p. 122°.

3-Chloro-2-methylbenzyltrimethylammonium iodide (IIId). This quaternary salt was prepared from 17.8 g. (0.097 mole) of 3-chloro-2-methylbenzyldimethylamine (IId) and 28.4 g. (0.200 mole) of methyl iodide. Yield, 31.3 g. (99%), m.p. 223.5–225.5° dec. After two recrystallizations from a mixture of acetone and ethanol the yield was 25.4 g. (84%), melting at a constant 238–238.5° dec.

Anal. Calcd. for $C_{11}H_{17}ClIN$: C, 40.57; H, 5.27; N, 4.31. Found: C, 40.76; H, 5.01; N, 4.30.

Rearrangement of quaternary salt IIId *to amine* IVd. To 26.4 g. (0.081 mole) of 3-chloro-2-methylbenzyltrimethylammonium iodide (IIId) in 300 ml. of liquid ammonia was added over a 10-min. period a suspension of 0.085 mole of sodium amide in 200 ml. of liquid ammonia (inverse addition). After 2.5 hr. the reaction mixture was neutralized with 4.56 g. (0.085 mole) of solid ammonium chloride and the ammonia replaced by ether. The product was worked up by the usual procedure, employing acid extraction.

(28) W. Bentley, R. Robinson, and C. Weizmann, *J. Chem. Soc.*, **91**, 110 (1907).

(29) See C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **81**, 1160, (1959).

(30) E. Noelting, *Ber.*, **37**, 1025 (1904).

(31) M. T. Bogert and L. Boroschek, *J. Am. Chem. Soc.*, **23**, 751 (1901).

The neutral fraction consisted of 5.0 g. of a light yellow amorphous solid.

The viscous amine fraction (1.5 g.) was distilled to give 0.32 g. (2%) of 4-chloro-2,3-dimethylbenzyldimethylamine (IVd), b.p. 126–127° at 10 mm., n_D^{25} 1.5309.

Anal. Calcd. for $C_{11}H_{16}ClN$: C, 66.82; H, 8.16; N, 7.09. Found: C, 67.04; H, 8.27; N, 7.25.

The methiodide, prepared in acetonitrile from a few drops of the amine and excess methyl iodide, melted at 235–235.5° after one recrystallization from a mixture of ethanol and hexane.

Anal. Calcd. for $C_{12}H_{19}ClIN$: C, 42.44; H, 5.63; N, 4.13. Found: C, 42.24; H, 5.47; N, 3.97.

The crude ether-insoluble salts were triturated in 150 ml. of water, and the insoluble portion was collected on a filter. After one recrystallization from ethanol 3.5 g. (14%) of the starting quaternary iodide IIId was recovered, m.p. 233–234°, mixed m.p. 238–238.5°.

Oxidation of 0.18 g. of amine IVd was effected with 0.49 g. of potassium permanganate added in four portions to the amine in 20 ml. of 0.5*N* sodium hydroxide solution. After filtration the solution was acidified, and the product was collected and recrystallized once from aqueous ethanol. A yield of 0.08 g. (49%) was obtained of 4-methoxy-2,3-dimethylbenzoic acid, m.p. 180–182°. Another recrystallization from ethanol and hexane raised the melting point to 183°.

Anal. Calcd. for $C_9H_9ClO_2$: C, 58.56; H, 4.82. Found: C, 58.73; H, 5.03.

4-Methylbenzyltrimethylammonium bromide (Xa). This salt was prepared from 55.5 g. (0.3 mole) of α-bromo-*p*-xylene (b.p. 105–106° at 20 mm.) as described for salt Ic. The yield was 74 g. (99%), m.p. 196–197°, reported m.p. 194°.[32]

Rearrangement of Xa *to form amine* XIa. This reaction was carried out with 24.4 g. (0.1 mole) of 4-methylbenzyltrimethylammonium bromide (Xa) and 0.2 mole of sodium amide in 300 ml. of liquid ammonia essentially as described for Ic. The addition period was 45 min., and the reaction was allowed to run for an additional 45 min. The initial deep red-violet color persisted throughout the reaction period.

The neutral fraction, 4.0 g. of yellow fluorescent solid, was recrystallized from 95% ethanol, yielding 1.0 g. (10%) of 4,4′-dimethylstilbene, m.p. 171–173°, lit.,[33] m.p. 178°. An additional recrystallization from 95% ethanol raised its melting point to 174–175°. It was oxidized with 3N nitric acid (18 hr. refluxing) to *p*-toluic acid, m.p. 174–175°, reported m.p. 177°.[34] Admixture with an authentic sample gave a melting point of 176–176.5°.

Distillation of the basic products yielded 10.25 g. (63%) of 2,5-dimethylbenzyldimethylamine (XIa), b.p. 89.5–90.7° at 11 mm., n_D^{25} 1.5044, and less than 1 g. of residue.

Anal. Calcd. for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58. Found: C, 80.89; H, 10.35; N, 8.57.

A picrate, after three recrystallizations from 95% ethanol, melted at 121.5–122°.

Anal. Calcd. for $C_{17}H_{20}N_4O_7$: C, 52.00; H, 5.14; N, 14.30. Found: C, 52.10; H, 4.94; N, 14.33.

Slightly lower yields of XIa (down to 53%) were obtained using a smaller volume of liquid ammonia.

Oxidation of a 2.0 g. sample of amine XIa was effected with 6.0 g. of potassium permanganate in 100 ml. of 0.5*N* sodium hydroxide solution. After recrystallization of the product once from aqueous ethanol a yield of 1.0 g. (54%) of 2,5-dimethylbenzoic acid was obtained, m.p. 129–130°, lit.,[35] m.p. 132°. Admixture with an authentic sample gave a melting point of 131.5–132°.

Vigorous oxidation of amine XIa *to trimellitic acid and conversion to its anhydride.* A 2.0 g. sample of amine XIa and 20 g. of potassium permanganate were added to 100 ml. of 0.1*N* sodium hydroxide solution and the mixture was refluxed for 17 hr. The manganese dioxide was removed by filtration through a mat of Hyflo Supercel. The resulting clear filtrate was made strongly acidic with hydrochloric acid and saturated with sodium sulfate. The product was extracted with three 100-ml. portions of ether, which were combined, dried, and evaporated. A yield of 1.9 g. (74%) of crude trimellitic acid, m.p. 217–218°, was obtained. One recrystallization from a mixture of benzene and methanol raised the melting point to 228°, lit.,[36] m.p. 224–225°.

A small portion of the product was boiled in a test tube, producing trimellitic anhydride, m.p. 159–160°, lit.,[37,38] m.p. 162.5–163.5°, 157–158°.

2,5-Dimethylbenzyltrimethylammonium iodide (XIIa). This salt was obtained in 99% yield from 26.08 g. (0.16 mole) of 2,5-dimethylbenzyldimethylamine (XIa) and 43 g. (0.30 mole) of methyl iodide as described for IIIc. The melting point was 250° (darkened at 245°) and was not changed by recrystallization from acetonitrile.

Anal. Calcd. for $C_{12}H_{20}IN$: C, 47.25; H, 6.56; N, 4.59. Found: C, 47.28; H, 6.74; N, 4.79.

Rearrangement of XIIa *to form amine* XIIIa. This rearrangement was carried out with 45.75 g. (0.15 mole) of 2,5-dimethylbenzyltrimethylammonium iodide (XIIa) and 0.30 mole of sodium amide in 750 ml. of liquid ammonia essentially as described for Ic. The addition period was 45 min., and the reaction was allowed to proceed for an additional 1.75 hr. Distillation of the crude products[26] yielded 22.17 g. (84%) of 2,3,6-trimethylbenzyldimethylamine (XIIIa), b.p. 108–110.5° at 10 mm., n_D^{25} 1.5160, and 1.22 g. of amine residue.

Anal. Calcd. for $C_{12}H_{19}N$: C, 81.30; H, 10.80; N, 7.90. Found: C, 81.50; H, 10.94; N, 7.90.

2,3,6-Trimethylbenzyltrimethylammonium iodide. This salt was obtained in 93% yield from 10.62 g. (0.06 mole) of 2,3,6-trimethylbenzyldimethylamine (XIIIa) and 14.2 g. (0.10 mole) of methyl iodide as described for IIIc. The melting point was 194° dec.

Anal. Calcd. for $C_{13}H_{22}IN$: C, 48.91; H, 6.95; N, 4.39. Found: C, 48.78; H, 6.98; N, 4.40.

Emde reduction to form prehnitene. The *Org. Syntheses* procedure used for the preparation of hemimellitene[19] was employed, using 15.95 g. (0.05 mole) of 2,3,6-trimethylbenzyltrimethylammonium iodide and 210 g. of 5% sodium amalgam. The product was isolated in this case by steam distillation and extraction of the steam distillate with ether. Distillation of the dried ether extracts yielded 5.02 g. (75%) of prehnitene, b.p. 95–97° at 25 mm., n_D^{25} 1.5185, reported b.p. 97–98° at 25 mm., n_D^{25} 1.5183.[39] The infrared spectrum was identical with that of an authentic sample.

4-Isopropylbenzyltrimethylammonium bromide (Xb). 4-Isopropylbenzyl alcohol (60 g., 0.4 mole) was treated with 54.2 g. (0.2 mole) of phosphorus tribromide essentially as described in the preparation of Ic. The reaction period was only 1 hr. Distillation of the product yielded 71.2 g. (84%) of *p*-isopropylbenzyl bromide, b.p. 118–120° at 14 mm., lit.,[40] b.p. 108–109° at 14 mm.

This bromide (71.0 g., 0.33 mole) was treated with 40 g. (60 ml., 0.67 mole) of liquid trimethylamine as described for Ic. The salt was difficult to crystallize upon addition of the ether, presumably because of its extremely hygroscopic character. It was handled in a dry box. A yield of 81.4 g.

(32) J. von Braun and H. Engel, *Ann.*, **436**, 299 (1924).

(33) E. Spath, *Monatsh.*, **35**, 470 (1914).

(34) 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, p. 279.

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

(36) A. Baeyer and V. Villiger, *Ber.*, **32**, 2445 (1899).

(37) W. Schultze, *Ann.*, **359**, 143 (1908).

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(39) C. R. Hauser and D. N. Van Eenam, *J. Org. Chem.*, **23**, 865 (1958).

(40) J. W. Baker and W. S. Nathan, *J. Chem. Soc.*, **1935**, 1844.

(90%) of 4-isopropylbenzyltrimethylammonium bromide (Xb) was thus obtained, m.p. 139–140° (softening at 125°).

Anal. Calcd. for $C_{13}H_{22}BrN$: C, 57.35; H, 8.15; N, 5.15. Found: C, 57.53; H, 8.35; N, 5.16.

Rearrangement of Xb *to form amine* XIb. The rearrangement was effected during 1.5 hr. with 27.2 g. (0.1 mole) of 4-isopropylbenzyltrimethylammonium bromide (Xb) and 0.2 mole of sodium amide in 300 ml. of liquid ammonia essentially as described for Ic.[26] Distillation yielded 17.46 g. (92%) of 5-isopropyl-2-methylbenzyldimethylamine (XIb), b.p. 108–111.5° at 10 mm., n_D^{25} 1.4989.

Anal. Calcd. for $C_{13}H_{21}N$: C, 81.61; H, 11.06; N, 7.32. Found: C, 81.82; H, 11.03; N, 7.23.

Independent synthesis of amine XIb. (A) *Dimethylaminomethyl isobutyl ether.* This compound was prepared in 25% yield by the directions of Robinson and Robinson.[15] Its boiling point was 129.5–131.5°, reported b.p. 124–126°.

(B) *Reaction with 2-p-cymyl magnesium bromide.* The reaction was carried out with 25.6 g. (0.12 mole) of 2-bromo-*p*-cymene, 3.49 g. (0.16 g. atom) of magnesium turnings, and 10.5 g. (0.08 mole) of the above dimethylaminomethyl isobutyl ether according to the general procedure of Stewart and Hauser[41] for the addition of Grignard reagents to α-amino ethers. A yield of 9.74 g. (64%) of 5-isopropyl-2-methylbenzyldimethylamine b.p. 108–111° at 10 mm., n_D^{25} 1.4975, was obtained. Redistillation of the product yielded 7.70 g. (50%), b.p. 108–109.5° at 9.8 mm., n_D^{25} 1.4978. An infrared spectrum was identical with that of amine XIb.

A methiodide, prepared from the above amine and methyl iodide, melted at 190–191° dec. Admixture with a sample of methiodide XIIb produced no depression of the melting point.

5-Isopropyl-2-methylbenzyltrimethylammonium iodide (XIIb). This quaternary salt was obtained in 98% yield from 21.01 g. (0.11 mole) of 5-isopropyl-2-methylbenzyldimethylamine (XIb) and 22.72 g. (0.16 mole) of methyl iodide as described for IIIa. The melting point was 190–191° dec.

Anal. Calcd. for $C_{14}H_{24}IN$: C, 50.45; H, 7.25; N, 4.20. Found: C, 50.51; H, 7.25; N, 4.38.

Rearrangement of XIIb *to form amine* XIIIb. This reaction was effected with 33.3 g. (0.1 mole) of 5-isopropyl-2-methylbenzyltrimethylammonium iodide (XIIb) and 0.2 mole of sodium amide in 300 ml. of liquid ammonia essentially as described for Ia. The initial deep blue color changed rapidly to violet, which persisted.

The neutral fraction, 1.9 g. of dark liquid, yielded no distillable material.

The basic products were distilled in two fractions: 12.90 g., b.p. 121–124° at 9 mm., n_D^{25} 1.5090; 0.90 g., b.p. 124–126° at 9 mm., n_D^{25} 1.5098; 1.73 g. of residue left in the pot. The two distillable fractions were combined as 2,3-dimethyl-6-isopropylbenzyldimethylamine (XIIIb), 13.80 g. (68%); the analytical sample was taken from the first fraction.

Anal. Calcd. for $C_{14}H_{23}N$: C, 80.76; H, 11.99; N, 7.25. Found: C, 81.02; H, 11.79; N, 7.07.

The picrate, after two recrystallizations from 95% ethanol, melted at 152.0–152.5°.

Anal. Calcd. for $C_{20}H_{26}N_4O_7$: C, 55.29; H, 6.03; N, 12.90. Found: C, 55.40; H, 6.26; N, 13.10.

2,3-Dimethyl-6-isopropylbenzyltrimethylammonium iodide. This salt was prepared in 99% yield from 6.30 g. (0.0307 mole) of 2,3-dimethyl-6-isopropylbenzyldimethylamine (XIIIb) and 8.52 g. (0.06 mole) of methyl iodide as described for IIIc. Its melting point was 169–169.5° dec.

Anal. Calcd. for $C_{15}H_{26}IN$: C, 51.84; H, 7.55; N, 4.03. Found: C, 51.60; H, 7.78; N, 4.13.

Emde reduction to form 2,3,4-trimethylisopropylbenzene. This reduction was carried out with 10.00 g. (0.0288 mole) of 2,3-dimethyl-6-isopropylbenzyltrimethylammonium iodide and 120 g. of 5% sodium amalgam essentially in accordance with the *Org. Syntheses* procedure for the preparation of hemimellitene.[19] The product was steam distilled from the reaction mixture and extracted with ether from the steam distillate. The dried ether extractions were distilled yielding 3.08 g. (66%) of 2,3,4-trimethylisopropylbenzene, b.p. 95–98° at 8.3–8.6 mm., n_D^{25} 1.5127. Its infrared spectrum was very similar to that of 1,2,3,4-tetramethylbenzene (prehnitene).

Anal. Calcd. for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 88.63; H, 11.16.

4-Methoxybenzyltrimethylammonium bromide (Xc). Anisyl alcohol (69.0 g., 0.5 mole) was treated with 68 g. (0.25 mole) of phosphorus tribromide as described for Ia. The reaction period was 1 hr. A yield of 87.3 g. (87%) of 4-methoxybenzyl bromide, b.p. 124–126° at 12 mm., lit.,[24] b.p. 126° at 12 mm., was obtained.

The halide (89 g., 0.44 mole) was treated with excess trimethylamine in acetonitrile as described for Ic. A yield of 110 g. (96%) of 4-methoxybenzyltrimethylammonium bromide (Xc), m.p. 148.5–149°, reported m.p. 146°,[42] was obtained.

Rearrangement of Xc *to form amine* XIc. To a suspension of 0.20 mole of sodium amide in 250 ml. of liquid ammonia was added over a 30-sec. period a solution of 26.0 g. (0.10 mole) of 4-methoxybenzyltrimethylammonium bromide (Xc) in 150 ml. of liquid ammonia. No color change was observed. At the end of 5.0 min. a solution of 10.7 g. (0.20 mole) of ammonium chloride in liquid ammonia was added rapidly. The ammonia was replaced by ether and the inorganic salts removed by filtration. Distillation yielded 16.53 g. (93%) of 5-methoxy-2-methylbenzyldimethylamine (XIc), b.p. 106–108.5° at 7.3 mm., n_D^{25} 1.5133.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.74; H, 9.49; N, 7.83. Found: C, 73.58; H, 9.43; N, 7.90.

The picrate, after two recrystallizations from ethanol, melted at 129–129.5°.

Anal. Calcd. for $C_{17}H_{22}N_4O_8$: C, 50.00; H, 4.94; N, 13.72. Found: C, 50.28; H, 5.14; N, 13.49.

Oxidation of a 1.0 g. sample of XIc with 3.0 g. of potassium permanganate in 50 ml. of 0.5*N* sodium hydroxide solution yielded, after one recrystallization from aqueous ethanol, 0.77 g. (83%) of 5-methoxy-2-methylbenzoic acid, m.p. m.p. 146°, lit.,[43] m.p. 146°.

Further oxidation of a 0.2 g. sample of the above monoacid was accomplished with 0.38 g. of potassium permanganate in the usual manner. There was obtained 0.14 g. of 4-methoxyphthalic acid, m.p. 168.5–169.5°. One recrystallization from a mixture of ethanol and hexane raised the melting point to 169–170°, lit.,[44] m.p. 170°.

A small sample of the above diacid was boiled in a test tube, producing 4-methoxyphthalic anhydride, m.p. 93.5–94°, lit.,[45] m.p. 93°.

5-Methoxy-2-methylbenzyltrimethylammonium iodide (XIIc). This salt was prepared in 99% yield from 15.43 g. (0.086 mole) of 5-methoxy-2-methylbenzyldimethylamine (XIc) and excess methyl iodide as described for IIIc. The melting point was 166–167°.

Anal. Calcd. for $C_{12}H_{20}INO$: C, 44.73; H, 6.25; N, 4.35. Found: C, 44.50; H, 6.34; N, 4.34.

Rearrangement of XIIc *to form amine* XIIIc. The reaction was effected with 27.0 g. (0.0844 mole) of 5-methoxy-2-methylbenzyldimethylamine (XIIc) and 0.10 mole of sodium amide in 300 ml. of liquid ammonia essentially as described for Ia. The initial maroon color did not fade.

Only 0.1 g. of neutral material was obtained.

(41) A. T. Stewart, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **77**, 1098 (1955).

(42) J. von Braun, W. May, and R. Michaelis, *Ann.*, **490**, 189 (1931).

(43) O. Jacobsen, *Ber.*, **15**, 1964 (1883).

(44) M. Freund and E. Gobel, *Ber.*, **30**, 1392 (1897).

(45) C. Schall, *Ber.*, **12**, 829 (1879).

Distillation of the amine fraction yielded 12.63 g. (78%) of 2,3-dimethyl-6-methoxybenzyldimethylamine (XIIIc), b.p. 121–123° at 9.5 mm., n_D^{25} 1.5178.

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.93; H, 9.89; N, 7.56.

The methiodide was prepared from 2.0 g. of amine XIIIc and excess methyl iodide in acetonitrile. When the product was precipitated gradually by the slow addition of anhydrous ether to the hot solution, a yield of 3.38 g. (98%) of 2,3-dimethyl-6-methoxybenzyltrimethylammonium iodide, m.p. 167.5–168°, was obtained.

Anal. Calcd. for $C_{13}H_{22}INO$: C, 46.58; H, 6.62; N, 4.18. Found: C, 46.82; H, 6.48; N, 4.04.

Mild oxidation of a 2.0 g. sample of amine XIIIc was effected with 5.5 g. of potassium permanganate by the usual procedure. After one recrystallization from aqueous ethanol, 0.48 g. (25%) of 2,3-dimethyl-6-methoxybenzoic acid, m.p. 154.5–156°, was obtained. A second recrystallization from ethanol and hexane raised the melting point to 156.5–158°.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.77; H, 6.79.

4-Chlorobenzyltrimethylammonium iodide (Xd). 4-Chlorobenzyl chloride (48.3 g., 0.3 mole) was treated with excess trimethylamine as described for Ic. A yield of 63 g. (96%) of 4-chlorobenzyltrimethylammonium chloride, m.p. 195–197°, was obtained. One recrystallization from acetonitrile and ether raised the melting point to 201.5–202°. This salt was extremely hygroscopic, so it was converted to its iodide.

The above chloride (17.5 g., 0.0795 mole) was dissolved in a minimum amount of hot acetonitrile. A solution of 11.9 g. (0.0795 mole) of sodium iodide in 300 ml. of hot acetonitrile was added gradually with stirring. The mixture was heated to boiling and filtered while hot. Anhydrous ether (1000 ml.) was added to the cooled filtrate, and the quaternary iodide was collected on a filter. A yield of 19.3 g. (78%) of 4-chlorobenzyltrimethylammonium iodide (Xd), m.p. 249.5–250°, was obtained.

Anal. Calcd. for $C_{10}H_{15}ClIN$: C, 38.54; H, 4.84; N, 4.49. Found: C, 38.61; H, 4.85; N, 4.51.

Rearrangement of Xd *to form amine* XId. This reaction was effected with 21.8 g. (0.070 mole) of 4-chlorobenzyltrimethylammonium iodide (Xd) and 0.074 mole of sodium amide as described for IIId (inverse addition). The yield was 7.65 g. (60%) of 5-chloro-2-methylbenzyldimethylamine (XId), b.p. 102–105° at 9.7 mm., n_D^{25} 1.5219. Most of the product (7.45 g., 58%) boiled at 104–105° at 9.7 mm.

Anal. Calcd. for $C_{10}H_{14}ClN$: C, 65.39; H, 7.68; N, 7.63; Cl, 19.30. Found: C, 65.61; H, 7.74; N, 7.60; Cl, 19.48.

Oxidation of a 2.0 g. sample of amine XId was accomplished by the usual procedure with 6.0 g. of potassium permanganate. After one recrystallization from aqueous ethanol a yield of 1.25 g. (67%) of 5-chloro-2-methylbenzoic acid, m.p. 165.5–166.5°, lit.,[46] m.p. 168.5–169.5°, was obtained.

Further oxidation of a 0.2 g. sample of the above monoacid was effected in the usual manner with 0.39 g. of potassium permanganate. A yield of 0.18 g. of residue was left from the ether extractions. After a washing with benzene the 4-chlorophthalic acid melted at 152–153°, lit.,[47] m.p. 150.0–150.5°.

A small sample of the above diacid was boiled in a test tube, producing 4-chlorophthalic anhydride, m.p. 94.5–95.5°, lit.,[44] m.p. 98.5°.

5-Chloro-2-methylbenzyltrimethylammonium iodide (XIId). This salt was prepared in 99% yield from 18.39 g. (0.10 mole) of 5-chloro-2-methylbenzyldimethylamine (XId) and 28.4 g. (0.2 mole) of methyl iodide essentially as described for IIIc. The melting point was 226° dec.

Anal. Calcd. for $C_{11}H_{17}ClIN$: C, 40.57; H, 5.27; N, 4.31. Found: C, 40.64; H, 5.54; N, 4.55.

Rearrangement of XIId *to form amine* XIIId. This rearrangement was carried out with 32 g. (0.0985 mole) of 5-chloro-2-methylbenzyltrimethylammonia iodide (XIId) and 0.105 mole of sodium amide as described for the rearrangement of IIId. The reaction period was 6 hr., the green color of the anion persisting throughout.

The neutral fraction contained 4.0 g. of light yellow amorphous material.

The amine fraction yielded 1.51 g. (8%) of 6-chloro-2,3-dimethyl benzyldimethylamine (XIIId), b.p. 119–121° at 11 mm., n_D^{25} 1.5290.

Anal. Calcd. for $C_{11}H_{16}ClN$: C, 66.82; H, 8.16; N, 7.09. Found: C, 66.92; H, 8.30; N, 7.29.

A picrate, recrystallized once from 95% ethanol, melted at 176–177°.

Anal. Calcd. for $C_{17}H_{19}ClN_4O_7$: C, 47.81; H, 4.49; N, 13.12. Found: C, 47.92; H, 4.70; N, 13.07.

The ether-insoluble salts exhibited an infrared spectrum identical with that of the starting quaternary salt with two additional bands characteristic of the ammonium chloride known to be present. When this mixture was triturated with acetonitrile, filtered, and treated with excess ether, a precipitate of 18.3 g. (57%) of recovered 5-chloro-2-methylbenzyltrimethylammonium iodide (XIId), m.p. 216–218° dec., was obtained. Admixture with an authentic sample produced no depression of the melting point.

Mild oxidation of a 1.0 g. sample of amine XIIId with 2.5 g. of potassium permanganate by the usual procedure yielded after one recrystallization from aqueous ethanol 0.15 g. (16%) of 6-chloro-2,3-dimethylbenzoic acid, m.p. 144.5–145°.

Anal. Calcd. for $C_9H_9ClO_2$: C, 58.56; H, 4.82. Found: C, 58.43; H, 4.82.

4-Cyanobenzyltrimethylammonium bromide (Xe). 4-Cyanobenzyl bromide[48] (49 g., 0.25 mole) was treated with excess liquid trimethylamine as described for Ia. The yield was 62.0 g. (97%) of 4-cyanobenzyltrimethylammonium bromide (Xe), m.p. 235–235.5°.

Anal. Calcd. for $C_{11}H_{13}BrN_2$: C, 51.77; H, 5.92; N, 10.98. Found: C, 51.76; H, 5.91; N, 10.89.

Treatment of Xe *with sodium amide in liquid ammonia.* 4-Cyanobenzyltrimethylammonium bromide (Xe) (30.2 g., 0.10 mole) was added quickly to a suspension of 0.102 mole of sodium amide in 300 ml. of liquid ammonia. Throughout the 3-hr. reaction period the color remained a bright pea-green. After neutralization with 5.4 g. (0.102 mole) of ammonium chloride, the ammonia was replaced by ether. The mixture was filtered. No residue remained upon evaporation of the filtrate.

The ether-insoluble material was extracted with acetonitrile in a Soxhlet extractor. Upon treatment of the extract with a large excess of ether, 28 g. (93%) of recovered 4-cyanobenzyltrimethylammonium bromide (Xe), m.p. 229–231°, was obtained. Admixture with an authentic sample produced no depression of the melting point.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Isocycloheximide

A. J. LEMIN AND J. H. FORD

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Isocycloheximide has been shown to be a stereoisomer of cycloheximide.

Increasing interest in antibiotics as potential anti-tumor and pesticidal agents has resulted in the discovery of a number of new cycloheximide analogues and isomers.[1-5]

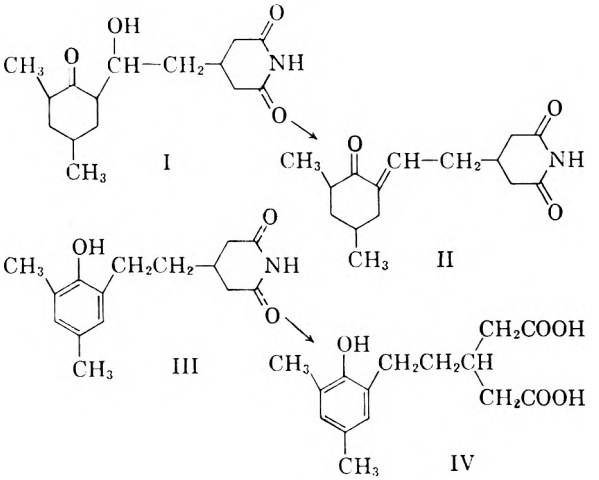
During the work-up of pooled mother liquors from the crystallization of cycloheximide[6] a compound with a sharp melting point lower than that of cycloheximide was isolated. The empirical formula, $C_{15}H_{23}NO_4$, was the same as that of cycloheximide and the infrared absorption spectrum was almost identical with that of cycloheximide. Although the new substance was apparently closely related to cycloheximide, the fact that they were different was confirmed by the preparation of an acetate from the new compound which was shown to differ from cycloheximide acetate. Since cycloheximide has four centers of asymmetry it was suspected that the new compound was a stereo-isomer and it was provisionally named isocycloheximide.

Isocycloheximide was found to have about 30 per cent of the activity of cycloheximide by *Saccharomyces pastorianus* bioassay[7] and about 30 per cent of the toxicity when determined intravenously in mice.[8]

Proof that isocycloheximide was stereoisomeric with cycloheximide and some indication of the centers involved were obtained as follows. When cycloheximide was chromatographed on acetic acid–deactivated alumina, a small amount of isocycloheximide was formed. Shaking cycloheximide with acid-deactivated alumina also produced isocycloheximide. The separation of isocycloheximide from cycloheximide proved to be difficult and hence the product was identified as the acetate.

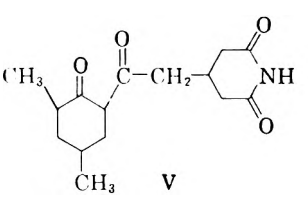
Dehydration of both cycloheximide (I) and isocycloheximide (I) by treatment with pyridine hydrochloride gave the same anhydrocycloheximide[6b] (II) indicating that isocycloheximide and cycloheximide have the same glutarimide and cyclohexanone structures.

Further evidence for the arrangement of carbons and the ketonic oxygen was afforded by bromination experiments. Bromination of cycloheximide with one molar equivalent of bromine followed by spontaneous dehydrobromination and dehydration led to the production of a phenol (III).



Bromination-dehydrobromination of isocycloheximide gave the same phenol, which on hydrolysis gave the glutaric acid (IV).

The secondary hydroxyl group is not involved in the isomerization of cycloheximide to isocycloheximide. This is shown by the fact that the isomerization of dehydrocycloheximide[6b] (V) gives the same product, isodehydrocycloheximide, that is obtained by the oxidation of isocycloheximide with chromic acid.



Rigorous proof of the stereochemical relationship between isocycloheximide and cycloheximide is lacking. However, since carbon-4 is distant from activating centers, it appears that this center retains its configuration[9] during the isomerizations.

(1) T. Okuda, M. Suzuki, Y. Egawa, and K. Astimo, *Chem. and Pharm. Bull. (Japan)*, **6**, 328 (1958).

(2) K. V. Rao and W. P. Cullen, 134th Meeting ACS, Chicago, Ill., September 1958.

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(5) R. R. Herr, 6th Ann. Symposium on Antibiotics, Washington, D. C., October 1958.

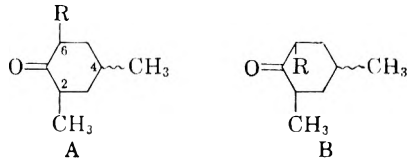
(6) (a) J. H. Ford and B. E. Leach, *J. Am. Chem. Soc.*, **70**, 1223 (1948). (b) E. C. Kornfeld, R. G. Jones, and T. V. Parke, *J. Am. Chem. Soc.*, **71**, 150 (1949).

(7) A. J. Whiffen, *J. Bact.*, **56**, 283 (1948)

(8) O. F. Swoap, unpublished data.

(9) The absolute configuration at carbon-4 is known: C. Djerassi, E. J. Eisenbraun, and J. Osiecke, *J. Am. Chem. Soc.*, **80**, 1261 (1958).

Further since two isomeric dehydrocycloheximides can be obtained, at least one of the remaining asymmetric centers (2 or 6) must be inverted. Since the same anhydrocycloheximide is obtained from both isomers, it is possible that the only center involved in the isomerizations is at carbon 6. This provisional hypothesis leads to configurations A and B for cycloheximide and isocycloheximide, isomerization being from 2,6-*trans* to 2,6-*cis* systems.



A somewhat similar change in the configuration of the 19-methyl group in the ketone obtained by the oxidation of taraxastene is known. This epimerization was also carried out by alumina treatment of the ketone.[10]

EXPERIMENTAL

Isocycloheximide. (a) *From the mother liquors from cycloheximide crystallizations.* The mother liquors from several batch crystallizations of cycloheximide (a total of 30 l. of amyl acetate solution) which had been allowed to stand at 5–10° for up to 18 months were evaporated under reduced pressure. Water was added to the resulting brown sticky mass and the residual amyl acetate removed by vacuum distillation as the water azeotrope. The aqueous concentrate was extracted with chloroform and the extract was treated with 3 kg. of carbon to effect a partial decolorization. The decolorized solution was concentrated under reduced pressure to a thick sirup and 25 l. of isopropanol was added. Most of the remaining chloroform was removed by concentrating the solution under vacuum to a volume of 20 l. After three months of storage at 5–10° the solution gave 1218 g. of crude isocycloheximide, m.p. 100–102°, $[\alpha]_D^{23}$ +36° (c = 10, CH_3OH).

Anal. Calcd. for $C_{15}H_{23}NO_4$: C, 64.02; H, 8.24. Found: C, 64.06; H, 8.04.

An infrared absorption spectrum in chloroform solution was found to have functional group bands identical with those of cycloheximide but there were slight differences in the low cm.$^{-1}$ regions.

Chromatography of 5.0 g. of the crude isocycloheximide on a mixture of 50 g. of activated carbon (Darco G-60) and 50 g. of kieselguhr (Celite 545) and elution with acetone-water mixtures gave the following solid fractions: with 1.2 l. of 30% acetone-water, 1.61 g., m.p. 75–83°, $[\alpha]_D^{25}$ +29.5° (c = 1.0, CH_3OH), with 400 cc. of 40% acetone-water, 0.43 g., m.p. 74–85° $[\alpha]_D^{25}$ +32° (c = 1.0 CH_3OH), with 400 cc. of 80% acetone-water, 0.72 g. m.p. 95–99°, $[\alpha]_D^{25}$ +32° (c = 1.0, CH_3OH).

Recrystallization of the highest melting fraction gave isocycloheximide identical with the sample obtained by recrystallizating the crude preparation.

A 200-tube counter-current distribution of the crude product using a two phase system consisting of benzene (10 parts), methanol (5 parts), and water (1 part) gave only one peak consisting of isocycloheximide identical with the sample obtained by recrystallizing the crude product.

(b) *By isomerizing cycloheximide using deactivated alumina.* Alumina, (Brockman Grade 1, Fisher Scientific Company, 80–200 mesh, 457 g.) was deactivated by suspending in 600 cc. of dry benzene, adding 27.42 cc. of 10% acetic acid and shaking the mixture for 15 hr. Cycloheximide (20 g.) was then added and the mixture shaken. At intervals of 1 hr., about 20 g. of the alumina was removed, filtered, and the solid extracted with 50 cc. of chloroform. Evaporation of the chloroform left a white solid the specific rotation of which was measured (CH_3OH). After 6.5 hr. shaking at room temperature the sample melted at 77–84°, and the rotation had reached a maximum of $[\alpha]_D^{25}$ +26° (CH_3OH), (70% conversion as calculated from the rotation).

The isomerization product was identified by a counter-current distribution of 2.75 g. of the isomerization mixture between benzene (10 parts), methanol (5 parts), and water (1 part) using ten funnels each containing 200 cc. of each phase. Funnel 8 contained 0.62 g. of impure isocycloheximide, m.p. 87–93° identified by a comparison of its infrared absorption spectrum with that of the authentic isocycloheximide. Funnel 7 contained 0.49 g. of solid, m.p. 83–90°, which on acetylation (acetic anhydride–pyridine) gave isocycloheximide acetate, m.p. 156–159° $[\alpha]_D^{25}$ +51° (c = 1.0 CH_3OH). A mixture melting point with isocycloheximide acetate prepared from authentic isocycloheximide was not depressed. The infrared absorption spectra of the two samples were identical.

Anal. Calcd. for $C_{17}H_{25}NO_5$: C, 63.15; H, 7.79; N, 4.33. Found: C, 62.94; H, 7.80; N, 4.43.

Dehydration of cycloheximide and isocycloheximide. A solution of 28 g. of cycloheximide in 100 cc. of pyridine containing 20 cc. of concentrated hydrochloric acid was refluxed for 7 hr. Addition of water (100 cc.) and cooling gave a white crystalline precipitate, m.p. 132–133° (27.5 g.) undepressed on admixture with anhydrocycloheximide, and having an infrared absorption spectrum identical with that of anhydrocycloheximide.[6b]

A similar reaction using isocycloheximide gave the same product identified by melting point, mixture melting point, and infrared absorption spectra comparisons.

3-[2-(2-Hydroxy-3,5-xylyl) ethyl] glutarimide. To a solution of 25 g. of cycloheximide in 500 cc. of chloroform was added a solution of 15 g. of bromine in 150 cc. of chloroform. The mixture was allowed to stand at room temperature until colorless, and then washed with 1% pyridine solution, 5% hydrochloric acid, and with water until the washings were neutral. Evaporation of the solvent under reduced pressure gave 22.3 g. of a brown oil which crystallized from ether, m.p. 148–155°.

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 69.0: H, 7.38; N, 5.37. Found: C, 69.19; H, 7.25; N, 5.29.

This product contained traces of bromine. However, on refluxing 5.0 g. of the solid with 25 cc. of γ-collidine for 1 hr. and work up by dilution with water, extraction with chloroform, washing the chloroform with dilute hydrochloric acid and with water, followed by removal of the solvent, 3.63 g. of the product, 3-[2-(2-hydroxy-3,5-xylyl)ethyl]-glutarimide, m.p. 153–157° was obtained. This sample was bromine free. Recrystallization from methanol gave the analytical sample, m.p. 155–157° $[\alpha]_D^{25}$ ±0° (c = 1.0 CH_3OH).

Anal. Calcd. for $C_{15}H_{19}NO_5$: C, 69.0; H, 7.38; N, 5.37. Found: C, 69.28; H, 7.52; N, 5.38.

The ultraviolet absorption spectrum had a maximum at 278 mμ, ϵ = 2050, and the compound was freely soluble in dilute sodium hydroxide solution.

Bromination of isocycloheximide. Bromination of 1.0 g. of isocycloheximide in 20 cc. of chloroform using 0.57 g. of bromine in 5.7 cc. of chloroform and working up as described for the bromination of cycloheximide gave 3-[2-(2-hydroxy-3,5-xylyl)ethyl]glutarimide m.p. 155–158°, undepressed on admixture with the sample obtained from cycloheximide.

Anal. Calcd. for $C_{15}H_{19}NO_5$: C, 69.0; H, 7.38; N, 5.37. Found: C, 69.03; H, 7.00; N, 5.43.

3-[2-(2-Hydroxy-3,5,-xylyl)ethyl]glutaric acid. A solution of 1.0 g. of 3-[2-(2-hydroxy-3,5-xylyl)ethyl]glutarimide in

(10) T. R. Ames, J. L. Beton, A. Bowers, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 1907 (1954).

20 cc. of 10% aqueous potassium hydroxide solution was refluxed for 1 hr. Cooling, addition of water, and extraction with ether removed neutral products. Acidification of the aqueous solution, extraction with ether and washing the ether with water until the washings were neutral and evaporation of the solvent gave 3-[2-(2-hydroxy-3,5-xylyl)ethyl]-glutaric acid, m.p. 131–132.5°.

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.3; H, 7.55. Found: C, 64.25; H, 7.56.

Dehydroisocyclohexirnide. (a) *From isocyclohexirnide.* A solution of 1.0 g. of isocycloheximide in 20 cc. of acetone was oxidized by the addition of a chromic acid–sulfuric acid mixture.[11] When the mixture retained a brown color for 5 min., 20 cc. of water was added. The mixture was extracted with ether, the ether solution washed with water until the washings were neutral and the extract dried over anhydrous sodium sulfate. Distillation of the solvent and crystallization of the oily residue from aqueous acetone gave 0.81 g. of dehydroisocycloheximide, m.p. 152–154°, $[\alpha]_D^{25}$ −20° (c = 1.0 CH_3OH).

Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.05. Found: C, 64.67; H, 7.30; N, 5.05.

(11) R. Curtis, *J. Chem. Soc.*, 461 (1953).

When a solution of dehydroisocycloheximide in aqueous acetone was added to an excess of aqueous copper acetate a green precipitate of the copper complex formed immediately.

(b) *From dehydrocycloheximide.* To a solution of 1 g. of dehydrocycloheximide[6b] in 20 cc. of pyridine was added 6 cc. of concentrated hydrochloric acid and the mixture was refluxed for 3 hr. Addition of 20 cc. of water to the hot solution followed by cooling gave 0.9 g. of dehydroisocycloheximide, m.p. 151–154°, $[\alpha]_D^{25}$ −23° (c = 1.0 CH_3OH) identified by a mixture melting point (undepressed) and by comparison of the appropriate infrared absorption spectra.

Anal. Calcd. for $C_{15}H_{21}NO_4$: N, 5.05. Found: N, 4.99.

Acknowledgment. The authors wish to express their appreciation to W. A. Struck and associates for microanalyses and rotations, to F. R. Hanson for bioassays, to O. F. Swoap for toxicity determinations, and to Dr. D. J. Cram and Dr. A. K. Bose for helpful discussions.

KALAMAZOO, MICH.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Cyclic and Acyclic Amides of *cis*-β-(*p*-Bromobenzoyl)-β-methylacrylic Acid

ROBERT E. LUTZ, CARROLL T. CLARK,[2,3] AND JOSEPH P. FEIFER

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Assigned structures of cyclic and acyclic *cis*-β-bromobenzoyl-β-methylacrylic "amides" II–IV, of the cyclic pseudo "acid chloride" V, and of the cyclic and acyclic esters VII–VIII, have been confirmed by ultraviolet and infrared absorption studies. The γ-hydroxylactams show relative pK_a' values of 11.7–11.8, the *cis* acid (the γ-hydroxylactone, Xa) 6.4, the *trans* acid 4.4, and the γ-anilinolactone IIIa 8.4. The anions of the γ-hydroxylactams are cyclic XIII whereas the anions of the acid XIa and the γ-anilinolactone XVI are acyclic. Diazomethane converts the γ-anilinolactone to the acyclic (*cis*) anil-ester XVIII. The cyclic pseudo acid chloride is shown to undergo attack at the chloride group by alcohol and by aromatic amines, but reacts at the lactone carbonyl group with the more basic aliphatic secondary amines.

This paper elaborates upon earlier studies[4,5] of ring-chain tautomerism of *cis*-β-(*p*-bromobenzoyl)-β-methylacrylic acid (Xa), its "acid chloride" which is believed to have the γ-chlorolactone structure V, and its three types of "amides,"[5] the acyclic (normal or true) amides II, the γ-aminolactones III, and the γ-hydroxylactams IV. Examples of all three of the "amide" types had been obtained by reactions between ammonia or amines and the "acid chloride" V. Ammonia and methylamine produced γ-hydroxylactams IVa and IVb; aniline and methylaniline gave γ-aminolactones IIIa and IIIb; and dimethylamine gave the normal (true) *cis* amide IIa. Stereoisomerization by irradiation of the *trans* tertiary amides, the dimethylamide (Id) and the methylanilide (Ie), gave the normal *cis* amides (IIa and IIb), but the *trans* primary amide (Ia) and two *trans* secondary amides (the methylamide Ib and the anilide Ic) went beyond stereoisomerization with subsequent cyclization to the γ-hydroxylactams IVa–c.

The cyclic structure for the acid chloride V had been assigned because of the low rate of alcoholysis and hydrolysis,[6] and because the ester produced by alcoholysis was cyclic (VII). However, this is not sound evidence because the rate of alcoholysis of an acyl chloride group in an acyclic structure of type VI would depend on the steric hindrance involved in this configuration and on its concentra-

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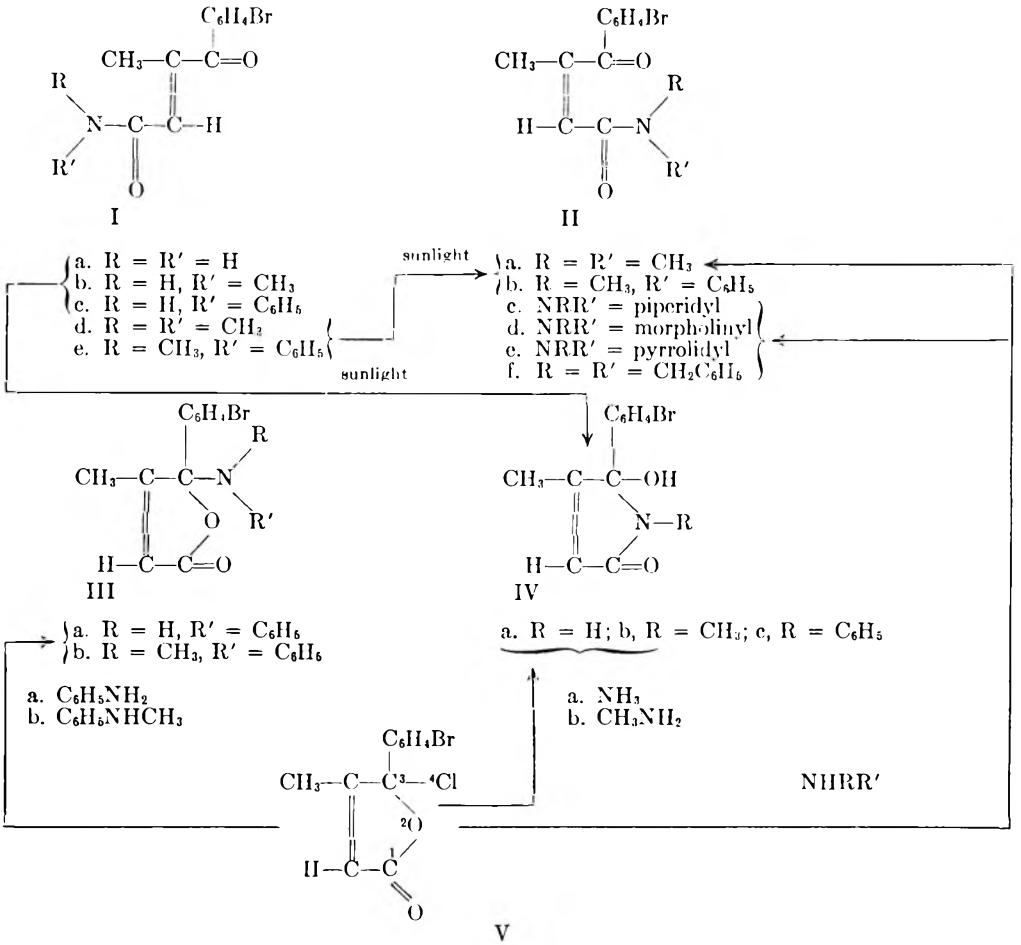
(2) (a) Present address: University of Georgia, Athens, Ga. (b) This paper is based on a dissertation by C.T.C., University of Virginia, 1958. (c) The work was reported at the Atlantic City A.C.S. Meeting, September 1959, abstr. p. 14p. (*Cf.* also ref. 3.)

(3) R. E. Lutz and C. T. Clark, *J. Org. Chem.*, in press.

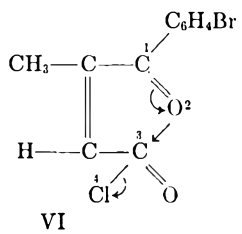
(4) (a) R. E. Lutz, P. S. Bailey, C-K. Dien, and J. W. Rinker, *J. Am. Chem. Soc.*, **75**, 5039 (1953), and references cited therein; (b) J. W. Rinker, Dissertation, University of Virginia, 1955.

(5) (a) R. E. Lutz and F. B. Hill, *J. Org. Chem.*, **6**, 175 (1940); (b) F. B. Hill, Dissertation, University of Virginia, 1940; (c) See references cited in (a) and (b). (d) *Cf.* also polarographic studies by S. Wawzonek, H. A. Laitinen, and S. J. Kwiatkowski, *J. Am. Chem. Soc.*, 66, 827 (1944).

(6) R. E. Lutz and R. J. Taylor, *J. Am. Chem. Soc.*, **55**, 1168 (1933).



tion if in equilibrium with the cyclic form V, and because of the possibility of a 1,4 reaction mechanism involving a contributing chelate resonance form or transition as indicated in VI.[7]



VI

The ultraviolet absorption spectrum of the acid chloride in isooctane, or immediately upon solution in methanol before elapse of sufficient time for alcoholysis to occur, showed no *p*-bromobenzoyl type band in the 260–265 mμ region, and this result confirms the postulated cyclic structure V and excludes VI.[9] Infrared absorption of the acid chloride in chloroform solution or in the solid state showed a doublet peak at 5.55–5.64 μ which, although much like that of a conjugated true acid chloride group, must be due rather to the lactone ring carbonyl of the cyclic form V because of the absence of a prominent absorption band at *ca.* 6.00 μ characteristic of the aroyl carbonyl group which would necessarily be present in the acyclic form VI (*cf.* ref. 12). Actually there is a moderately strong 6.04 μ band in this and in spectra of other compounds in this series including IIIa and IIIb which have no bromobenzoyl groups, and it is attributed to the conjugated propylene double bond. Identity of the infrared absorption spectra of the acid chloride in chloroform solution and in the solid state shows that the amount of acyclic form in equilibrium in solution, if any at all, is negligible in amount.

It has been shown previously that the "acid chloride" reacts slowly with alcohol.[6] The ultraviolet absorptivity observed immediately upon solution in ethanol must therefore truly represent the "acid chloride" and not the cyclic ester which

(7) It has been reported that acyclic and cyclic *o*-benzoylbenzoyl chlorides exist and undergo alcoholysis to the acyclic and cyclic esters respectively.[8]

(8) H. Meyer, *Monatsh*, **25**, 475 (1904); **28**, 1211, 1231 (1907).

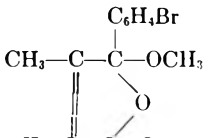
(9) It is assumed that chelation of the type illustrated in VI (2 → 3) would not seriously alter the absorption characteristics of the two carbonyl groups (*cf.* ref. 10, 11).

(10) R. E. Lutz and C-K. Dien, *J. Org. Chem.*, **23**, 1861 (see p. 1866) (1958).

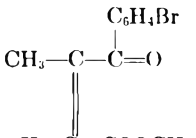
(11) R. E. Lutz and M. G. Reese, *J. Am. Chem. Soc.*, **81**, 127 (1959).

(12) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, 1958.

is ultimately produced from it. This absorptivity, which initially is small in the region characteristic of the aroyl group (ϵ 5,100 at 255 mμ), slowly changes and becomes constant within an hour at a somewhat lower level (ϵ 2,600) close to that of the cyclic ester VII and strikingly different from that of the acyclic ester VIII which absorbs strongly at *ca.* 268 mμ. In a separate experiment under slightly acidic conditions such as would develop during alcoholysis of the acid chloride, the normal ester VIII was shown, by retention of the characteristic ultraviolet absorption of the solution, to be stable and therefore not to be intermediate in the reaction. Thus, it can be said that the "acid chloride" and its alcoholysis product are both cyclic, and that alcoholysis occurs by direct attack at the γ-chloride link (*cf.* ref. 7), presumably by an ionization mechanism.



VII

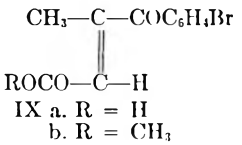


VIII

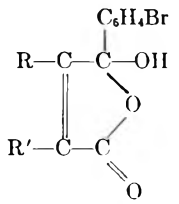
Ultraviolet and infrared absorption determinations confirm the structures previously assigned to the "amides" II–IV on classical chemical grounds. The acyclic types I and II are characterizable by strong 260–265 mμ absorption bands which are due to the aroyl groups necessarily present (*cf.* refs. 13–18), and by overlapping infrared absorption bands at *ca.* 5.9–6.0 μ due respectively to amide and aroyl type carbonyl groups (*cf.* ref. 19). The two cyclic types of "amides," the γ-aminolactones and γ-hydroxylactams III and IV, would show no strong aroyl type ultraviolet absorption and would give rise each to only a single infrared absorption band of *ca.* 5.7 or 5.9 μ respectively.

Specifically the γ-hydroxylactams IVa–c, which were obtained by the action of ammonia and methylamine on the *cis* "acid chloride" V, by ammonolysis of the *cis* esters VII and VIII, and by stereoisomerization of the *trans* anilide, showed no aroyl type ultraviolet absorption at 260–265 mμ as would be required of acyclic compounds of type II.[20] They showed in each case a strong infrared band at 5.8–5.9 μ characterizing the lactam carbonyl group, and a strong 3.0 μ hydroxylic absorption band.

The hydroxyl groups of the γ-hydroxylactams IV, and the N–H group of the γ-anilinolactone IIIa, are significantly though weakly acidic, as is shown by their alkali solubility.[5,22] Putting this to test quantitatively, relative pK_a' values in 50% ethanol were determined for two of the γ-hydroxylyactams, IVa and IVb, for the related largely-cyclic *cis* acid Xa, and for the *trans* acid IXa. The *trans* acid showed the relative pK_a' 4.4, the largely cyclic *cis* acid Xa, 6.4, and the γ-hydroxylactams IVa and IVb, 11.8 and 11.7 respectively. The *cis* α,β-dimethyl acid Xc,[23] which according to absorption spectrum appears to be much closer to completely cyclic at high dilution, showed pK_a' 8.7.

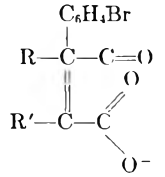


IX a. R = H
b. R = CH_3

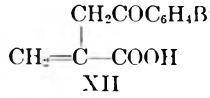


X a. R = CH_3, R' = H
b. R = H, R' = CH_3
c. R = R' = CH_3

The anions of the *cis* acids Xa,[4] Xb,[4] and Xc[17] in solution are shown actually to be acyclic as formulated in XI, by the intense ultraviolet conjugated-aroyl type absorption at *ca.* 260 mμ of strongly basic solutions of these compounds. In one case, Xa, this was demonstrated also in the solid state by using the crystalline sodium salt which gave strong overlapping infrared acid and aroyl type carbonyl bands at 5.8–6.0 μ and no lactone type carbonyl absorption at *ca.* 5.75 μ. On the other hand the acids themselves in the solid state (Xa, Xb, and Xc) are completely cyclic as shown by their strong single infrared carbonyl absorption bands at *ca.* 5.75 μ which characterize the lactone carbonyl group, and by the sharp and intense hydroxyl absorptions at *ca.* 3.0–3.1 μ which are at a somewhat longer wave length than for an ordinary and less acidic alcoholic hydroxyl (the free carboxyl group would not absorb sharply at this point[12]).



XI a. R = CH_3; R' = H
b. R = H; R' = CH_3



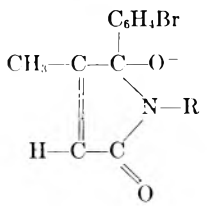
XII

(13) A. Hantzsch and A. Schwiete, *Ber.*, **49**, 213 (1916).
(14) Buu-Hoï and P. Cagniant, *Compt. rend.*, **212**, 268 (1941).
(15) T. Y. Shen and M. C. Whiting, *J. Chem. Soc.*, 1772 (1950).
(16) M. S. Newman and C. W. Muth, *J. Am. Chem. Soc.*, **73**, 4627 (1951).
(17) R. E. Lutz and R. J. Taylor, *J. Am. Chem. Soc.*, **55**, 1593 (1933).
(18) C. L. Browne and R. E. Lutz, *J. Org. Chem.*, **18**, 1638 (1953).
(19) J. F. Grove and A. A. Willis, *J. Chem. Soc.*, 877, 883 (1951).
(20) In all of the anilino compounds the aniline type absorptivity at 235–240 mμ[21] is of course superimposed upon those of the systems being given primary consideration here.
(21) R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley and Sons, Inc., New York, 1951.
(22) *Cf.* also S. Racine, *Ann.*, **239**, 78 (1887).
(23) R. E. Lutz and M. Couper, *J. Org. Chem.*, **6**, 77 (1941).

It should be noted here that the α-methylene isomer of the acid Xb, namely XII, is shown to be completely acyclic in the solid state, as it is in solution,[4] by its lack of hydroxylic infrared absorption band at *ca.* 3.0 μ, by its carboxylic type absorption in the 3.25–3.86 μ region and by the strong bifurcated peak at 5.79–5.84 μ which represents overlapping aroyl and carboxyl carbonyl absorptions.

The existence of the γ-hydroxylactam, apparently completely in the cyclic form IV even at high dilution (5×10^{-5} *M*), is in contrast with the incomplete cyclization at comparable dilution in the case of the more acidic γ-hydroxylactone-*cis*-acid equilibrium (X); in view of the relative pK_a' of 6.4 some observable degree of ionization would be expected. This difference, both in relative stabilities of the cyclic anions and in the facility of cyclization, was predicted from the greater basicity of nitrogen as compared with oxygen.

The three γ-hydroxylactams (IVa–c) when dissolved in 0.1*N* 50% ethanolic–sodium hydroxide showed no significant change in ultraviolet absorption and there developed no band at 260–265 mμ. Thus, the anions of these compounds are in the cyclic forms XIII and are less active than the normal carbamide (acyclic) anions which are not formed to any observable extent. This is in sharp contrast with the *cis* acid Xa which gives the relatively stable acyclic and true carboxylic type anion XIa.[4]



XIII a. R = H
b. R = CH_3
c. R = C_6H_5

The postulated[5] acyclic structure of the *cis* dimethylamide IIa, the product of condensation of the cyclic acid chloride V with the secondary amine dimethylamine, which is also obtained by stereoisomerization of the necessarily acyclic *trans* dimethylamide Id, is confirmed by the strong ultraviolet absorptivity at 260 mμ which could result only from this form, and by the strong infrared absorptivity at 6.02 μ which is presumed to arise from the similarly absorbing keto and amide carbonyl groups. Four other secondary aliphatic amines also produced similarly absorbing acyclic amides, IIe–f.

The γ-aminolactones IIIa and IIIb obtained by the consistently different reactions of V with the weaker bases, aniline and methylaniline,[5] are distinguished from the only alternative II by the lack of aroyl type ultraviolet and infrared absorptions at *ca.* 260 mμ and 6.0 μ respectively, and by the single infrared absorption band for each at *ca.* 5.7 μ which denotes the lactone carbonyl.

The acyclic *cis* methylanilide IIb made by irradiation of the necessarily acyclic *trans* methylanilide Ic shows the characteristic aroyl ultraviolet and infrared absorptivities as strong bands at 265 mμ and 6.0 μ, the latter a superposition of carbamido- and ethylenic bands. There is no indication of a shorter wave length ring–carbonyl band at *ca.* 5.7 μ. These absorptivities are a repetition of those of the *trans* anilide and *trans* methylanilide, Ic and Ie, the structures of which are certain.

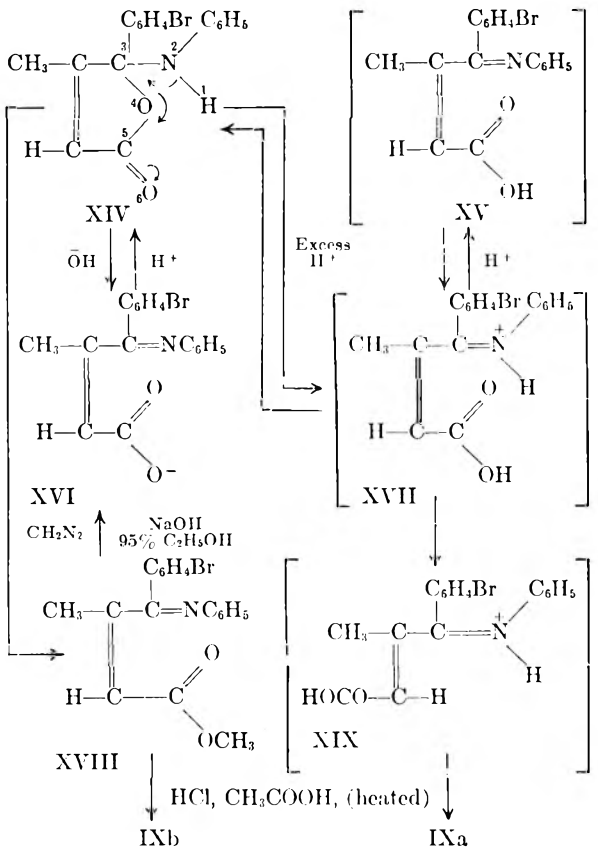
The structure of the *N*-phenyl-γ-hydroxylactam IVc,[5] made from the *trans* anilide Ic under irradiation or acid catalysis, presumably by conversion to and subsequent cyclization of the as yet unknown labile *cis* (acyclic) anilide of type II, is now confirmed by the lack of aroyl type ultraviolet absorptivity at *ca.* 260 mμ, and by the lone infrared lactone-type carbonyl band at 5.78 μ.

To the earlier mechanistic postulates for the reaction by which some of the "amides" I–IV are formed from the cyclic acid chloride V,[5,24] may be added the suggestion that possibly two mechanisms are involved, depending on whether the attacking amine is moderately basic (aliphatic) or weakly basic (aromatic). The active aliphatic amines may well be attacking the lactone carbonyl whose activity is enhanced by the γ-chlorine, with explusion of the chloride ion (SN_2, or in classical terminology, a 1,4-reaction as numbered in V), followed by release of a proton from nitrogen. The less active aryl amines on the other hand, may not be sufficiently basic to initiate this mode of attack, but may be attracted rather to the readily ionizing quaternary γ-carbon in an SN_1 mechanism. Rate studies are in progress to test these ideas.

It is noteworthy that the one γ-aminolactone obtained which carries an N–H group, the anilino compound XIV (IIIa), was shown to be quite acidic in that it formed a sodium salt with sodium hydroxide and was regenerated upon acidification.[5] In 50% ethanol the compound shows an ultraviolet absorptivity of ε 21,000 at its maximum at 235 mμ and falling through ε 5,000 at 262.5 mμ which is the position of the maximum for the acyclic anion XVI (shown below) and for the acyclic anil ester XVIII. Acidification of the 5×10^{-5} *M* solution to 0.1*N* in hydrochloric acid did not alter the absorption curve nor significantly increase the absorptivity at 262.5 mμ as it would have done if there had been an appreciable (and suppressible) equilibrium concentration of the acyclic anil form XV or XVI. The compound is thus shown in highly dilute solution to be chiefly in the γ-anilinolactone form XIV. Infrared analyses in 10% chloroform solution and in potassium bromide pellet consistently show the characteristic absorptivity for the lactone carbonyl and absence of the conjugated carbonyl and anilide group absorptions. There was no observable spectral indication of basic reaction in the sense of conversion into a cation of the anil type XVII in mod-

(24) It is possible, though seemingly unlikely here, that there occurs an actual completed rearrangement step from the cyclic V to a more active acyclic form of the chloride VI which then reacts in the two ways suggested (above).

erately acidic solution as doubtless must happen to some small extent under very strongly acid conditions (*e.g.* during oxindole formation[3]).



The development of an intense ultraviolet absorption maximum at 262.5 mμ when the 5×10^{-5} *M* 50% ethanol solution is made 0.2*N* in sodium hydroxide (ϵ 23,850 which is only slightly above the value at 0.1*N*) shows that ionization is essentially complete under these conditions and that the ion is in the anil or Schiff base form XVI. The disappearance of this absorption band upon neutralization or acidification to 0.1*N* in hydrochloric acid, and reversion to an absorption pattern exactly the same as that initially, show complete regeneration of the γ-anilinolactone XIV. The relatively high order of the acid strength of the γ-anilinolactone is evident from the further fact that at 5×10^{-5} *M*, 1.7 equivalents of sodium hydroxide cause formation of approximately 70% of the anion, a percentage estimated from the increase in absorptivity at 262.5 mμ toward the maximum ϵ value for the anion determined in the presence of a large concentration of base where dissociation must be essentially complete. In a futher and quantitative test the γ-anilinolactone was shown to have a relative pK_a' of 8.4 which is close to that of the largely cyclic β-bromobenzoyl-α,β-dimethylacrylic acid (Xc). This acidity, like that of Xc, is accounted for in terms of the ability readily to lose the proton from the nitrogen and thus to give directly the relatively stable carboxylate type anion.

It has been pointed out earlier[5a] that the γ-anilinolactone XIV undergoes hydrolytic and alcoholytic elimination of aniline and stereoinversion to the *trans* acid (or ester) IX under strongly acidic conditions, and that it behaves quite differently from the γ-methylanilino analog IIIb which is rearranged under these conditions to the β-bromophenacyloxindole.[3] This hydrolysis or alcoholysis of XIV does not involve either the *cis* acid Xa, the *cis* cyclic or acyclic ester VII or VIII, or the *cis* or *trans* anilides IVc or Ic, all of which are known and either are stable or react differently under the same conditions.[5] With the information now available it is possible to explain these results. Simple hydrolytic or alcoholytic elimination of methylaniline from IIIb is undoubtedly impeded seriously by the steric hindrance to which the *N*-methyl group contributes very materially, and the slow and somewhat difficult rearrangement to the oxindole[3] is thus allowed to compete successfully. Without the *N*-methyl group, the anilino group of the parent γ-anilinolactone XIV is hydrolytically or alcoholytically eliminated much more easily, probably by the following steps illustrating hydrolysis (alcoholysis would be similar but would involve acid-ester equilibration at the several points): concerted protonation at the lactone bridge or carbonyl oxygen and ring opening to the protonated anil-onium ion, XIV → XVII; stereoisomerization to the *trans* anil XIX; and subsequent *but not prior* hydrolysis of the anil group to the ketone, IX. The point at which the steric effect of the N-methyl in the γ-methylanilinolactone IIIb must operate to block this reaction course, presumably is the step involving formation of the *N*-methyl analog of XVII where the necessary approach to planarity of the *N*-methylanilonium system would face considerable, perhaps prohibitive, steric interference. The steric interference involved in the anilino compound itself at XV or XVII, even though not prohibitive, obviously would greatly increase the lability of the *cis* configuration and would reasonably account for the facile stereoinversion under the strongly acidic conditions which are without effect on the labile, but evidently less labile, *cis* acid or its ester (Xa or VIII).

The γ-anilinolactone XIV, consistent with and supporting the formulations XIV and XVI and the possibility of equilibrations involving the acyclic anil forms XV and XVII, reacted albeit somewhat slowly with diazomethane to give the expected acyclic methyl ester which must have the fixed anil structure XVIII (it is isomeric with the γ-methoxy-*N*-phenyllactam obtained by acid-catalyzed methylation of the hydroxylactam IVc, and it is isomeric with the γ-methylanilinolactone IIIb). Its structure was shown by basic hydrolysis to the original γ-anilinolactone XIV, by the acid-catalyzed configurational inversion with hydrolytic elimination of aniline to give the *trans* ester IXb, by the intense

ultraviolet absorption maximum of 262.5 mμ, ε 23,500, and by the infrared absorptions at 5.81 and 6.06 μ which represent ester and anil groups respectively. The diazomethylation reaction may involve a concerted (1,4) mechanism (XIV), prior removal of the proton of XIV, or possibly actual tautomerization through XV. This problem is being explored further.

EXPERIMENTAL[25]

cis-β-(p-Bromobenzoyl)-β-methylacrylyl piperidide and morpholinide, IIc and IId, were made by addition to an 80-ml. sodium-dried dioxane solution of 0.1 mol. of the acid chloride V[5] at 50°, 0.2 mol. of piperidine or morpholine, under stirring; it was then allowed to stand at this temperature for 1 hr. The mixture containing the precipitated amine hydrochloride was cooled and treated with excess water, and the precipitated amide was filtered, washed, dried, and recrystallized. The *pyrrolidide* and *dibenzylamide* were similarly prepared but by working entirely at room temperature. The *dimethylamide*[5] was also obtained working at 10° using 100 ml. of dry benzene saturated with dimethylamine, adding V, allowing the mixture to warm to room temperature, filtering, evaporating, and treating the residue with petroleum hexane. Repetition of the preparation of the γ-anilinolactone IIIa[5] was less successful (yield 70%), and hydrolysis by an acetic–concentrated hydrochloric acid mixture to purified IXa was only 27%.

Sodium β-(p-bromobenzoyl)-β-methylacrylate was prepared by mixing 2.9 g. of Xa with 80 ml. of 20% sodium hydroxide, filtering the resulting paste, and washing with hot benzene. Xa was recovered upon treatment with 5% hydrochloric acid.

Anal. (Vanadium pentoxide added to aid combustion, otherwise analyses were consistently low). Calcd. for $C_{11}H_8BrNaO_3$: C, 45.39; H, 2.77. Found: C, 45.52; H, 3.03.

II	NR_2	M.P.	Yield, %	Cryst. from
a[5]	$N(CH_3)_2$	115–116.5	50	C_6H_6-C_6H_{14}
c	Piperidyl	141–142	96	65% CH_3OH
d	Morpholinyl	150.5–151.5	82	65% CH_3OH
e	Pyrrolidyl	120–121	75	C_6H_6; C_2H_5OH
f	$N(CH_2C_6H_5)_2$	103–104	78	C_6H_6; C_2H_5OH

		C		H	
Anal.		Calcd.	Found	Calcd.	Found
a	$C_{13}H_{14}BrNO_2$	52.72	53.03	4.76	4.99
c	$C_{16}H_{18}BrNO_2$	57.23	57.08	5.39	5.28
d	$C_{15}H_{16}BrNO_3$	53.27	53.31	4.77	4.63
e	$C_{15}H_{16}BrNO_2$	55.91	55.92	5.00	5.15
f	$C_{25}H_{22}BrNO_2$	66.96	67.25	4.94	5.05

β-(p-Bromobenzoyl)-β-methylacrylic methyl ester anil (XVIII). Excess of diazomethane in 100 ml. of ether was added to a solution of 8.9 g. (0.0258 mol.) of the γ-anilinolactone (XIV) in 100 ml. of ether. The solution was allowed to stand for 36 hr. at 5° and 24 hr. at room temperature (the reaction is slow). Evaporation gave 9.3 g. (nearly quantitative) of crude product of m.p. 93–97°. Extraction with 0.1*N* sodium hydroxide solution and two recrystallizations from benzene and two from hexane gave an analytical sample, m.p. 101–102.5°.

(25) (a) Microanalyses were by Mrs. Margaret Logan. (b) Ultraviolet determinations were at *ca.* $5 \times 10^{-5}M$ in 95% ethanol unless otherwise specified, using a Beckman DU quartz spectrophotometer. (c) Infrared determinations were made with a Perkin-Elmer spectrophotometer, model 21 or Infracord.

Anal. (Vanadium pentoxide added to aid combustion). Calcd. for $C_{18}H_{16}BrNO_2$: C, 60.34; H, 4.50. Found: C, 60.45, 60.63; H, 4.29, 4.50. Three analyses in which the use

TABLE I

ULTRAVIOLET AND INFRARED ABSORPTION MAXIMA[m]

Ic, mμ[a] 238, 267 ε 18,100, 17,700.

Ie, mμ[a] 264, ε 15,900; μ[f] 6.03s, 6.12s (shoulder), 6.29s, 6.67s.

IIa, mμ[a] 260, ε 21,000; μ[f] 6.00s, 6.17s, 6.29s, 6.74s, 6.94s.

IIb, mμ[a] 261, ε 26,000; μ[e] 6.00–6.04bs, 6.16s, 6.27s, 6.69s, 6.92s.

IIc, mμ[a] 262, ε 21,200; μ[f] 5.96s, 6.04s, 6.18s, 6.29s, 6.84s, 6.95m.

IId, mμ[a] 262, ε 21,700; IIe, 260, ε 22,000;[a] IIf, 260, ε 21,000[a].

IIIa (XIV), mμ[a] 236, ε 19,800. In 50% ethanol: mμ, 235, ε 21,000; when made 0.1*N* in NaOH, see XVI below; then, when neutralized, mμ, 235, ε 27,220; acidified to 0.1*N* HCl, mμ, 235, ε 27,260. mμ,[c] 235, ε 19,320, sloping through 262.5 mμ, ε 2,500; after addition of two equivalents of sodium methoxide solution, 235 mμ, ε 17,000, sloping through shoulder at 262.5 mμ, ε 9,450. μ[e] 5.68s, 6.05w, 6.24m; μ[f] 2.97s, 5.76s, 6.06m, 6.23s, 6.58s, 6.67s, 6.73s, 6.95s.

IIIb, mμ[a] 240, ε 14,600; μ[e] 5.71s, 6.05s, 6.25–6.30bm; μ[f] 5.68s, 6.04m, 6.24m, 6.67s (shoulder 6.72m), 6.95bm.

IVa, mμ[a] 229–250, ε 10,700–3,600; [g,h] μ[f] 2.95–2.99–3.05s (trifurcation), 5.20w, 5.90bs, 6.02m (shoulder), 6.25m, 6.32m, 6.68s, 6.95s.

IVb, mμ[a] 230, ε 12,700;[h,i] μ[f] 3.04s, 3.33–3.37m, 3.47m, 4.23w, 4.55w, 5.20w, 5.89bs, 6.03s, 6.23m, 6.29m, 6.67s, 6.76s, 6.95s, 7.15s, 7.26s.

IVc, mμ[a] 230–280, ε 16,800–3,000.[g,h,j]

V, mμ[d] 243–267, ε 8,700–1,600;[g] μ[e] 3.31m, 4.30m, 5.64s, 6.05m, 6.28w, 6.72m, 7.17m, 7.74w, 8.30s, 8.56w, 9.30m; μ[f] 5.51s, 5.61s, 6.02s, 6.25m, 6.69s, 6.95m.

VII, mμ[c] 232.5, ε 10,800; μ[f] 5.69bs, 6.05s, 6.28w, 6.36w, 6.73m, 6.98m.

VIII, mμ[c] 262.5, ε 18,400; μ[f] 5.81s, 5.95s, 6.06s, 6.28s, 6.74m, 6.94s.

IXa, μ[f] 3.30bm, 5.84–5.94–6.03s (trifurcation), 6.32s, 6.76w, 6.97m.

IXb, μ[f] 5.80s, 6.03s (shoulder 6.10m), 6.30s (shoulder 6.36m), 6.99m.

Xa, μ[f] 3.11bs, 5.76s (shoulder 5.83m), 6.06m, 6.28m, 6.73m, 6.97s, 7.18m, 7.27m, 7.65m, 7.96bs, 8.22s, 8.48m, 8.70s, 9.06m, 11.00bs.

Xb, μ[f] 3.40bm, 5.85–5.94s (bifurcation), 6.31s, 6.83m, 7.00m.

Xc, mμ[a] 230, ε 13,400. Anion:[k] mμ[a] 256, ε 15,500.

XIa, sodium salt, μ[f] 6.00–6.05bs, 6.21s, 6.33bs, 6.74m, 6.87s, 7.02–7.15bs.

XII, μ[f] 3.25–3.86m (broad, serrated), 5.79s–5.85s (bifurcation), 6.05m, 6.25s, 6.91bm, (no band at *ca.* 11 μ).

XVI, determined in 0.1*N* sodium hydroxide–50% ethanol, $5 \times 10^{-5}M$: mμ 262.5, ε 23,410; in 0.2*N* NaOH, ε 23,850.

XVIII, mμ[b] 262.5, ε 22,450 (minimum, 237.5 mμ, ε 12,880); mμ[c] 262.5, ε 23,500[l]. μ[f] 5.81s, 6.06s, 6.19s, 6.32s, 6.40s, 6.76s, 6.96s.

Solvent: [a] 95% C_2H_5OH; [b] abs. C_2H_5OH; [c] CH_3OH; [d] 2,2,4-trimethylpentane (isooctane); [e] $CHCl_3$; [f] potassium bromide pellet. [g] No maximum; slope defined by the two figures given. [h] The absorption curve is negligibly affected by addition to the solution of a small amount of strong base. [i] Sloping through 244 mμ, ε 5,000. [j] Very broad shoulder centering at 276 mμ, ε 2,800. [k] Produced by adding a small amount of strong base to the solution. [l] On standing in sunlight for 2 days the ε value dropped to a half and after 11 days practically to zero. [m] For ultraviolet, important shoulders or absorption areas are footnoted. For infrared, important bands up to 7 μ are given, with s = strong, m = medium, w = weak, b = broad.

of vanadium pentoxide was omitted were consistently low in carbon by 0.77–0.81%, and indicated incomplete combustion.

Hydrolysis of 0.35 g. of XVIII in 20 ml. of glacial acetic acid and 3 drops of concentrated hydrochloric acid, with refluxing for 30 min., gave 0.18 g. (65%) of IXb, m.p. 72–73°, which was identified by recrystallization from hexane (m.p. 73–74°) and mixture m.p., and by identity of infrared spectrum with that of an authentic sample.

Hydrolysis of 0.53 g. of XVIII in 8 ml. of 95% ethanol containing 0.07 g. of dissolved sodium (24 hr. at room temperature) gave 0.38 g. (75%) of crude XIV which on two recrystallizations from benzene was identified by m.p. 168–168.5°, mixture melting point, and infrared absorption spectrum identical with that of an authentic sample.

Determination of acidities (pK_a').[2b] Because of difficult solubilities in water the determinations were made in 50% ethanol at 25° and they are therefore relative only. The true acids (*trans*), and the *cis* acids, which are partly or largely in the γ-hydroxylactone forms, and the γ-anilinolactone XIV, were sufficiently acidic so that the relative pK_a' values could be calculated from the apparent *p*H values at half neutralization as determined by means of a Beckman Model G *p*H meter. For calculation of the relative pK_a' values for the very weak acids, the γ-hydroxylactams, the apparent *p*H values were determined by the use of trinitrotoluene as an indicator for the range involved and a series of standard sodium hydroxide solutions, and by measuring absorptivities at 450 mμ, with time standardization to allow for slow deterioration of the standards. The relative pK_a' values were: Xa (*cis*), 6.39; IXa (*trans*), 4.37; Xc, 8.69; IVa, 11.8; IVb, 11.7; XIV, 8.40.

CHARLOTTESVILLE, VA.

[CONTRIBUTION FROM THE PIONEERING RESEARCH DIVISION, TEXTILE FIBERS DEPARTMENT, E. I. DU PONT DE NEMOURS & COMPANY, INC.]

Some Reactions of *p*-Toluenesulfonyl Isocyanate

C. KING

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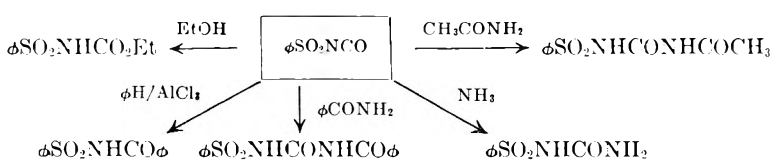
Several new reactions of *p*-toluenesulfonyl isocyanate (I) are reported. Reaction with *N,N*-dialkylamides gives *N,N*-dialkyl-*N'*-*p*-toluenesulfonylamidines (II), with elimination of carbon dioxide. Monoalkylamides give rise to *N*-alkyl-*N*-acyl-*N'*-*p*-toluenesulfonylureas (III) by simple addition, or to *N*-alkyl-*N'*-*p*-toluenesulfonylamidines (IV), with elimination of carbon dioxide. Isobutyraldehyde reacts to give VI. Dimethyl sulfoxide yields *N*-*p*-toluenesulfonyl dimethyl sulfilimine (VII).

Recent published work[1] has described reactions of *p*-toluenesulfonyl isocyanate (I), with monoalkyl- and dialkylamides. We wish to report work done independently in this laboratory on these and other unusual reactions of *p*-toluenesulfonyl isocyanate.

Sulfonyl isocyanates have only recently become readily and economically accessible from high temperature phosgenation of sulfonamides in inert solvents.[2] Billeter[3] had prepared methane- and benzenesulfonyl isocyanates by treating the appropriate sulfonyl chlorides with silver cyanate at 120–140°. With benzenesulfonyl isocyanate he observed typical addition reactions of isocyanates. He further noted that sulfonyl isocyanates undergo ready hydrolysis to sulfonamides, rather than to ureas, which are the usual hydolysis products of isocyanates. Prior to the work of Logemann this appears to be the only reported work on sulfonyl isocyanates.

The work in this paper deals with reactions on *p*-toluenesulfonyl isocyanate, for which a convenient preparation has been described in the patent literature.[2]

Reaction with N,N-dialkylamides. Smooth, rapid reaction occurred when *p*-toluenesulfonyl isocyanate was added to an excess of *N,N*-dialkylamide at room temperature. Reactions were exothermic, and it was not found necessary to add solvent or catalyst. Good yields of crystalline solids were obtained which were products of intermolecular elimination of carbon dioxide. Dialkylamides found to react in this manner were dimethylformamide, dimethylacetamide, *N*-formylpiperidine, *N*-acetylpiperidine, and *N*-methylpyrrolidone. It is believed that the reaction proceeds through a cyclic intermediate, leading to *N,N*-dialkyl-*N'*-*p*-toluenesulfonylamidines. Thus, for the reaction with dimethylformamide:



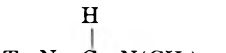
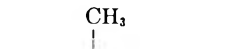
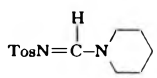
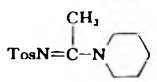
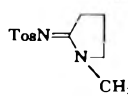
(1) W. Logemann, D. Artini, G. Tosolini, and F. Piccini, *Ber.* **90**, 2527 (1957); **91**, 951, 2566 (1958).

(2) British Patent **692,360**, June 3, 1953.

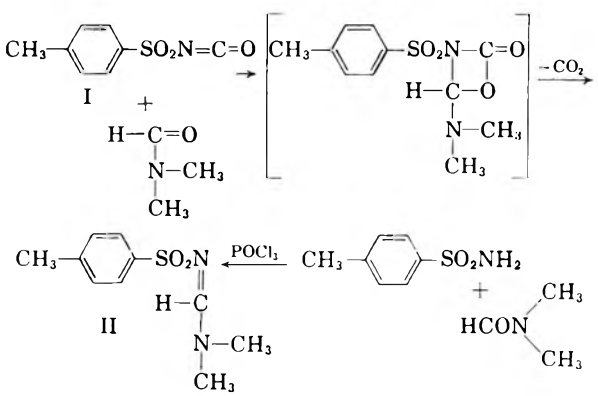
(3) O. C. Billeter, *Ber.*, **36**, 690–6 (1904); **37**, 2013–15 (1905).

TABLE I

N,N-DIALKYL-*N'*-*p*-TOLUENESULFONYL AMIDINES

Sulfonylamidine	M.P.	Yield, %	Analyses	Infrared
	133–133.5[a]	67	Calcd. for $C_{10}H_{14}SO_2N_2$: C, 53.07; H, 6.25; N, 12.38; S, 14.25. Found: C, 53.2; H, 6.0; N, 11.9; S, 14.0.	—C=N— Absorption 1630 cm.$^{-1}$ 6.11 μ
	120.5–121[a]	95	Calcd. for $C_{11}H_{16}SO_2N_2$: C, 54.95; H, 6.72; N, 11.66; S, 13.33. Found: C, 55.0; H, 6.53; N, 11.35; S, 13.29.	1580 cm.$^{-1}$ 6.31 μ
	147.5–149[a]	46	Calcd. for $C_{13}H_{18}SO_2N_2$: C, 58.61; H, 6.82; N, 10.32; S, 12.03. Found: C, 57.9; H, 6.8; N, 10.2; S, 12.1.	1540 cm.$^{-1}$ 6.5 μ
	145–147	64	Calcd. for $C_{14}H_{20}SO_2N_2$: C, 59.96; H, 7.20; N, 9.99; S, 11.43. Found: C, 59.1; H, 7.0; N, 9.8; S, 11.6.	1610 cm.$^{-1}$ 6.2 μ
	163–164	32	Calcd. for $C_{12}H_{16}SO_2N_2$: C, 57.12; H, 6.39; N, 11.10; S, 12.71. Found: C, 57.1; H, 6.3; N, 11.1; S, 12.8.	1600 cm.$^{-1}$ 6.25 μ

[a] Logemann reports 133–134°, 121–124°, and 146–148° for these compounds, respectively.



Structural assignment of II was based on elemental and infrared analysis, and on establishing its identity by mixture melting point with *N,N*-dimethyl-*N'*-*p*-toluenesulfonyl formamidine prepared from condensation of *p*-toluenesulfonamide with dimethylformamide. This latter preparation was adapted from a recently disclosed[4] method.

The cyclic mechanism postulated above for sulfonylamidine formation seems plausible, particularly in view of the high polarity of the reactants. The isocyanate function is rendered highly electrophilic by the adjacent sulfonyl groups, and would be highly attracted to the electron-rich carbonyl of a dialkylamide.

Analogous amidine formation is known for ordinary isocyanates. Thus, treatment of benzanilide with phenyl isocyanate at 200–220° gives *N,N'*-diphenylbenzamidine.[5]

Table I summarizes the data on reaction products from dialkylamides.

Reaction with unsubstituted amides. Acetamide and formamide gave products of simple addition, *N*-toluenesulfonyl-*N'*-acylureas. A second product, however, was isolated from the reaction with formamide. It melted at 195–196°, and had the elemental composition of *N*-*p*-toluenesulfonyl urea. This latter product arose apparently from hydrolysis during work up of the primary product, *N*-*p*-toluenesulfonyl-*N'*-formyl urea. *N*-*p*-toluenesulfonyl urea is reported to melt at 192°.[6]

No evidence was found for reaction at the carbonyl group, as in the case of the dialkylamides.

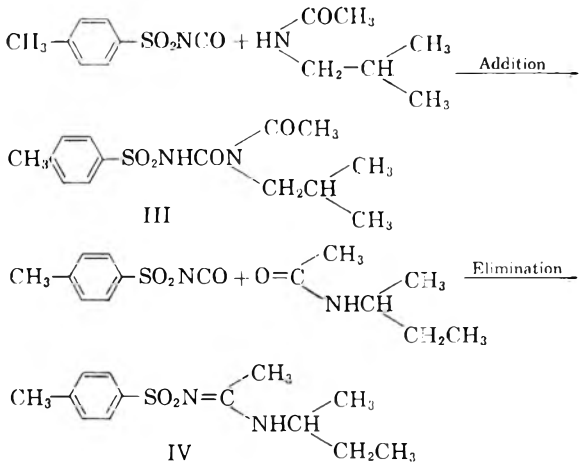
Reaction with monosubstituted amides. Reaction of *p*-toluenesulfonyl isocyanate with *mono*alkylamides was not so clean as those with unsubstituted or dialkylamides. Crystalline products were obtained only as minor constituents, while for the most part reaction mixtures were noncrystallizable, frequently dark, oils. Reaction mixtures involving formamides occasionally had a carbylamine-like odor, arising presumably from dehydration of the formamides.

Crystalline compounds were isolated, however, which were products of simple addition, as for the unsubstituted amides, and products formed by elimination of carbon dioxide, as for the dialkylamides. Thus, *N*-isobutylacetamide reacted by addition, and *N*-*sec*-butylacetamide reacted by elimination. These products were identified by infrared and elemental analysis.

(4) German Patent 949,285, Sept. 20, 1956.

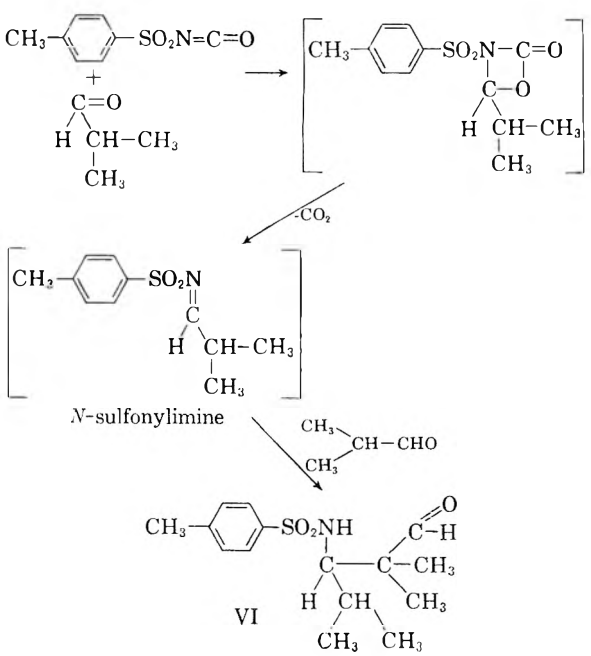
(5) P. F. Wiley, *J. Am. Chem. Soc.*, 81, 3746 (1949).

(6) G. H. Cox and S. M. Raymond, Jr., *J. Am. Chem. Soc.*, 63, 300–301 (1941).



The crystalline product obtained from *N*-isobutylformamide was *N*-*p*-toluenesulfonyl-*N'*-isobutyl urea, (V), identified by infrared and elemental analysis, and by comparison with authentic urea prepared by addition of isobutylamine to *p*-toluenesulfonyl isocyanate. Formation of V could have arisen from hydrolysis of a product-by-addition (analogous to III) or from hydration of a product-by-elimination (analogous to IV). In either case, the urea is a product of a secondary reaction, occurring presumably during work up.

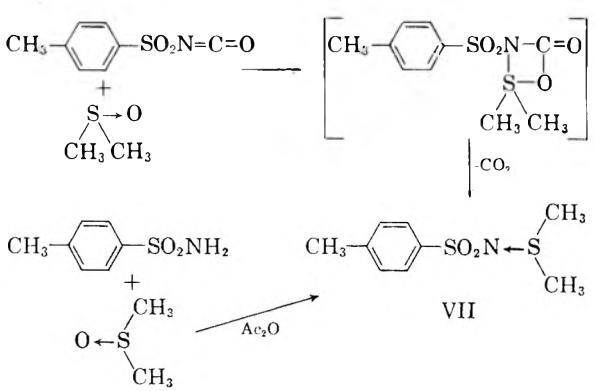
Reaction with aldehydes and ketones. Isobutyraldehyde reacted moderately fast to give a somewhat unstable crystalline solid, m.p. 147.5–148°, having the composition $C_{15}H_{23}SO_3N$. This composition indicates that two molecules of isobutyraldehyde reacted with one of *p*-toluenesulfonyl isocyanate, with elimination of carbon dioxide. The reaction may be formulated as sulfonylimine formation followed by addition of isobutyraldehyde. Infrared analysis disclosed the presence of —NH and of >C=O, which had the



appearance of a hydrogen-bonded carbonyl. The carbonyl group might well be expected to bond with the sulfonamide hydrogen. An attempt to prepare a sulfonylimine with *p*-methylbenzaldehyde (no α-hydrogen for further addition) failed, presumably because of hydrolysis. Reaction with this aldehyde gave solid which initially melted at 90–93° but which, on attempted purification, yielded only *p*-toluenesulfonamide contaminated with aldehyde.

The ready reaction of *p*-toluenesulfonyl isocyanate with amides and aldehydes suggested that reaction might occur with other carbonyl compounds. No reaction was observed, however, with acetone, cyclohexanone, benzophenone, acetyl chloride, or ethyl acetate.

Reaction with sulfoxides. With dimethyl sulfoxide a rapid exothermic reaction occurred, giving crystalline product in high yield. This product proved to be *N*-*p*-toluenesulfonyl dimethyl sulfilimine (VII), since it had the appropriate elemental composition and did not depress the melting point of an anthentic sample prepared by condensing *p*-toluenesulfonamide with dimethyl sulfoxide in acetic anhydride. Infrared spectra of samples from both preparations were identical. Sulfilimine formation may, formally, at least, proceed through a cyclic intermediate.



Reaction with amines and mercaptans. A number of more conventional derivatives of *p*-toluenesulfonyl isocyanate were prepared. Five amines gave the expected ureas by simple addition. Dodecyl mercaptan reacted slowly to give the thiourethane, m.p. 61–63°. Table II summarizes these results.

EXPERIMENTAL

p-Toluenesulfonyl isocyanate (I). The following procedure is substantially that of British Patent 692,360. Phosgene, 700 ml., was condensed in a 1-l. round bottomed flask and allowed to evaporate at room temperature through a stirred, refluxing solution of 1000 g. *p*-toluenesulfonamide in 3500 ml. 1,2,4-trichlorobenzene. After completion of the addition the trichlorobenzene was removed by distillation at reduced pressure through a 6-in. Vigreux column (90° at 100 mm.); distillation was continued until the head temperature was 110°. The residue was distilled at 0.05 mm., and, after a short forerun, the main portion passed over at 87–90°; a little was collected up to 107°. Fractionation of this dis-

TABLE II

PRODUCTS FROM AMINES AND MERCAPTANS

Urea	M.P.	Yield, %	Analyses
TosNHCONHΦ	169–170	83	Calcd. for $C_{14}H_{14}SO_3N_2$: C, 57.91; H, 4.87; N, 9.65; S, 11.04. Found: C, 58.0; H, 4.8; N, 9.5; S, 10.8.
TosNHCONH-*iso*-Bu	169–169.5[a]	74	Calcd. for $C_{12}H_{18}SO_3N_2$: C, 53.30; H, 6.72; N, 10.38; S, 11.86. Found: C, 53.1; H, 6.63; N, 10.3; S, 11.8.
TosNHCO-N⟨⟩	148–149	65	
TosNHCONH-*sec*-Bu	123–125[a]	81	
TosNHCONH-*n*-Bu	117–122[a]	44	
$TosNHCOSC_{12}H_{25}$	61–63	90	

[a] Logemann reports 168–170°, 124–126°, and 124–126° for these compounds, respectively.

tillate through a 12-in. glass helix packed column afforded 597 g. of pure *p*-toluenesulfonyl isocyanate, b.p. 90–93° at 0.05 mm. (54%). It was necessary to store this compound under dry nitrogen in tightly stoppered bottles, since even short exposure to atmospheric moisture caused hydrolysis to *p*-toluenesulfonamide. The boiling range has previously been recorded as 114–116° at 0.3 to 0.5 mm.[2]

N,N-Dimethyl-N'-p-toluenesulfonyl formamidine (II). A. Ten g. of I was slowly added to 15 ml. dry dimethylformamide swirled in a 50-ml. Erlenmeyer flask. Rapid heating occurred, with rapid evolution of carbon dioxide. The colorless mixture was allowed to stand at room temperature overnight, and was then poured into water to precipitate product, which was collected on a filter. Recrystallization from an ethanol-water mixture gave white crystals, m.p. 133–134°, 8.8 g. (67%). Strong absorption in the infrared at 6.11 μ indicated a —C=N-grouping.

B. A solution of 10.3 g. (0.06 mole) of *p*-toluenesulfonamide, 6.0 g. (0.10 mole) dimethylformamide, and 11.6 g. (0.076 mole) phosphorus oxychloride in 40 ml. dry toluene was refluxed for 4 hr. The reaction mixture was cooled, stirred into 150 ml. ice water, and then neutralized with sodium bicarbonate. The crystals which separated were collected on a filter and then recrystallized from benzene. Product melted at 132–134°, and amounted to 3.3 g. (26%). The melting point of a mixture of product from A and B was 133–134°. The infrared spectrum of B was identical with that of A.

N-p-Toluenesulfonyl-N'-acetylurea. Acetamide, 5 g. (0.083 mole) was added with shaking to 10 g. (0.058 mole) (I). When the acetamide was nearly all dissolved a vigorous reaction occurred and the reaction mixture solidified. Crystallization from ethanol afforded 11.7 g. (79%) of white crystals, m.p. 178–179°. Infrared analysis showed —NH absorption at 3.17 μ, and the split carbonyl absorption expected for the grouping —C(=O)—N(—)—C(=O)— (5.75 and 5.94 μ).

Anal. Calcd. for $C_{10}H_{12}SO_4N_2$: C, 46.86; H, 4.73; N, 10.93; S, 12.82. Found: C, 46.9; H, 4.7; N, 10.9; S, 12.9.

N-p-Toluenesulfonyl-N'-formylurea. Formamide, 15 ml., was mixed with 10 g. (0.058 mole) (I), and the mixture was allowed to stand for 4 days at room temperature. The product purified by crystallization from water amounted to 10.0 g. (57%), m.p. 155–156°. Infrared absorption at 5.72 and 5.9 μ indicated —C(=O)—N(—)—C(=O)—.

Anal. Calcd. for $C_9H_{10}SO_4N_2$: C, 44.61; H, 4.17; N, 11.56; S, 13.23. Found: C, 44.8; H, 4.3; N, 11.5; S, 13.2. Concentration of the mother liquors yielded 2.7 g. of a white solid melting at 193–197°. Crystallization from ethanol-water gave pure *N-p*-toluenesulfonyl urea, m.p. 195–196° (lit.[2] 192°).

Anal. Calcd. for $C_8H_{10}SO_3N_2$: C, 44.83; H, 4.71; N, 13.08. Found: C, 44.7; H, 4.6; N, 12.9.

N-p-Toluenesulfonyl-N'-isobutylurea (III). Ten g. of I (0.058 mole) was added to 15 ml. *N*-isobutylacetamide at room temperature. Reaction was slow, with slow evolution of gas. The mixture was allowed to stand at room temperature overnight, and was then taken up in ethanol. Addition of water with cooling in ice caused separation of crystals which were purified by recrystallization from ethanol-water. Yield was 1.7 g. (6%); m.p. 80–81°. Infrared absorption at 5.82 and 5.99 μ indicated the grouping —C(=O)—N(—)—C(=O)—.

Anal. Calcd. for $C_{14}H_{23}SO_3N_2$: C, 53.31; H, 7.36; N, 8.88; S, 10.16. Found: C, 53.77; H, 6.40; N, 8.9; S, 10.2.

N-sec-Butyl-N'-p-toluenesulfonylacetamidine (IV). Ten g. of I (0.058 mole) was mixed with 15 ml. *N-sec*-butylacetamide. A moderately vigorous reaction occurred with gas evolution to give a thick yellowish liquid. A small amount of white solid was obtained when this liquid was cooled and mixed with water. Recrystallization from ethanol-water gave 0.46 g. (2.3%) of crystalline product, m.p. 86.5–88°. Infrared absorption at 3.07 μ indicated —NH, and that at 6.47 μ indicated —C=N—. The remaining oil was not further examined.

Anal. Calcd. for $C_{13}H_{20}SO_2N_2$: C, 58.17; H, 7.53; N, 10.44; S, 11.94. Found: C, 58.23; H, 7.49; N, 10.4; S, 11.9.

N-p-Toluenesulfonyl-N'-isobutylurea. A. *N*-Isobutylformamide, 15 ml., was mixed with 10 g. (0.058 mole) of (I). A very rapid darkening occurred, with evolution of gas. The reaction mixture was a dark oil having the odor of a carbylamine. It was allowed to stand 3 days, and then stirred into cold water. A small amount of solid which separated was crystallized several times from ethanol-water. Yield was 0.36 g. of white crystals melting at 169.5–70.5°.

Anal. Calcd. for $C_{12}H_{18}SO_3N_2$: C, 53.50; H, 6.72; N, 10.36; S, 11.86. Found: C, 53.4; H, 6.3; N, 10.3; S, 11.8.

B. To 15 ml. of isobutylamine was added, in portions at room temperature, 10 g. (0.058 mole) I. The reaction was very vigorous. Product crystallized from ethanol-water melted at 169–170°, and amounted to 11.4 g. (74%). The melting point of a mixture of product from A and B melted at 169–170°.

Reaction with isobutyraldehyde (VI). Isobutyraldehyde, 15 ml., was mixed with 10 g. (0.058 mole) I at room temperature. After a short induction period the reaction mixture warmed to about 50° and evolved gas. The mixture was allowed to stand overnight, and was then taken up in methylene chloride and cooled in Dry Ice. White solid which separated was collected on a filter and washed with cold ether. When dry the product melted at 143–145°. Three recrystallizations from chloroform–petroleum ether afforded 3.9 g. (23%), m.p. 147.5–148.5°. The compound was somewhat unstable; a strong odor of isobutyraldehyde developed from purified samples that had stood for about

a week. Infrared analysis disclosed —NH absorption at 3.01 μ, and the absorption of a hydrogen-bonded carbonyl at 5.83 μ.

Anal. Calcd. for $C_{15}H_{23}SO_3N_2$: C, 60.65; H, 7.81; N, 4.71; S, 10.78. Found: C, 60.4; H, 7.6; N, 4.65; S, 10.7.

N-p-Toluenesulfonyl dimethyl sulfilimine (VII). A. Ten g. (0.058 mole) of I was added slowly to 15 g. (0.19 mole) of dry dimethyl sulfoxide with stirring. Rapid heating occurred, with evolution of gas. The colorless reaction mixture was allowed to stand at room temperature for 5 hr. The product was then isolated by precipitation with water, followed by crystallization from ethanol-water mixture. Yield of pure sulfilimine, m.p. 157–158°, was 11.7 g. (87%).

B. This preparation was adapted from the procedure of Tarbell and Weaver[7] for sulfilimine formation. A solution of 8.6 g. *p*-toluenesulfonamide (0.05 mole) and 3.9 g. (0.05 mole) dimethyl sulfoxide in 25.5 g. acetic anhydride was heated over a steam bath for 1 hr. The solution was then cooled to room temperature and stirred into an ice-cold solution of 20 g. sodium hydroxide in 60 ml. water. The white crystals which separated were collected on a filter and then recrystallized from benzene. Yield was 5.5 g. (47%), m.p. 157–158°. Infrared spectra of samples from A and B were identical.

WILMINGTON 98, DEL.

(7) D. S. Tarbell and C. Weaver, *J. Am. Chem. Soc.*, **63**, 2939 (1941).

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

Acenaphthene Chemistry. VI.[1,2] Preparation and Reactions of Some Pyracene Glycols

HENRY J. RICHTER AND WILLIAM C. FEIST

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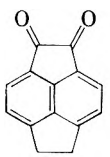
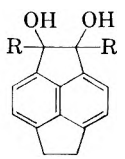
1,2-Diphenylpyracenediol reacts with 47% aqueous hydriodic acid to form the stable orange-colored 1,2-diphenyl-5,6-dihydropyracylene (III). With iodine in glacial acetic acid, the diol is converted to 2,2-diphenylpyracenone-1. The reduction of 1,2-diketopyracene with sodium borohydride produces an equimolar mixture of *cis* and *trans* 1,2-pyracenediols. The rearrangement of these diols affords pyracenone-1.

A number of derivatives of pyracene have been described in the literature.[1,3–5] There are also described some attempts to prepare the conjugated-unsaturated nonalternate hydrocarbon pyracylene.[5b] Anderson and Anderson discuss the calculated resonance energy and the 1,2- and 5,6-bond distances and conclude that such a molecule could exist. With the preparation of 1,2-diketopyracene[1] (I), the introduction of groups into the pyracene molecule has been simplified. This paper describes the preparation and reactions of a number of these derivatives.

1,2-Diketopyracene (I) was prepared as described by Richter and Stocker[1] and treated with phenylmagnesium bromide to form the *trans* pinacol II. The pinacol II reacted with 47% hydriodic acid to afford 66% of 1,2-diphenyl-5,6-dihydropyracylene (III). This bright orange compound is stable even at its melting point of 226°. The unsubstituted hydrocarbon, 1,2-dihydropyracylene, prepared by Anderson and Anderson[5b] is reported to decompose at room temperature.



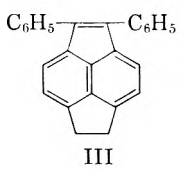
I



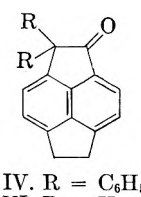
II. R = C_6H_5
Va. R = H, *cis*
Vb. R = H, *trans*

A similar elimination with 47% hydriodic acid was observed with 1,2-diphenylacenaphthenediol-1,2 which formed 1,2-diphenylacenaphthylene in good yield. The course of this elimination is uncertain as no iodine color is observed. This does not exclude the formation and decomposition of a 1,2-diiodo compound as iodine dissolves in 47% hydriodic acid to form a colorless solution.[6]

When II was treated with iodine in boiling glacial acetic acid according to Bachmann and Chu,[7] rearrangement of the pinacol led to the formation of 2,2-diphenylpyracenone-1 (IV) in 73.5% yield.



III



IV. R = C_6H_5
VI. R = H

(1) Previous paper: H. J. Richter and F. B. Stocker, *J. Org. Chem.*, **24**, 366 (1959).

(2) This work was supported by the National Institute of Health, Grant Cy-2997-C3.

(3) M. C. Kloetzel and F. L. Chub, *J. Am. Chem. Soc.*, **72**, 150 (1950).

(4) A. G. Anderson, Jr., and R. H. Wade, *J. Am. Chem. Soc.*, **74**, 2274 (1952).

(5) A. G. Anderson, Jr., and R. G. Anderson, (a) *J. Org. Chem.*, **22**, 1197 (1957). (b) *J. Org. Chem.*, **23**, 517 (1958).

(6) C. A. Jacobsen, *Encyclopedia of Chemical Reactions*, Vol. III, Reinhold Publishing Corp., New York, N. Y., 1949, p. 709.

(7) W. E. Bachmann and E. J. Chu, *J. Am. Chem. Soc.*, **58**, 1118 (1936).

Rearrangement of II in boiling glacial acetic acid with a trace of hydrochloric acid[8] gave considerable decomposition. Chromatographic separation of this latter product afforded a 30% yield of crude ketone IV and a 10% yield of impure diphenyldihydropyracylene III. It is of interest to note that 1,2-diphenylacenaphthenediol-1,2 under similar conditions formed an 85% yield of 2,2-diphenylacenaphthenone-1.

The diketone I is reduced quantitatively by sodium borohydride to form a mixture of *cis* and *trans* diols Va and Vb. A diol melting at 264–265° separated from the reaction mixture in 51.5% yield. This compound formed an isopropylidene derivative with acetone and is thus shown to be the *cis* isomer Va. The *trans* diol Vb m.p. 188–189° was isolated in 48.5% yield from the mother liquor. A reaction time of two hours was required for complete reduction of the pyracene diketone I whereas acenaphthenequinone under similar conditions is reduced almost instantaneously to a mixture of *cis* and *trans* diols.

A mixture of the above diols in glacial acetic acid with iodine as the catalyst rearranged to form pyracenone-1 (VI). This compound was described previously by Anderson and Anderson.[5b] The mixture of *cis* and *trans* acenaphthenediols under similar conditions did not yield any identifiable products.

EXPERIMENTAL

1,2-Diketopyracene (I). This compound was prepared as described by Richter and Stocker.[1] With highly purified oxalyl bromide and technical grade aluminum bromide, the yields were 8–10%.

With naphthalene instead of acenaphthene and identical reaction conditions, the only product obtained was α-naphthoic acid. This was obtained in 75% pure yield. Unchanged naphthalene (25%) was isolated from the carbon disulfide liquor. No acenaphthenequinone was detected.

trans-1,2-Diphenylpyracenediol-1,2 (II). This compound was obtained in 38% yield by Richter and Stocker.[1] A more satisfactory preparation is described. Phenylmagnesium bromide was prepared from 5.4 g. of bromobenzene and 0.85 g. of magnesium turnings in 100 ml. of absolute ether. To this ethereal solution, 1,2-diketopyracene (I) (1.50 g., 0.007 mole) was added in small portions. A vigorous reaction occurred and the light brown Grignard solution turned orange. An additional 100 ml. of absolute ether was added and the solution was refluxed for 2 hr. The mixture was decomposed by pouring into iced acetic acid. The ether layer was separated and the acetic acid solution was extracted twice with additional ether. The combined ether extracts were washed with 10% sodium carbonate solution and with water and dried over anhydrous sodium sulfate. Filtration and evaporation of the solvent *in vacuo* yielded 2.5 g. (98%) of a light yellow solid, m.p. 120–160°. This product was crystallized from ethanol-water with decolorizing charcoal and yielded white needles, 1.85 g. (69%), m.p. 179–181° (lit.[1] 180–181°) of II.

Treatment of II with dry acetone containing 1% anhydrous hydrogen chloride yielded only starting material confirming the formation of *trans*-1,2-diphenylpyracenediol-1,2 (II).

1,2-Diphenyl-5,6-dihydropyracylene (III). 1,2-Diphenylpyracenediol-1,2 (II) (0.5 g.) was treated with 30 ml. of 47% aqueous hydriodic acid at room temperature with stirring. The white suspension of II was warmed on a steam bath for 1 hr. during which time it slowly turned to an orange suspension. Glacial acetic acid (10 ml.) was added and the orange suspension was warmed on a steam bath for 1 hr. It was poured into aqueous sodium bisulfite solution and filtration yielded 0.45 g. of orange III, m.p. 217–220° in quantitative yield. Crystallization from acetone–ethanol–water yielded orange needles, (0.3 g., 66%), m.p. 226–227°.

Anal. Calcd. for $C_{26}H_{18}$: C, 94.51; H, 5.49. Found: C, 94.72; H, 5.50.

A solution of III (0.1773 g., 0.0005 mole) in absolute ethanol took up 0.0005 mole of hydrogen over 10% palladium on charcoal catalyst at one atmosphere pressure and room temperature to give 0.180 g. (97%) of 1,2-diphenylpyracene, m.p. 197–198.5°. This product formed white needles from ethanol-water.

Anal. Calcd. for $C_{26}H_{20}$: C, 93.94; H, 6.06. Found: C, 93.44; H, 6.17.

In a similar reaction, 0.5 g. of 1,2-diphenylacenaphthenediol-1,2 was treated with 47% aqueous hydriodic acid and yielded 0.35 g. (81.5%) of 1,2-diphenylacenaphthylene, m.p. 162–163° (lit.[7] m.p. 161.3°). Both 1,2-diphenylacenaphthylene and 1,2-diphenyl-5,6-dihydropyracylene (III) exhibited deep blue colors with concentrated sulfuric acid.

1,2-Diphenylacenaphthylene (0.0064 mole) in absolute ethanol absorbed 0.0067 mole of hydrogen over 10% palladium on charcoal catalyst at one atmosphere pressure and room temperature to give 98% of 1,2-diphenylacenaphthene, m.p. 146–147° which separated as white needles from ethanol-water.

Anal. Calcd. for $C_{24}H_{18}$: C, 94.08; H, 5.92. Found: C, 94.30; H, 5.74.

1,2-Diphenyl-5,6-dihydropyracylene (III), like 1,2-diphenylacenaphthylene, was very stable even at its melting point. A sample at room temperature in air showed no decrease in melting point after 6 weeks and the melting point of a once melted sample showed no decrease.

Bachmann and Chu[7] report the formation of 1,2-diphenyl-1,2-dichloroacenaphthene in good yield by passing anhydrous hydrogen chloride through a dry chloroform solution of 1,2-diphenylacenaphthenediol-1,2 at 0°. Under similar conditions, 1,2-diphenylpyracenediol-1,2 (II) produces a mixture of products. These products did not contain chlorine. The mixture was not characterized further.

2,2-Diphenylpyracenone-1 (IV). The pinacol rearrangement of 1,2-diphenylpyracenediol-1,2 (II) was carried out as described by Bachmann and Chu.[7] One-half g. of II was added in one portion to a solution of iodine (2.5 g.) in 250 ml. of glacial acetic acid. This solution was heated at reflux for 30 min. After cooling, the deep purple solution was poured into aqueous sulfur dioxide and the resulting gray precipitate was collected on a filter, 0.45 g., m.p. 160–175°. This product was crystallized from an ethanol-water mixture with decolorizing charcoal to afford light yellow needles, 0.35 g. (73.5%), m.p. 191–192°. The infrared spectrum exhibited absorptions at 1710 cm.$^{-1}$ and 1682 cm.$^{-1}$ 2,2-Diphenylacenaphthenone-1 exhibited only one absorption at 1715 cm.$^{-1}$ This double absorption for the carbonyl group was common to all pyracene compounds containing a carbonyl group.

Anal. Calcd. for $C_{26}H_{18}O$: C, 90.14; H, 5.24. Found: C, 89.94; H, 5.31.

When the pinacol rearrangement was carried out on II according to Beschke[8] using boiling glacial acetic acid and concentrated hydrochloric acid as catalyst, a black product was formed. Only a low yield of crude IV in addition to some III could be isolated by crystallization from ethanol-water followed by chromatographic separation on alumina.

The rearrangement of 1,2-diphenylacenaphthenediol-1,2 using glacial acetic acid and concentrated hydrochloric acid gave a clean reaction with no decomposition and an 85%

(8) E. Beschke, *Ann.*, **369**, 184 (1909).

yield of 2,2-diphenylacenaphthenone-1, m.p. 172–173° (lit.[7] 171.3–172.4°). Both the acenaphthene and pyracene diphenyl ketones gave an orange color with concentrated sulfuric acid.

1,2-Pyracenediols. A. cis-1,2-Pyracenediol (Va). To a yellow-orange suspension of 1 g. of 1,2-diketopyracene (I) in 150 ml. of ethanol there was added in one portion 0.5 g. of sodium borohydride. This suspension was stirred for 2 hr. at room temperature during which time the orange solid dissolved to form a nearly colorless solution which showed a blue fluorescence. An additional 0.1 g. of sodium borohydride was added and stirring continued for 20 min. The reaction mixture was then decomposed by the drop-wise addition of excess 10% hydrochloric acid followed by 300 ml. of water. The white precipitate which slowly separated was collected on a filter. There was obtained 0.52 g. of crude Va, m.p. 240–250° dec. This product was crystallized from ethanol to form white needles, (40%), m.p. 264–265° dec.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.23; H, 5.70. Found: C, 79.18; H, 5.75.

B. trans-1,2-Pyracenediol (Vb). The filtrate from the above preparation of the *cis* diol was saturated with salt and extracted exhaustively with ether. The ethereal solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure leaving 0.5 g. of crude *trans*-1,2-pyracenediol (Vb), m.p. 130–138° which was crystallized from 400 ml. of water to yield white cubes, (35%), m.p. 188–189°.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.23; H, 5.70. Found: C, 79.19; H, 5.86.

The high melting diol Va (0.2 g.) was suspended in 5 ml. of the acetone–hydrochloric acid solution and anhydrous sodium sulfate (0.1 g.) was added. The white solid slowly dissolved over a period of 14 hr. at room temperature. The solution was filtered and the solvent evaporated. There was obtained 0.2 g. of 1,2-isopropylidenedioxypyracene, m.p. 120–135° dec. Crystallization from petroleum ether (b.p. 40–50°) yielded white needles, m.p. 164–165°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.78; H, 6.55.

The low melting diol Vb (0.2 g.) was subjected to the same reaction conditions as described above but was recovered unchanged.

When acenaphthenequinone was reduced with sodium borohydride as described for 1,2-diketopyracene (I), the reaction was instantaneous and quantitative. A 50–50 mixture of the known *cis* and *trans* acenaphthenediols[9] was obtained although separation proved more difficult.

Pyracenone-1 (VI). A mixture of the *cis* and *trans* 1,2-pyracenediols (Va and Vb) (0.2 g.) was subjected to the conditions of the pinacol rearrangement using glacial acetic acid and iodine.[7] The mixture was poured into aqueous sulfur dioxide. The precipitated gray solid (0.2 g.) melted at 140–165° and then formed a black residue which did not melt above 270°. Approximately one half of this gray product dissolved in hot ethanol. This solution was treated with decolorizing charcoal, filtered, and on cooling very light yellow crystals formed. There was obtained 0.08 g. (40%) of pyracenone-1 (VI), m.p. 180–181° (lit.[5b] m.p. 182–183°). The infrared spectrum showed absorption peaks at 1670 cm.$^{-1}$ and 1715 cm.$^{-1}$ Pyracenone-1 gave an orange-yellow color with concentrated sulfuric acid similar to that obtained with acenaphthenone-1.

A mixture of *cis* and *trans* acenaphthenediols was subjected to the same reaction conditions above but no acenaphthenone-1 was isolable.

BOULDER, COLO.

(9) R. Criegee, L. Kraft, and B. Rank, *Ann.*, **507**, 159 (1933).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, AIN SHAMS UNIVERSITY]

Studies of Quinoid Structures. IV.[1] Action of Grignard Reagents on Anthraquinone Monoanil

W. I. AWAD, A. K. FATEEN, AND M. A. ZAYED

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Grignard reagents add preferentially to the carbonyl group of anthraquinone monoanil under ordinary conditions. The constitution of the products is discussed.

It has been found[1–3] in these laboratories that Grignard reagents add preferentially to the carbonyl group of phenanthrenequinonimine, chrysenequinonimine, phenanthrenequinone monoxime, chrysenequinone monoxime, phenanthrene-quinone and chrysenequinone monosemicarbazones and benzil monosemicarbazone. This study is now extended to *p*-quinoid structures, *e.g.* anthraquinone monoanil (I). Grignard reagents add under normal conditions preferentially to the carbonyl group of I as shown in Scheme A.

The constitution of II is based on: (i) hydrolysis to give a nitrogen free keto compound (III), (ii) infrared spectrum showing the presence of C=N stretching frequency at 1639 cm^{-1}[4,5] and —OH stretching frequency at 3333 cm^{-1},[6] and (iii) elemental analysis. The ketone (III) showed clear carbonyl stretching frequency at 1680 cm^{-1},[7] but it did not show a free —OH stretching fre-

(1) Studies of Quinoid Structures. III. Action of Grignard reagents on phenanthrenequinone monosemicarbazone, chrysenequinone monosemicarbazone and benzil monosemicarbazone. W. I. Awad, A. R. A. Raouf, and Miss A. M. Kamel (*J. Org. Chem.* in press).

(2) W. I. Awad and A. R. A. Raouf, *J. Org. Chem.*, **22**, 881 (1957).

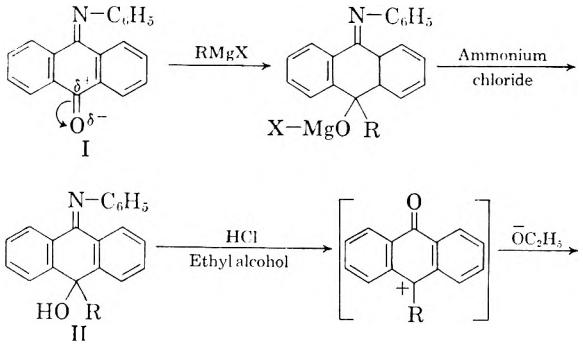
(3) W. I. Awad and A. R. A. Raouf, *J. Org. Chem.*, **23**, 282 (1958).

(4) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Metheun, London, 1957, p. 223.

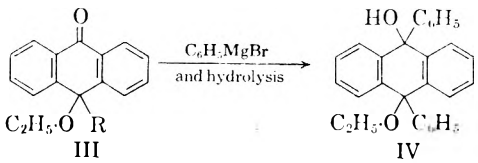
(5) W. I. Awad, *Egypt J. Chem.*, **1**, 87 (1958).

(6) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Metheun, London, 1957, p. 84.

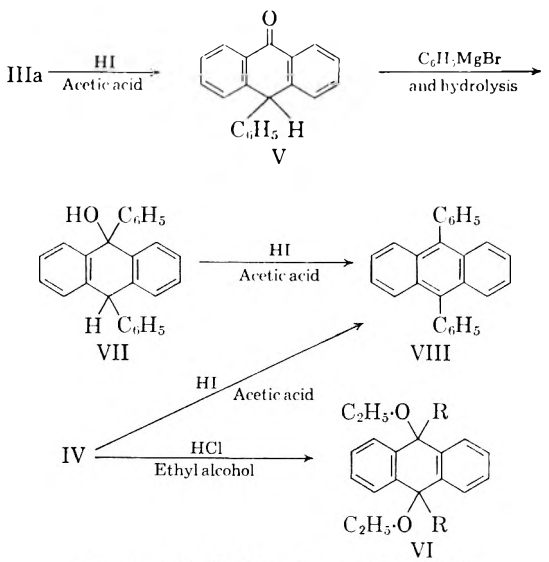
(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Metheun, London, 1957, p. 176.



IIa. R = C_6H_5; IIb. R = p-$CH_3OC_6H_4$; IIc. R = $C_{10}H_7$; IId. R = CH_3; IIe. R = C_2H_5



IIIa. R = C_6H_5; IIIb. R = p-$CH_3OC_6H_4$; IIIc. R = $C_{10}H_7$

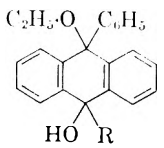


VIa. R = C_6H_5; VIb, R = p-$CH_3OC_6H_4$

Scheme A

quency, and since the hydrolysis has been carried out in a hydrochloric acid–ethyl alcohol mixture, etherification of the free —OH has also taken place. This has been proved by the action of an ethyl alcohol–hydrochloric acid mixture on 9-hydroxy-9-phenyl anthrone (m.p. and mixture m.p. experiment). The melting point of IIIa was similar to that previously described by Liebermann and Lindenbaum.[8] When IIIa was treated with a hydroiodic acid–acetic acid mixture de-ethylation and reduction took place to give 10-phenylanthrone (V), (similar to the same reaction on 10-phenyl-10-methoxyanthrone by Schlenk and Bergmann[9]). Furthermore IIIa was treated by Grignard reagent to give IV which was de-ethylated and reduced with loss of water by the action of a hydriodic acetic acid mixture to give 9,10-diphenylanthracene (VIII). Ethylation of IV gave 9,10-diphenyl-9,10-diethoxyanthracene (VI). The action of a Grignard reagent on V gave VII[9] which was converted to VIII by heating with a hydriodic–acetic acid mixture. It is to be noted that the hydroxyl group in position 10 in II is not stable in acid medium compared with that in 10-hydroxy-10-phenyl-9-(10H)phenanthrone[2] under the same conditions. It seems that the hydroxyl in II is eliminated in the form of a water molecule by the proton of the medium. The carbonium ion formed (which is stabilized by the resonance with the benzene rings) is then attacked by the ethoxyl group of the alcohol to give the more stable ether (III). This was also confirmed by the fact that when IIIa was heated with a hydriodic–acetic acid mixture de-ethylation and reduction to V took place. The same applies to the de-ethylation of IV where it is followed by reduction and removal of water to give VIII.

10-Phenyl-10-ethoxy anthrone (IIIa) was allowed to react with anisyl- and α-naphthylmagnesium bromide to yield 9-hydroxy-9-anisyl-10-phenyl-10-ethoxy-9,10-dihydro-anthracene (IXa) and 9-hydroxy-9-naphthyl-10-phenyl-10-ethoxy-9,-10-dihydro-anthracene (IXb), respectively.



IXa. R = p-$CH_3OC_6H_4$; IXb. R = $C_{10}H_7$

EXPERIMENTAL

Melting points are not corrected. Microanalyses were carried out by Alfred Bernhardt, im Max-Plank Institut, Mulheim (Ruhr) Germany. Infrared measurements were made on a Perkin-Elmer infracord Model 137 in nujol mulls or carbon tetrachloride solution.

(a) *Action of phenylmagnesium bromide on anthraquinone monoanil.*[10] A solution of anthraquinone anil (16.8 g.) in a hot mixture of dry benzene and dry ether (150 ml.) was added to an ethereal solution of phenylmagnesium bromide (from bromobenzene, 10.8 g., and magnesium, 1.44 g.) and the reaction mixture was heated at reflux for 2 hr. and left overnight. The product was hydrolyzed with a saturated solution of ammonium chloride, and the ether-benzene layer was separated, dried over anhydrous sodium sulfate, filtered and the solvent distilled. IIa was crystallized from petroleum ether (60–80°) to give 14.2 g. of yellow crystals, m.p. 158°.

Anal. Calcd. for $C_{26}H_{19}ON$: C, 86.42; H, 5.26; N, 3.87. Found: C, 86.18; H, 5.67; N, 3.51.

(b) *Hydrolysis of* IIa. IIa (2 g.) was heated at reflux for 2 hr. with a mixture of ethyl alcohol (25 ml.), and hydrochloric acid (25 ml.). On cooling, IIIa was filtered and crystallized from petroleum ether (60–80°) to give 1.4 g. of

(8) C. Liebermann and S. Lindenbaum, *Ber.*, **38**, 799 (1905).

(9) von W. Schlenk and E. Bergmann, *Ann.* **463**, 98, 161, 174, 181 (1928).

(10) L. Sander, *Ber.*, **58**, 824 (1925).

yellow crystals, m.p. 157°. It was insoluble in sodium hydroxide solution.

Anal. Calcd. for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 83.99; H, 5.46.

10-Phenyl-10-ethoxyanthrone was also prepared by the action of an ethyl alcohol–hydrochloric acid mixture on 10-phenyl-10-hydroxyanthrone[11] and mixture melting point gave no depression.

Preparation of 9,10-diphenyl-9-hydroxy-10-ethoxy-9,10-dihydroanthracene (IV). A solution of 10-phenyl-10-ethoxyanthrone (2.86 g.) in a mixture of dry benzene and dry ether (50 ml.) was added to an ethereal solution of phenylmagnesium bromide (from bromobenzene, 1.57 g., and magnesium, 0.24 g.) and the reaction mixture was treated as in (a). The product was crystallized from methyl alcohol to give 1.9 g. of colorless crystals, m.p. 224°. It gave an indigo color with concentrated sulfuric acid.

Anal. Calcd. for $C_{28}H_{24}O_2$: C, 85.68; H, 6.16. Found: C, 85.48; H, 5.92.

Action of a hydrochloric acid–ethyl alcohol mixture on IV. 9,10-Diphenyl-9-hydroxy-10-ethoxy-9,10-dihydroanthracene (2 g.) was treated as in (b). VI was crystallized from benzene to give 1.6 g. of pale yellow crystals, m.p. 275°.

Anal. Calcd. for $C_{30}H_{28}O_2$: C, 85.68; H, 6.71. Found: C, 85.39; H, 6.59.

(c) *Action of a hydriodic acetic acid mixture on 10-phenyl-10-ethoxy anthrone* (III). Hydriodic acid (5 ml.) was added to a hot solution of III (1 g.) in acetic acid (3 ml.) and the reaction mixture was refluxed for 2 hr. The product was poured on cold water, and extracted with ether. The ethereal layer was washed with sodium bisulfite solution, then with sodium bicarbonate solution and water, then dried over anhydrous sodium sulfate. The ether was filtered and distilled, leaving a sticky product. It was triturated with petroleum ether (60–80°), then crystallized from petroleum ether (60–80°) to give 0.7 g. of V as yellow crystals, m.p. 146°.

Anal. Calcd. for $C_{20}H_{14}O$: C, 88.88; H, 5.18. Found: C, 89.08; H, 5.22.

Action of a hydriodic-acetic acid mixture on 9,10-diphenyl-9-hydroxy-10-ethoxy-9,10-dihydro-anthracene. Hydriodic acid (1.7 sp. g.) (3 ml.) was added to a hot solution of 9,10-diphenyl-9-hydroxy-10-ethoxy-9,10-dihydro-anthracene (0.4 g.) in acetic acid (2 ml.) and the reaction mixture was treated as in (c). The product was crystallized from petroleum ether (60–80°) to give 0.25 g. of canary yellow crystals, m.p. 245–246° undepressed on admixture with an authentic sample of 9,10-diphenylanthracene.[12]

Anal. Calcd. for $C_{26}H_{18}$: C, 94.54; H, 5.45. Found: C, 94.37; H, 5.46.

Action of a hydriodic-acetic acid mixture on VII. Hydriodic acid (1.7 sp. g.) (2 ml.) was added to a hot solution of VII (0.2 g.) in acetic acid (2 ml.) and the reaction mixture was refluxed for 2 hr. The sticky product was triturated with petroleum ether (60–80°), then crystallized from acetic acid to give 0.1 g. of VIII as light yellow crystals, m.p. 245–246°, undepressed on admixture with an authentic specimen.

Action of anisylmagnesium bromide on I. A solution of anthraquinone anil (11.2 g.) in a hot mixture of dry benzene and dry ether (150 ml.) was added to an ethereal solution of anisylmagnesium bromide (from *p*-bromoanisole, 7.2 g., and magnesium, 0.96 g.) and the reaction mixture was completed as in (a). IIb was crystallized from petroleum ether (60–80°) to give 10.5 g. of yellow crystals, m.p. 147°.

Anal. Calcd. for $C_{27}H_{21}NO_2$: C, 82.86; H, 5.37; N, 3.58. Found: C, 83.01; H, 5.41; N, 3.52.

Hydrolysis of IIb. IIb (3.2 g.) was treated as in (b). IIIb was crystallized from petroleum ether (60–80°) to give 2 g. of yellow crystalline product, m.p. 181°.

Anal. Calcd. for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 80.18; H, 5.72.

Preparation of 9,10-dianisyl-9,10-diethoxy-9,10-dihydroanthracene. A solution of 10-anisyl-10-ethoxyanthrone (1.14 g.) in a mixture of dry benzene and dry ether (50 ml.) was added to an ethereal solution of anisylmagnesium bromide (from *p*-bromoanisole, 0.63 g., and magnesium, 0.08 g.) and the reaction mixture was treated as in (a). The product was crystallized from methyl alcohol to give 0.8 g. of colorless crystals, m.p. 210°. This product (0.7 g.) was heated under reflux for 2 hr. with a mixture of ethyl alcohol (20 ml.) and hydrochloric acid (7 ml.). On cooling, VIb was filtered and crystallized from petroleum ether (80–100°) to give 0.7 g. as colorless crystals, m.p. 276°.

Anal. Calcd. for $C_{32}H_{32}O_4$: C, 79.97; H, 6.71. Found: C, 79.80; H, 6.68.

Action of naphthylmagnesium bromide on I. A solution of anthraquinone anil (14.1 g.) in a hot mixture of dry benzene and dry ether (150 ml.) was added to an ethereal solution of naphthylmagnesium bromide (α-bromonaphthalene, 10.35 g., and magnesium, 1.21 g.) and the reaction mixture was treated as in (a). IIc was crystallized from petroleum ether (40–60°) to give 16.2 g. of yellow crystals, m.p. 161–162°.

Anal. Calcd. for $C_{30}H_{21}NO$: C, 87.56; H, 5.14; N, 3.4. Found: C, 87.47; H, 5.37; N, 3.60.

Hydrolysis of IIc. IIc (1.6 g.) was treated as in (b). The product was crystallized from petroleum ether (60–80°) to give 1.3 g. of IIIc as colorless crystals, m.p. 256°.

Anal. Calcd. for $C_{26}H_{20}O_2$: C, 85.69; H, 5.53. Found: C, 86.01; H, 5.36.

Action of methylmagnesium iodide on I. A solution of anthraquinone anil (9.43 g.) in hot mixture of dry benzene and dry ether (150 ml.) was added to an ethereal solution of methylmagnesium iodide (from methyl iodide, 4.73 g., and magnesium, 0.81 g.) and the reaction was completed as in (a). IId was crystallized from petroleum ether (60–80°) to give 5.4 g. of yellow crystals, m.p. 224°.

Anal. Calcd. for $C_{21}H_{17}ON$: C, 84.25; H, 5.72; N, 4.68. Found: C, 83.75; H, 5.61; N, 4.72.

Action of ethylmagnesium bromide on I. A solution of anthraquinone anil (7.1 g.) in a hot mixture of dry benzene and dry ether (100 ml.) was added to an ethereal solution of ethylmagnesium bromide (ethyl bromide, 2.72 g., and magnesium, 0.6 g.) and the reaction mixture was treated as in (a). IIe was crystallized from petroleum ether (60–80°) to give 4.3 g. of yellow crystals, m.p. 176°.

Anal. Calcd. for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.38; H, 5.94; N, 4.59.

Action of anisylmagnesium bromide on III. A solution of III (2.1 g.) in a mixture of dry benzene and dry ether (50 ml.) was added to an ethereal solution of anisylmagnesium bromide (from *p*-bromoanisole, 1.24 g., and magnesium, 0.16 g.) and the reaction mixture was treated as in (a). IXa was crystallized from ethyl alcohol to give 0.6 g. of colorless crystals, m.p. 186°.

Anal. Calcd. for $C_{29}H_{26}O_3$: C, 82.46; H, 6.16. Found: C, 82.38; H, 6.36.

Action of naphthylmagnesium bromide on III. A solution of III (3.14 g.) in a mixture of dry ether and dry benzene (100 ml.) was added to an ethereal solution of naphthylmagnesium bromide (from α-bromonaphthalene, 2.07 g., and magnesium, 0.24 g.) and the reaction mixture was treated as in (a). IXb was crystallized from a mixture of petroleum ether (40–60°) and benzene to give 1.2 g. of colorless crystals, m.p. 265°.

Anal. Calcd. for $C_{32}H_{26}O_2$: C, 86.87; H, 5.88. Found: C, 86.74; H, 5.93.

ABBASSIA-CAIRO
EGYPT-U.A.R.

(11) A. Haller and A. Guyot, *Compt. rend.*, 138, 1251 (1904).

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

[COMMUNICATION NO. 1998, FROM THE KODAK RESEARCH LABORATORIES]

Structure of Certain Polyazaindenes. V. Syntheses.

C. F. H. ALLEN, G. A. REYNOLDS, J. F. TINKER, AND L. A. WILLIAMS[1a]

Received December 8, 1959

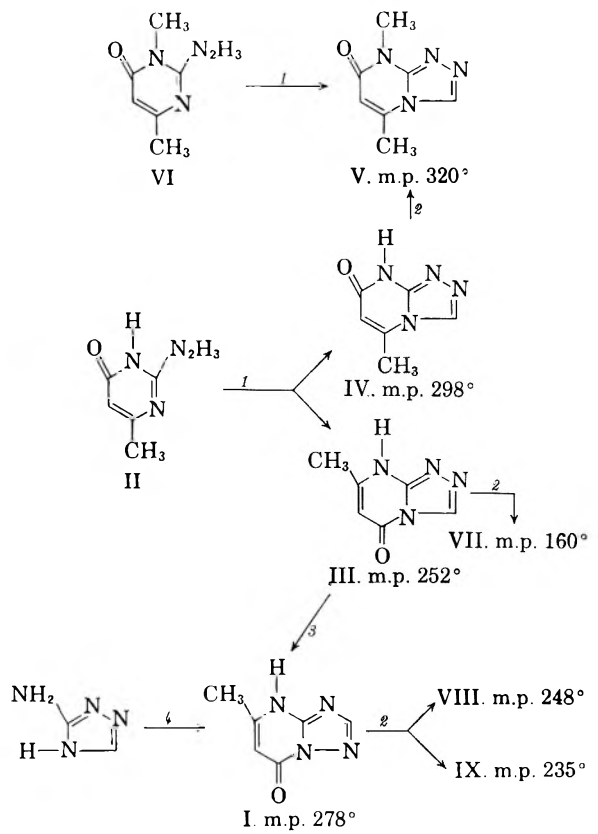
Syntheses of 6-methyl-4-oxo-1,3,3a,7-tetrazaindene, 4-methyl-6-oxo-1,2,3a,7-tetrazaindene, the methylation product of the latter, and a number of related substances are described. This chemical evidence furnishes independent corroboration of the structures deduced by other methods.

The reaction product of ethyl acetoacetate with 3-amino-1,2,4-triazole has previously been shown to be 6-methyl-4-oxo-1,3,3a,7-tetrazaindene[1b] on the basis of spectral evidence.[1b,2]

In view of the diversity of opinion which exists in this field,[3-7] it was deemed desirable to confirm this conclusion by a proof of structure of I based on chemical evidence. With this end in view, 2 - hydrazino - 4 - hydroxy - 6 - methylpyrimidine (II) was treated with ethyl orthoformate; both possible products, 6-methyl-4-oxo-1,2,3a,7-tetrazaindene (III) and 4-methyl-6-oxo-1,2,3a,7-tetrazaindene (IV), were formed. Methylation of IV gave 4,7 - dimethyl - 6 - oxo - 1,2,3a,7 - tetrazaindene (V), as proved by its identity with the substance obtained by the same cyclization of 1,4-dimethyl-2-hydrazino-6-pyrimidone (VI). The latter resulted from the action of hydrazine upon 1,4-dimethyl-2-methyl - 2 - methylmercapto - 6 - pyrimidone, a substance of known structure.[8] These reactions established the structures of IV and V. The second and only other product formed in the reaction must be III, which results from the alternate mode of cyclization. Methylation of III gives *x*,6-dimethyl-4-oxo-1,2,3a,7-tetrazaindene (VII), a substance quite different from the product obtained by ring closure of VI, indicating that III is not related to the 6-one series. It has been previously shown that III is rearranged to I by acid, a reaction which can readily be accounted for.[2]

Further evidence for these formulations was forthcoming from the synthesis and identification

CHART I



Reagents: *1*, ethyl orthoformate; *2*, methyl sulfate and alkali; *3*, hot formic acid; *4*, ethyl acetoacetate.

of three of the isomeric methylmercapto compounds. Treatment of the hydrazine II with carbon disulfide produced both possible products, 4-methyl-6-oxo-1,2,3a,7-tetrazaindene-3-thiol (X) and 6-methyl-4-oxo-1,2,3a,7-tetrazaindene-3-thiol (XI). The conversion of X to IV by oxidation with dilute nitric acid confirms the structure of X as a 6-one. Therefore, XI must be the 4-one, as indicated. Dethiolation of XI yields the expected 4-one III. Stepwise methylation of X gave the 4-methyl-3-methylmercapto-6-oxo-1,2,3a,7-tetrazaindene (XII) and 4,7-dimethyl-3-methylmercapto-6-oxo-1,2,3a,-7-tetrazaindene (XIII), respectively. This latter substance is also obtained by ring closure of VI with phenyl isothiocyanate to give 4,7-dimethyl-6-oxo-1,2,3a,7-tetrazaindene-3-thiol (XIV), followed by methylation. This sequence of reactions

(1a) At the Research Laboratories, Kodak Limited, Harrow, England.

(1b) Part I, C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. VanAllan, *J. Org. Chem.*, **24**, 779 (1959).

(2) Part II, C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. VanAllan, *J. Org. Chem.*, **24**, 787 (1959).

(3) E. J. Birr, *Z. wiss. Phot.*, **47**, 2927 (1952).

(4) E. J. Birr and W. Walther, *Ber.*, **86**, 1401 (1953).

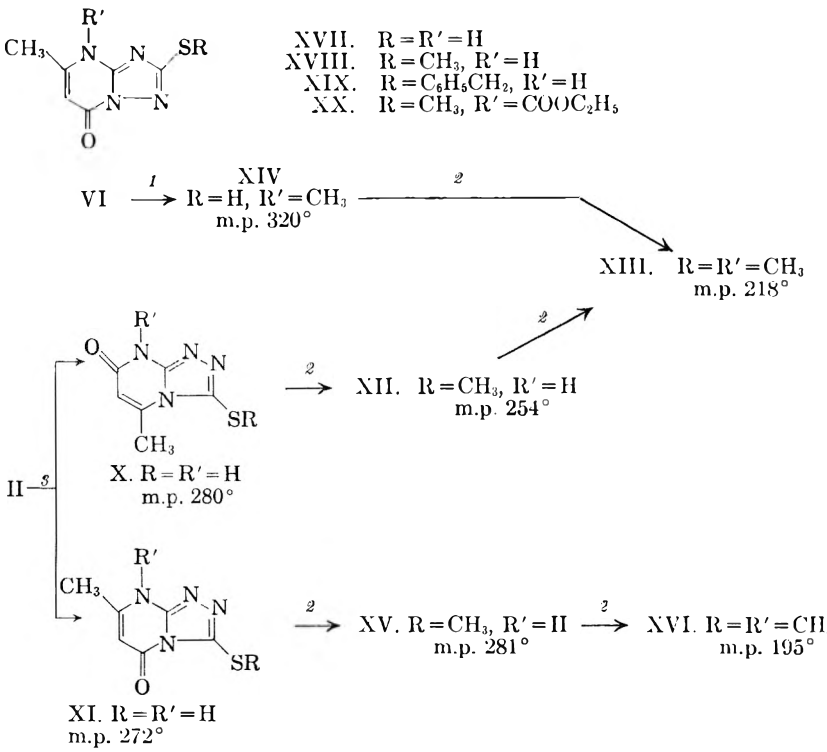
(5) J. D. Bower and F. P. Doyle, *J. Chem. Soc.*, 727 (1957).

(6) D. J. Fry and B. Whitear, Résumés des Communications. Tome II. Division de Chimie Organique. XVIe Congrès International de Chimie Pure and Appliquée, Paris, July 1957, p. 166.

(7) D. J. Fry, U. S. Patent **2,566,629** 1951. [*Chem. Abstr.*, **46**, 1380 (1952)].

(8) H. L. Wheeler and D. F. McFarland, *Am. Chem. J.*, **42**, 106 (1909).

CHART II



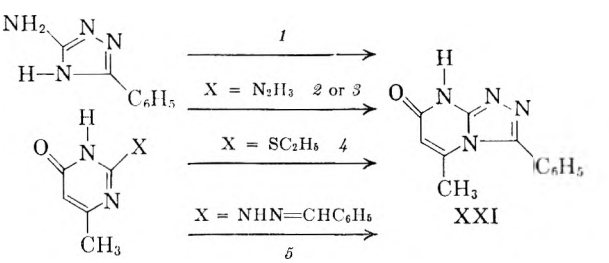
Reagents: *1*, phenyl isothiocyanate; *2*, methyl sulfate and alkali; *3*, carbon disulfide and pyridine.

establishes the structures of XI and XIII and confirms the structure of X. In a similar manner, methylation of XI gives 6-methyl-3-methylmercapto-4-oxo-1,2,3a,7-tetrazaindene (XV) and 6,7-dimethyl-3-methylmercapto-4-oxo-1,2,3a,7-tetrazaindene (XVI). The third isomer, 6-methyl-2-methylmercapto-4-oxo-1,3,3a,7-tetrazaindene (XVIII), is described in the literature.[7] Each of the derivatives, X, XI, and XVIII, has been dethiolated to the corresponding tetrazaindene. The preparation and dethiolation of the benzyl ether XIX is described in the experimental section. The dethiolation of XVIII proceeded more smoothly when the acidic hydrogen was acylated, yielding XX; the loss of the carbethoxyl group, owing to the alkali present in the catalyst preparation, was slower than the removal of the sulfur atom. The reported[7] preparation of XVII from amino mercaptotriazole could not be duplicated.

It is quite surprising to find that the five reactions outlined in chart III all lead to 4-methyl-3-phenyl-6-oxo-1,2,3a,7-tetrazaindene (XXI), since different products have been claimed previously.[5] The identity of these products was established by comparison of their infrared and ultraviolet absorption spectra. The structure of XXI is based solely on the similarity of its ultraviolet absorption spectrum to that of other known 6-ones.[1]

Change of the aminotriazole substituent from hydrogen, methyl, or methylmercapto to phenyl has altered the course of the reaction so that the product changes from a 4-oxo-1,3,3a,7-tetrazaindene to a 6-oxo-1,2,3a,7-tetrazaindene. Evidently the phenyl substituent has reduced the basicity of the two nitrogen atoms conjugated with it (N^2 and N^α), so that amide formation is faster than aminocrotonate formation. The resulting amide lacks the charge distribution of the aminocrotonate, since the acylated N^α is not basic. Subsequent reaction is that of the most basic nitrogen, N^4, in Michael addition to the enolic form of the ketoamide (compare ref. 2). It is surprising that the four alternate reactions shown in Chart III failed to yield any trace of compounds representing ring closure into position 3 of the pyrimidine ring. Like other 6-ones, XXI is stable to acid, so that but one aryl compound is available.

CHART III

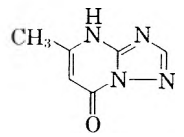


Reagents: *1*, ethyl acetoacetate; *2*, phenyl benzoate; *3*, ethyl orthobenzoate; *4*, benzhydrazide; *5*, lead tetraacetate.

The ultraviolet absorption data for the 6-methyl-4-oxo-1,3,3a,7-tetrazaindenes are collected in Table I. All show the same type of absorption. In particular, the ratio of absorption coefficients of band c

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF 6-METHYL-4-OXO-1,2,3A,7-TETRAZAINDENES

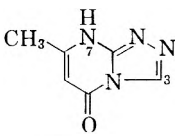


Substituent	M.P.	λ_a	λ_b	λ_c	λ_c/λ_b[f]
I None[a,b]	278	[e]	256 (6.4)[c]	278 (10.8)	1.7
VIII x-CH_3[d]	248	[e]	245 (4.8)	275 (11.5)	2.4
IX x-CH_3[d]	235	[e]	246 (7.9)	282 (18.4)	2.3
XVIII 2-SCH_3	284–286	229 (24.7)	267 (10.2)		0.41[g]
XX 7-$CO_2C_2H_5$	183	[e]	248 (4.5)	278 (9.3)	2.0
XXII 5-CH_3[b]	305	[e]	248 (4.3)	289 (10.5)	2.4
XXXII 2-CH_3[b]	310	210 (23.5)	238 (2.8)	272 (9.5)	3.4
XXXIII 2-SCH_3-7-CH_3	160–170	231 (22.0)	270 (9.8)		0.45[g]
XXXV 2-SCH_3-7-$CO_2C_2H_5$	191	228 (25.0)	259 (9.4)	273 (9.0)	

[a] In neutral solution this compound shows a single peak 272 (9.9); a trace of base yields the spectrum shown. [b] The syntheses of these substances have been reported in previous papers.[1,2,10] [c] All ϵ values are to be multiplied by 10^3; solvent is methanol; wave lengths in mμ. [d] VIII and IX are the products obtained by methylation of I. [e] Curves not run to shorter wave lengths. [f] Ratio of ϵ values. [g] Ratio ϵ of band b to band a.

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF 6-METHYL-4-OXO-1,2,3A,7-TETRAZAINDENES



Substituent	M.P.	λ_a	λ_b	λ_c	λ_c/λ_b[b]
III None	252	210 (17.7)	246 (4.8)	294 (6.8)	1.4
VII x-CH_3[a]	160		245 (5.0)	303 (12.7)	2.54
XI 3-SH	270–272	245 (12.0)	284 (8.3)	325 (7.5)	0.90
XV 3-SCH_3	281–282	231 (14.2)	260 (7.0)	309 (7.1)	1.0
XVI 3-SCH_3-7-CH_3	195	235 (8.0)	263 (9.0)	314 (10.4)	1.1

[a] Obtained by methylation of III. [b] Ratio of ϵ values.

to band b varies between 1.5 to 3.4, in line with previous observations of the spectra of related 4-one type compounds.[1] It is interesting to note that I gives two monomethylation products, VIII and IX, which differ greatly in solubility, and considerably in melting point and ultraviolet spectra; yet the absorption properties fall within the limits deduced as proper for this structure.[1] Negative Zeisel determinations indicated lack of *O*-methylation,[9] and the C-methyl product, 5,6-dimethyl-4-oxo-1,3,3a,7-tetrazaindene (XXII),[3] also differed from both VIII and IX.

Table II shows that the 4-oxo-1,2,3a,7-tetrazaindenes as a class absorb at longer wave lengths than the 4-oxo-1,3,3a,7-tetrazaindene series and have a somewhat lower λc/λb ratio. The general shape of the curves, however, is similar to those in Table I.

A pronounced change occurs in the character of the ultraviolet absorption spectra of the 6-oxo-1,2,3a,7-tetrazaindenes, compared to those of the 4-oxo compounds, as is evidenced by the data in Table III. This series is characterized by a single, high-intensity band, with inflections occurring at about 250 and 300 mμ. Only in the case of IV and X are these inflections developed into real bands.

It may be well to emphasize again the need for obtaining *all* physical data in comparing and determining identity of these polyazaindenes. For instance, melting points and mixed melting points by themselves are inadequate and may even be misleading. The infrared *and* ultraviolet absorption spectra are of inestimable value. The numerous erroneous conclusions in the literature are undoubtedly drawn from insufficient data.

EXPERIMENTAL

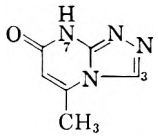
4-Methyl-6-oxo-1,2,3a,7-tetrazaindene (IV). *By oxidation of X.* Two g. of X was added to dilute nitric acid (10 ml. of nitric acid (d = 1.42) made up to 25 ml. with water). A vigorous reaction ensued, with the evolution of oxides of nitrogen. The clear, yellow solution was poured into water,

(9) The *O*-methyl compound could not be obtained from 4-chloro-6-methyl-1,3,3a,7-tetrazaindene[2] and sodium methoxide in carefully dried methanol, only I being obtained.

(10) Part III, C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. VanAllan, *J. Org. Chem.*, **24**, 793 (1959).

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA OF 4-METHYL-6-OXO-1,2,3A,7-TETRAZAINDENES



Substituent	M.P.	λ_a	λ_b	λ_c	λ_c/λ_b
IV None	298	210 (22.7)	248 (7.0)		
X 3-SH	280	229 (10.7)	258 (12.8)	315 (3.7)	0.29
XII 3-SCH_3	254	229 (22.4)		~300 (1.2)[a]	
XIII 3-SCH_3-7-CH_3	218	229 (19.4)		~300 (1.5)[a]	
XXI 3-C_6H_5	>330	242 (26.7)	~264 (18.4)[a]		
XXXIV x-CH_3-3-C_6H_5[b]	315–320	234 (14.5)		~282 (4.8)[a]	

[a] ~ denotes shoulder. [b] Obtained by methylation of XXI.

made alkaline with sodium bicarbonate, and the solid collected; this gave 1.2 g. of IV, m.p. 298°, after crystallization from butanol.

Anal. Calcd. for $C_6H_6N_4O$: C, 48.0; H, 4.0. Found: C, 48.0; H, 4.2.

Its identity with the product obtained by the ring closure of II with ethyl orthoformate was confirmed by infrared and ultraviolet spectral analysis.

4,7-Dimethyl-6-oxo-1,2,3a,7-tetrazaindene (V). (a) *By methylation of* IV. A mixture of 0.6 g. of IV, 10 ml. of water, 0.2 g. of sodium hydroxide, and 0.3 ml. of dimethyl sulfate was allowed to stand for 2 days. The product precipitated and was crystallized from water, giving 0.5 g. of V, m.p. 320°.

(b) *By ring closure of* VI. A solution of 0.6 g. of VI in 5 ml. of formic acid was refluxed for 2 hr. The formic acid was evaporated and the residue crystallized from water to give V, m.p. 320°.

Anal. Calcd. for $C_7H_8N_4O$: C, 51.2; H, 4.9; N, 34.0. Found: C, 51.2; H, 5.0; N, 34.1.

(c) A solution of 1.2 g. of VI in 10 ml. of ethyl orthoformate was refluxed for 3 hr., after which the solution was evaporated to dryness and the residue twice recrystallized from water to give colorless crystals, m.p. 320°.

Anal. Calcd. for $C_7H_8N_4O$: C, 51.2; H, 4.9; N, 34.0. Found: C, 51.4; H, 4.9; N, 33.5.

x,6-Dimethyl-4-oxo-1,2,3a,7-tetrazaindene (VII). A mixture of 4.0 g. of III, 35 ml. of water, and 1.75 g. of sodium hydroxide was treated with 3.4 g. (2.5 ml.) of dimethyl sulfate and allowed to stand 4 days in an open beaker. The precipitate was filtered off and crystallized from ligroin (b.p. 90–100°) to give VII, long needles, m.p. 160°. The yield was 2.1 g.

Anal. Calcd. for $C_7H_8N_4O$: C, 51.2; H, 4.9; N, 34.0. Found: C, 51.4; H, 5.0; N, 33.8.

2-Hydrazino-1,4-dimethyl-6-pyrimidone (VI).[11] A solution of 12 g. of 1,4-dimethyl-2-methylmercapto-6-pyrimidone[8] and an excess of 95% hydrazine (6 ml.) in 90 ml. of butanol was refluxed for 5 hr. The mixture was chilled overnight and filtered. The crude product (7.7 g.), m.p. 196–198.5°, after one crystallization from alcohol, gave pure VI, m.p. 198°.

Anal. Calcd. for $C_6H_{10}N_4O$: N, 36.3. Found: N, 36.5.

Isomeric x,6-dimethyl-4-oxo-1,3,3a,7-tetrazaindenes (VIII) and (IX). To 15 g. of the sodium salt of I in 25 ml. of water was added 12.9 g. (10 ml.) of dimethyl sulfate; the solution became quite hot. After the latter had stood for 1 week, about 4.0 g. was collected by filtration, m.p. 237–240°; it was recrystallized from dimethylformamide and gave VIII, plates, m.p. 246–248°. The original filtrate was treated with sodium carbonate and evaporated to dryness. The residue was extracted with hot dimethylformamide and filtered. On cooling, the white crystals which separated were collected and crystallized from butanol to give IX (1.5 g.), m.p. 234–235°. This isomer is very soluble in water and soluble in alcohol.

Anal. Calcd. for $C_7H_8N_4O$: C, 51.2; H, 4.9; N, 34.0. Found: (VIII), C, 51.2; H, 4.9; N, 34.1; (IX), C, 51.2; H, 5.2; N, 34.2.

6-Methyl-2-methylmercapto-4-oxo-1,3,3a,7-tetrazaindene (XVIII). A mixture of 100 g. (0.67 mole) of 2-amino-5-methylmercapto-1,2,4-triazole, 160 g. (1.2 moles) of ethyl acetoacetate, and 500 ml. of acetic acid was refluxed for 5 hr. and allowed to stand overnight. The solid was collected and recrystallized from water to yield 104 g. of product, melting at 285–286°.

4-Methyl-6-oxo-1,2,3a,7-tetrazaindene-3-thiol (X) and *6-methyl-4-oxo-1,2,3a,7-tetrazaindene-3-thiol* (XI) from II. The reaction was carried out using sodium hydroxide, or trimethylamine, or sodium hydroxide and pyridine with essentially the same results.

To a solution of 28 g. of II in 80 ml. of water and 8 g. of sodium hydroxide was added 140 ml. of pyridine, followed by 15.2 g. (12 ml.) of carbon bisulfide. The mixture was stirred for 15 min. and then heated on the steam bath for 1.5 hr. The solution was evaporated to dryness *in vacuo*, the residue dissolved in water, the solution acidified with hydrochloric acid, and the solid collected. The solid was extracted with 2 l. of water, filtered hot, and the filtrate cooled. The insoluble material (11.5 g.) was X, m.p. 277–279°, which can be recrystallized from a very large amount of water (m.p. 280°). The solid that separated from the filtrate on cooling was XI, which, after another recrystallization from water, melted at 270–272°. The filtrates were concentrated and cooled to yield more XI (total yield, 7.8 g.).

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.5; H, 3.3; N, 30.8. Found: (XI) C, 39.4; H, 3.6; N, 30.8; (X) C, 39.2; H, 3.4; N, 31.0.

6-Methyl-3-methylmercapto-4-oxo-1,2,3a,7-tetrazaindene (XV). To a solution of 7.8 g. of XI in 200 ml. of water and 2.8 g. of sodium hydroxide, was added 5.4 g. of dimethyl sulfate, with stirring. After it had been stirred 0.5 hr., the solution was acidified with concentrated hydrochloric acid, cooled in the refrigerator, and the solid collected and recrystallized from water to yield 7.5 g. of XV, m.p. 280–281°.

Anal. Calcd. for $C_7H_8N_4OS$ C, 42.8; H, 4.1; N, 28.6. Found C, 43.1; H, 4.0; N, 28.5.

4-Methyl-3-methylmercapto-6-oxo-1,2,3a,7-tetrazaindene (XII). To a solution of 7 g. of X in 50 ml. of water and 1.6 g. of sodium hydroxide was added 3.6 ml. of dimethyl sulfate. After it had been stirred 15 min., the solution was acidified with concentrated hydrochloric acid and the solid collected (m.p. 233–265°). The solid was extracted with 200 ml. of boiling water. The insoluble material and the material that separated from the filtrate were the starting material. The filtrates from the reaction mixture and the recrystalli-

(11) We are indebted to Miss J. Fournier, for the preparation of the substances VI and VIII.

zation were combined, concentrated to a small volume, and cooled. The solid that separated was recrystallized from a little water and then ethanol to yield 2 g. of XII, m.p. 254°.

Anal. Calcd. for $C_7H_8N_4OS$: C, 42.8; H, 4.1; N, 28.6. Found: C, 42.8; H, 4.1; N, 28.7.

4,7-Dimethyl-6-oxo-1,2,3a,7-tetrazaindene-3-thiol (XIV). A mixture of 3.1 g. (0.033 mole) of VI and 3.0 g. (1.82 ml.) of phenyl isothiocyanate in 50 ml. of methanol was refluxed for 1 hr. The precipitated product was collected by filtration to give 3.0 g. of XIV, m.p. 318–320°, which was cystallized from ethoxyethanol to give pure XIV, m.p. 320°.

Anal. Calcd. for $C_7H_8N_4OS$: C, 42.8; H, 4.1; N, 28.6. Found: C, 42.7; H, 4.0; N, 28.8.

4,7-Dimethyl-3-methylmercapto-6-oxo-1,2,3a,7-tetrazaindene (XIII). (a) *From* XIV. A mixture of 1.7 g. of XIV, 15 ml. of water, and 2 ml. of 50% sodium hydroxide solution was treated, dropwise, with 1.5 ml. of dimethyl sulfate. The reaction mixture solidified on shaking, and after it had stood for 2 hr., the product was filtered off and crystallized from ethanol to give 1.1 g. of fine, hairlike crystals, m.p. 218°.

Anal. Calcd. for $C_8H_{10}N_4OS$: C, 45.7; H, 4.8. Found: C, 45.6; H, 4.7.

(b) *From* XII. To a solution of 5.5 g. of XII and 1.5 g. of sodium hydroxide in 50 ml. of water was added 3 ml. of dimethyl sulfate, in portions, along with sufficient sodium hydroxide to keep the solution strongly basic. After the solution has been stirred for 0.5 hr., it was acidified, cooled in the refrigerator, and the solid collected and recrystallized from ethanol to yield 2.2 g. of XIII, m.p. 218–218.5°.

Anal. Calcd. for $C_8H_{10}N_4OS$: C, 45.7; H. 4.8; N, 26.6. Found: C, 45.8; H, 4.9; N, 26.6.

6,7-Dimethyl-3-methylmercapto-4-oxo-1,2,3a,7-tetrazaindene (XVI). To a solution of 4 g. of XV and 1 g. of sodium hydroxide in 100 ml. of water was added 2 ml. of dimethyl sulfate. After it had been stirred for 1 hr., the solid was collected and washed with water. Recrystallization from ethanol gave 2 g. of XVI, m.p. 195–196°.

Anal. Calcd. for $C_8H_{10}N_4OS$: C, 45.7; H, 4.8; N, 26.6. Found: C, 45.6; H, 5.1; N, 26.8.

4-Methyl-3-phenyl-6-oxo-1,2,3a,7-tetrazaindene (XXI). This substance was obtained by five different procedures. The identity of the products was shown by comparison of absorption curves. All but one were analyzed; the product from Method D gave the following results:

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.6; H, 4.4; N, 24.8. Found: C, 63.7; H, 4.4; N, 24.9.

Method A. A mixture of 5 g. of 2-hydrazino-4-hydroxy-6-methylpyrimidine and 25 g. of phenyl benzoate was refluxed for 3 hr. The mixture was steam distilled, the solid residue collected, washed with ethanol, and recrystallized from aqueous dimethylformamide three times, to yield 2.6 g. of XXI, m.p. >330°.

Method B. A mixture of 2.2 g. of 3-amino-5-phenyl-1,2,4-triazole, 2 ml. of ethyl acetoacetate, and 10 ml. of acetic acid was refluxed 3 hr., cooled, and the solid collected. Recrystallization from ethoxyethanol gave 2.5 g. of XXI, m.p. >325°.

Method C. A mixture of 7 g. of 2-hydrazino-4-hydroxy-6-methylpyrimidine and 100 ml. of ethyl orthobenzoate was heated at 190–200° for 12 hr., during which time 8.5 ml. of ethanol was collected (theoretical = 8 ml.). The dark solution was cooled and the solid collected and recrystallized from ethoxyethanol to yield XXI. Attempts to work up the reaction mixture in order to obtain another isomer were unsuccessful.

Method D. A mixture of 4.6 g. of 2-benzalhydrazino-6-methyl-4-pyrimidone and 9 g. of lead tetraacetate in 150 ml. of acetic acid was refluxed for 1 hr., and the solution concentrated and diluted with water. The solid was collected and recrystallized from methanol to yield 3.5 g. of XXI, m.p. >325°.

Method E. (a) *2-β-Benzhydrazido-4-hydroxy-6-methylpyrimidine.* A mixture of 34 g. of 2-ethylmercapto-4-hydroxypyrimidine, 27 g. of benzhydrazide, and 500 ml. of ethanol was refluxed 24 hr., concentrated to about 100 ml., cooled, and filtered. The white solid, sintered at about 122°, resolidified and remelted at 270–271°.

(b) *4-Methyl-3-phenyl-6-oxo-1,2,3a,7-tetrazaindene* (XXI). Ten g. of the hydrazide and 25 g. of phenol were heated on a steam cone for 1.5 hr., then refluxed for 4 hr. The phenol was steam distilled; the solid residue was digested with 800 ml. of water and recrystallized from dimethylformamide. One and seven-tenths g. of XXI was obtained.

Raney nickel dethiolation of the methylmercapto derivative. A mixture of 2 g. of the methylmercapto tetrazaindene (XVIII), 2 g. of potassium carbonate, 2 teaspoons of commercial Raney nickel, and 500 ml. of water was refluxed 2 hr., with stirring. The mixture was filtered hot, the Raney nickel washed thoroughly with hot water, the filtrate acidified with nitric acid, and the tetrazaindene precipitated by the addition of silver nitrate. The precipitated silver salt was washed with water until neutral, suspended in 200 ml. of boiling water, and hydrogen sulfide was passed through the suspension until no more silver sulfide separated. The hot mixture was filtered, the filtrate concentrated to 25 ml., treated with Norit, filtered, and cooled to yield 0.9 g. of material melting at 278–279° that proved to be identical with 6-methyl-4-oxo-1,3,3a,7-tetrazaindene (I).

Raney nickel dethiolation of the 3-thiol. In a similar manner, 0.7 g. of 6-methyl-4-oxo-1,3,3a,7-tetrazaindene (I) was obtained from 2 g. of 6-methyl-4-oxo-1,3,3a,7-tetrazindene-2-thiol (XVII).

Oxidative dethiolation of 3-mercapto-6-methyl-4-oxo-1,2,3a,7-tetrazaindene (XI). To a solution of 10 ml. of concentrated nitric acid and 15 ml. of water was added 2 g. of the mercapto compound XI. After the oxides of nitrogen were no longer evolved and the solid was completely dissolved, the solution was diluted with 275 ml. of water and silver nitrate added. The silver salt was collected, washed free of acid with water, suspended in 250 ml. of boiling water, and hydrogen sulfide was passed through the suspension until no more silver sulfide separated. The mixture was filtered and the filtrate treated with Norit, filtered, concentrated to 25 ml., and chilled, yielding 0.2 g. of solid, m.p. 248–250°, which proved to be identical with a sample of 6-methyl-4-oxo-1,2,3a,7-tetrazaindene (III).

Attempted oxidative dethiolation of 6-methyl-4-oxo-1,3,3a,7-tetrazaindene-2-thiol. Two g. of the mercapto compound XVII was added to 10 ml. of concentrated nitric acid and 15 ml. of water. The mixture was stirred at room temperature until no more brown fumes were evolved, and the solid was collected and washed with water. The solid was digested with 250 ml. of boiling water and dried to yield 1.3 g. of material, m.p. above 330°, which was considered to be the disulfide.

Anal. Calcd. for $C_{12}H_{10}N_8O_2S_2$: C, 38.9; H, 2.2; N, 31.0. Found: C, 39.3; H, 2.5; N, 31.1.

Dithiobiurea dibenzyl ether. Seventy-five g. (0.5 mole) of dithiobiurea was dissolved in a solution of 48 g. of sodium hydroxide in 800 ml. of water and 185 g. (1.1 moles) of benzyl bromide was slowly added, with stirring, the temperature being kept at about 15° by external cooling. The mixture was stirred at room temperature overnight and the solid was collected on a Büchner funnel and then recrystallized from a mixture of benzene and ligroin (b.p. 90–100°). Yield, 74 g. of the product as white plates, m.p. 88–89°.

Anal. Calcd. for $C_{16}H_{18}N_4S_2$: C, 58.2; H, 5.5; N, 17.0. Found: C, 58.5; H, 5.6; N, 17.1.

3-Amino-5-benzylmercapto-1,2,4-triazole. A mixture of 72 g. (0.22 mole) of the dibenzyl compound and 400 ml. of 1*N* sodium hydroxide solution was heated on the steam bath with stirring for 8 hr. The mixture was filtered and the cooled filtrate was neutralized with hydrochloric acid. An oil separated which solidified on chilling. The solid was collected, washed with water, and recrystallized from a mixture of benzene and alcohol. Yield, 20 g. of product, m.p. 105–106°.

Anal. Calcd. for $C_9H_{10}N_4S$: C, 52.4; H, 4.9; N, 27.2. Found: C, 52.6; H, 5.0; N, 26.9.

2-Benzylmercapto-6-methyl-4-oxo-1,3,3a,7-tetrazaindene (XIX). A mixture of 20 g. of the triazole and 15 ml. of acetoacetic ester in 150 ml. of acetic acid was refluxed 5 hr. and then cooled. The solid was collected and recrystallized from ethanol. Yield, 15 g. of product, m.p. 252°.

Anal. Calcd. for $C_{13}H_{12}N_4OS$: C, 57.3; H, 4.4; N, 20.6. Found: C, 57.4; H, 4.5; N, 19.9.

6-Methyl-4-oxo-1,3,3a,7-tetrazaindene-2-thiol (XVII). To a solution of 6.5 g. of XIX in 200 ml. of liquid ammonia was added small pieces of sodium until the blue color persisted. The ammonia was allowed to evaporate at room temperature and the residue was dissolved in water, filtered, and the filtrate acidified with hydrochloric acid and chilled. The solid was collected and recrystallized from water. Yield, 4.3 g. of product, m.p. 287–288°.

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.5; H, 3.3; N, 30.8. Found: C, 39.6; H, 3.3; N, 30.7.

A run in which acetic acid was used in place of hydrochloric acid for the neutralization yielded 3.5 g. of the sodium salt of the mercaptotetrazaindene, m.p. 310°, with decomposition.

Anal. Calcd. for $C_6H_5N_4OSNa$: C, 35.1; H, 2.9; N, 27.3. Found: C, 34.8; H, 2.7; N, 27.1.

7-Carbethoxy-6-methyl-2-methylmercapto-4-oxo-1,3,3a,7-tetrazaindene (XX). A solution of 5 g. of 6-methyl-2-methylmercapto-4-oxo-1,3,3a,7-tetrazaindene (XVIII) in 1 g. of sodium hydroxide and 50 ml. of water was evaporated to dryness *in vacuo* and to the residue was added 5 g. of ethyl chloroformate and 100 ml. of benzene. The mixture was stirred at room temperature for 24 hr., heated to boiling, filtered, and the filtrate chilled. The solid was collected and recrystallized from benzene. Yield, 2.5 g. of product, m.p. 190–191°.

Anal. Calcd. for $C_{10}H_{12}N_4O_3S$: C, 44.8; H, 4.5; N, 20.9. Found: C, 44.6; H, 4.4; N, 21.2.

7-Carbethoxy-6-methyl-4-oxo-1,3,3a,7-tetrazaindene (XXXV) A mixture of 5 g. of the sodium salt of 6-methyl-4-oxo-1,3,3a,-7-tetrazaindene (I), 10 ml. of ethyl chloroformate and 250 ml. of benzene was stirred 24 hr. at room temperature. The mixture was worked up as above to yield 2 g. of product, m.p. 182–183°, with decomposition.

Anal. Calcd. for $C_9H_{10}N_4O_3$: C, 48.6; H, 4.5; N, 25.2. Found: C, 48.5; H, 4.5; N, 24.8.

Dethiolation of 7-carbethoxy-6-methyl-2-methylmercapto-1,3,3a,7-tetrazaindene. A mixture of 2 g. of the tetrazindene XX, 2 teaspoons of Raney nickel, and 500 ml. of absolute ethanol was refluxed 4 hr. The mixture was filtered hot and the Raney nickel extracted with 500 ml. of hot alcohol. The combined alcohol solutions were evaporated to 25 ml. and chilled. Yield, 0.4 g. of 6-methyl-4-oxo-1,3,3a,7-tetrazaindene, (I).

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ROCHESTER 4, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS AND SCIENCES OF THE UNIVERSITY OF LOUISVILLE]

Pyridine Analogs of *p*-Terphenyl and *p*-Quaterphenyl

RICHARD H. WILEY, P. X. CALLAHAN, C. H. JARBOE, JR., J. T. NIELSEN, AND B. J. WAKEFIELD

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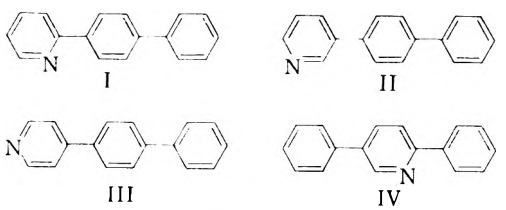
Four pyridine analogs of *p*-terphenyl and two of *p*-quaterphenyl have been synthesized for evaluation as scintillation solutes.

p-Terphenyl and its derivatives have been extensively studied as scintillation solutes.[1] A limitation on the usefulness of polyphenyls themselves for this purpose is their low solubility in toluene, the commonly used solvent. Although pyridine analogs of the polyphenyls offer a class of possible alternatives for use as scintillators, only a few such compounds are known. Of the twenty-five possible pyridine analogs of *p*-terphenyl, only four are reported in the literature. 4-(2-Pyridyl)biphenyl (I), 4-(3-pyridyl)biphenyl (II), and 4-(4-pyridyl)-biphenyl (III) have been synthesized by the reaction of the (*N*-nitrosoacetamidophenyl)pyridines with benzene.[2] The 2- and 4-isomers have also been prepared by the reaction of *p*-phenylbenzenediazonium chloride with pyridine.[2] An unseparated mixture of the six *p*-dipyridylbenzenes has been prepared[3] by the reaction of a mixture of diazotized



p-aminophenylpyridines with pyridine. None of the 2,5-diphenylpyridylpyridines or 2,5-dipyridylpyridines is known and no pyridine analogs of *p*-quaterphenyl are recorded. We wish to report at this time the results of a study of the synthesis and scintillation properties of some compounds of this type.

We have recently reported[4] the synthesis of 2,5-diphenylpyridine (IV), m.p. 174°, by the reaction of phenyllithium with 3-phenylpyridine. The structure of the product was proved by an alterna-

(1) F. N. Hayes, D. G. Ott, V. N. Kerr, and B. S. Rogers, *Nucleonics* **13**, #12, 38 (1955).

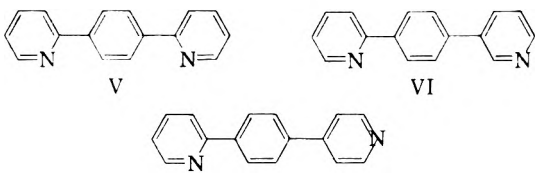
(2) I. M. Heilbron, D. H. Hey, and A. Lambert, *J. Chem. Soc.*, 1279 (1940).

(3) A. H. Cook, I. M. Heilbron, D. H. Hey, A. Lambert, and A. Spinks, *J. Chem. Soc.*, 404 (1943).

(4) R. H. Wiley, C. H. Jarboe, P. X. Callahan, and J. T. Nielsen, *J. Org. Chem.*, **23**, 780 (1958).

tive synthesis involving permanganate oxidation of 3-phenylbenzo(f)quinoline. Complete details of these experiments are given here. The *p*-dimethylamino analog has been prepared using *p*-dimethylaminophenyllithium to evaluate the effect of the dimethylamino group on scintillation properties. The 3-phenylpyridine used in these reactions was prepared by a new method. Cyclohexanone was treated with 3-pyridyllithium[5] and the product was dehydrated to give 3-(1-cyclohexenyl)pyridine in 77% yield. Dehydrogenation with sulfur or, better, with palladium on alumina at 360° gave 3-phenylpyridine in 50% yield.

We have synthesized and characterized three *p*-dipyridylbenzenes (V, VI, VII). *p*-Nitroaniline was diazotized and treated with pyridine[6] and



V VI

VII

the resulting 2-, 3-, and 4-(*p*-nitrophenyl)pyridines were separated by fractional crystallization of the bases and their salts. The structures of the (*p*-nitrophenyl)pyridines have been established.[6] The *p*-nitrophenylpyridines were reduced to the corresponding *p*-aminophenylpyridines with tin and hydrochloric acid. If three *p*-dipyridylbenzenes could be isolated from the reaction of each of the *p*-aminophenylpyridines with pyridine, the structures of the six isomeric products would be established. We have isolated three compounds from these reactions and some conclusions as to their structures have been established.

From the reaction of 2-(*p*-aminophenyl)pyridine we have isolated two compounds, m.p. 147–148° and 196–197°; from 3-(*p*-aminophenyl)pyridine one compound, m.p. 131–132°, and from 4-(*p*-aminophenyl)pyridine one compound, m.p. 196–197°. Elementary analyses confirmed that these compounds are dipyridylbenzenes. The two materials, m.p. 196–197°, were identical on the basis of mixed melting points and infrared absorption characteristics. From the starting materials involved, this product can be only *p*-di-(2,4-pyridyl)-benzene (VII). The other two products can be tentatively assigned 2-substituted structures since homolytic substitution of the pyridine ring normally takes place in the 2-position[2,3,7,8] and the 3-isomer is usually most difficult to isolate.[2,8] It is probable, therefore, that the compound, m.p. 147–148°, is *p*-di-(2,2-pyridyl)benzene (V) and that the compound, m.p. 131–132°, is *p*-di-(2,3-pyridyl)benzene (VI).

The physical properties of these dipyridylbenzenes are consistent with the assigned structures. Thus, the melting points of the 2,2- and 2,3-isomers are both lower than that of the 2,4- isomer. The 4-isomer is generally the highest melting of a series.[8] The ultraviolet spectrum of the 2,2-isomer (m.p. 147–148°) differs greatly from that of *p*-terphenyl, whereas those of the other compound are less different. Pyridine analogs of *p*-polyphenyls also show abnormalities when 2-pyridyl nuclei are present. The ultraviolet spectra are discussed in more detail below. The infrared spectra of the *p*-dipyridylbenzenes are complex and do not provide further information on the identity of the isomers. Detailed studies have been made[9–11] of the infrared spectra of substituted pyridines in the 1600 cm.$^{-1}$ to 1000 cm.$^{-1}$ region (chloroform solution). The correlations so established are useful in simple cases but are of little value for structural assignments in compounds with more than one type of pyridine substitution. The *p*-dipyridylbenzenes show strong bands in the 900 cm.$^{-1}$ to 600 cm.$^{-1}$ regions (potassium bromide disk), which can be assigned to out of plane hydrogen vibrations. Although assignments consistent with those for simple pyridines can be made, these are not sufficiently characteristic to serve as a proof of structure. These infrared spectra are discussed in more detail below.

Several attempts have been made to provide further confirmation of the identity of the supposed 2,2- and 2,3-isomers by degradation or by alternative synthesis. The 2,2-isomer (m.p. 147–148°) was recovered unchanged after heating with alkaline permanganate for 48 hours. In order to facilitate oxidation of the central ring, the compound was nitrated and the nitro-compound was reduced to the amine. Permanganate oxidation of the amine gave insufficient amounts of pyridinecarboxylic acids to be identified. Attempted synthetic routes utilized 2-(*p*-bromophenyl)pyridine and 2-(*p*-iodophenyl)pyridine prepared from 2-(*p*-aminophenyl)pyridine.[8] 2-(*p*-Bromophenyl)pyridine did not react with lithium. It has been reported that this compound does not form a Grignard reagent.[3] The aryllithium was formed normally, however, by metal exchange between *n*-butyllithium and 2-(*p*-bromophenyl)pyridine, but reaction of the *p*-(2-pyridyl)phenyllithium with pyridine gave only tars from which no identifiable products could be isolated. *p*-Di-(2,2-pyridyl)benzene was not

(5) H. Gilman and S. M. Spatz, *J. Am. Chem. Soc.*, 62, 446 (1940).

(6) J. W. Haworth, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.*, 349 (1940).

(7) D. H. Hey, J. M. Stirling, and G. H. Williams, *J. Chem. Soc.*, 3963 (1955).

(8) E. C. Butterworth, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.*, 357 (1940).

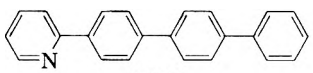
(9) A. R. Katritzky and J. N. Gardner, *J. Chem. Soc.*, 2198 (1958).

(10) A. R. Katritzky and A. R. Hands, *J. Chem. Soc.*, 2202 (1958).

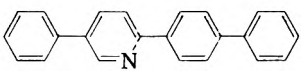
(11) A. R. Katritzky, A. R. Hands, and R. A. Jones, *J. Chem. Soc.*, 3165 (1958).

formed by mixed Ullman reactions[12] between 2-(*p*-bromophenyl)pyridine or 2-(*p*-iodophenyl)-pyridine and 2-bromopyridine. Even under conditions which converted the 2-bromopyridine to a tarry product, halophenylpyridine could be recovered. An attempt to synthesize 1-(2-pyridyl)-4-(4-methylpyridyl)benzenes by coupling diazotized 2-(*p*-aminophenyl)pyridine with γ-picoline gave tars.

Two pyridine analogs of *p*-quaterphenyl have been synthesized: 4-(2-pyridyl)-*p*-terphenyl (VIII) and 2-(4-biphenylyl)-5-phenylpyridine (IX). Nitration of biphenyl with concentrated nitric acid



VIII



IX

at 45° gave 4,4′-dinitrobiphenyl.[13] This was reduced to 4-amino-4′-nitrobiphenyl with sodium polysulfide[14] and the product was diazotized and coupled with pyridine. The only product isolated was 4-nitro-4′-(2-pyridyl)biphenyl, m.p. 214–215° (lit.[2] m.p. 213°). This compound was reduced to the amine with stannous chloride[2] and the amine was acetylated. Treatment of the 4-acetamido-4′-(2-pyridyl)biphenyl with nitrosyl chloride gave 4-(*N*-nitrosoacetamido)-4′-(2-pyridyl)biphenyl. This compound with benzene gave 4-(2-pyridyl)-*p*-terphenyl (VIII), m.p. 269–270°. 2-(4-Biphenylyl)-5-phenylpyridine (IX) was prepared by a method similar to that used for 2,5-diphenylpyridine. Metal exchange between *n*-butyllithium and 4-bromobiphenyl gave 4-biphenyllithium, which with 3-phenylpyridine gave the product m.p. 274–275°.

Scintillation data for some of the compounds described above and for some related compounds are recorded in Table I. The general conclusion drawn from these results is that while the introduction of a pyridine nucleus into a polyphenyl does increase its solubility in toluene, this advantage is overshadowed by a great reduction in scintillation response. The reduction is greater for a non-terminal pyridine (as in 2,5-diphenylpyridine and 2-(4-biphenylyl)-5-phenylpyridine than for a terminal pyridine (as in 4-(2-pyridyl)biphenylyl)-5-phenylpyridine. As was expected,[15] the introduction of a *p*-dimethylamino group into 2,5-diphenylpyridine produced a pronounced increase in scintillation response.

TABLE I

SCINTILLATION DATA[a]

Compound	R.P.H.[b]	Concentration g./l.	Solubility g./l. in toluene at 25°
p-Terphenyl[c]	0.94	3	8
4-(2-Pyridyl)biphenyl[c]	0.12	3	...
2,5-Diphenylpyridine	<0.10	3	13
2-(*p*-Dimethylamino-phenyl)-5-phenylpyridine	0.94	3	...
p-Di(2,4-pyridyl)benzene	<0.10	3	...
p-Quaterphenyl	...	...	<1
4-(2-Pyridyl)-*p*-terphenyl	0.70	1.02	1.02
2-(4-biphenylyl)-5-phenyl-pyridine	0.41	1.8	1.8

[a] Data obtained by Dr. F. N. Hayes and co-workers. [b] Pulse height relative to solution of 3 g./l. of 2,5-diphenyloxazole in toluene. [c] See ref. (15).

Ultraviolet absorption data have been recorded[16] for the 4-pyridylbiphenyls. The synthesis of further analogs of *p*-terphenyl makes possible some further correlations of the spectra of these compounds. Relevant information is recorded in Table II. It has been pointed out[16] that the spectra of the pyridine analogs of biphenyl and terphenyl are generally similar to those of the hydrocarbons but show a tendency to absorb at slightly longer wave lengths. Compounds containing 2-pyridine rings

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA

Compound	λ_{max} mμ	log ε	Solvent[a]	Ref.
Biphenyl	250	4.26	E	17
2-Phenylpyridine	245.5	4.10	E	16
	275.5	4.05		
3-Phenylpyridine	246	4.24	E	16
	275sh			
4-Phenylpyridine	257	4.20	E	16
2,2′-Bipyridine	237	4.04	H	16
	281	4.16		
4,4′-Bipyridine	238.5	4.10	H	16
p-Terphenyl	276	4.45	H	16
4-(2-Pyridyl)biphenyl	292	4.66	H	16
4-(3-Pyridyl)biphenyl	279	4.49	H	16
4-(4-Pyridyl)biphenyl	279	4.53	H	16
2,5-Diphenylpyridine	271	4.20	E	
	289.5	4.24		
p-Di(2,2-pyridyl)benzene	262	4.34	M	
	295	4.64		
p-Di(2,3-pyridyl)benzene	260sh		M	
	290	4.57		
p-Di(2,4-pyridyl)benzene	255sh		M	
	290	4.46		
2-(4-Biphenylyl)-5-phenylpyridine	280sh	4.47	M	
	307	4.63		

[a] The letters stand for the following solvents: E, ethanol; H, hexane; M, methanol.

(12) F. H. Burstall, *J. Chem. Soc.*, 1666 (1938).

(13) H. C. Gull and E. E. Turner, *J. Chem. Soc.*, 494 (1929).

(14) R. Belcher, A. J. Nutten, and W. I. Stephen, *J. Chem. Soc.*, 1334 (1953).

(15) F. N. Hayes *et al.*, *Survey of Organic Compounds as Primary Scintillation Solutes; a Status Report, U.S.A.E.C.*, 1958.

(16) A. E. Gillam, D. H. Hey, and A. Lambert, *J. Chem. Soc.*, 364 (1941).

(17) A. E. Gillam and D. H. Hey, *J. Chem. Soc.*, 1170 (1939).

TABLE III

INFRARED MAXIMA IN THE 900 CM.$^{-1}$ TO 650 CM.$^{-1}$ REGION

Normal range of vibrations[a]	One Hydrogen 900–860 cm.$^{-1}$	Two Hydrogens 860–800 cm.$^{-1}$	Three Hydrogens 810–750 cm.$^{-1}$	Four Hydrogens 770–735 cm.$^{-1}$	Five Hydrogens 770–730, 710–695 cm.$^{-1}$
Compound					
Pyridine					750
2-Picoline				755	
3-Picoline			790		
4-Picoline		800			
3-Phenylpyridine			807m		753vs(707s)-693s
4-(2-Pyridyl)biphenyl		846s		784m	752vs(708m)-682 vs
4-(4-Pyridyl)biphenyl		842s, 804s			761vs(701s)-688vs
2,5-Diphenylpyridine	904w	834m			749vvs(734s)-681vs
2-(4-Biphenylyl)-5-phenyl-pyridine	907m	856w, 827vs	780w		756vvs(749sh)-685vs
p-Di(2,2-pyridyl)benzene		861s		770vvs	(744w, 720w)
p-Di(2,3-pyridyl)benzene		848m	795m	774vs	(740w, 724w, 703s)
p-Di(2,4-pyridyl)benzene		860m, 818vs		779vvs	(738m, 711s)

[a] Bands in parentheses correlated with presence of pyridine nucleus. See ref. (18).

were however, abnormal. Thus, for example, 2,2′-bipyridine showed two absorption maxima. 4-(2-Pyridyl)biphenyl absorbed at a much longer wave length than did the 3-pyridyl- and 4-pyridyl-isomers. The fact that the *p*-dipyridylbenzene which has been assigned the 2,2 structure give two maxima, one at the same wave length as that of the absorption maximum of 4-(2-pyridyl)biphenyl, tends to confirm its identity. The other two isomers synthesized have very similar spectra with a pronounced maximum at the same wave length as that of 4-(2-pyridyl)biphenyl, and a shoulder at lower wave length. This suggests that both have one 2-substituted and one other pyridine ring and hence tends to confirm the identity of the supposed 2,2-isomer. 2,5-Diphenylpyridine has maxima both at the "normal" *p*-terphenyl frequency and at the "abnormal" 2-pyridine analog frequency.

Infrared absorption maxima and their approximate intensities for some pyridine analogs of polyphenyls and some related compounds in the 900 cm.$^{-1}$ to 650 cm.$^{-1}$ region are given in Table III. Maxima in this region have been correlated[18] with out of plane vibrations of different numbers of adjacent hydrogen atoms in aromatic nuclei. The ranges in which the maxima normally fall are indicated in the Table III. While it is generally easy to correlate bands in the spectra of known compounds with the number of adjacent hydrogen atoms present, it is less easy to deduce the structure of an unknown compound from the maxima. For example, the band at 800 cm.$^{-1}$ in 4-picoline is clearly due to the vibration of two adjacent hydrogens but a band at this frequency in an unknown compound might be due to two or to three adjacent hydrogens. Correlation appears to be particularly difficult when pyridine, as well as benzene nuclei are present, as in these cases bands may be found at the extremes of, or outside, their normal ranges. A band in the 710–730 cm.$^{-1}$ range has been correlated with a pyridine nucleus.[18] The proposed correlations for the maxima given by the analogs of the polyphenyls are indicated by their positions in Table III.

(18) L. J. Bellamy, *The Infra red Spectra of Complex Molecules*, 2nd. ed., Wiley, New York, 1958.

EXPERIMENTAL

Ultraviolet spectra were measured with a Beckman DK-2 recording spectrophotometer using spectral grade methanol or ethanol as solvent. Infrared spectra were run on a Baird recording double beam spectrometer in potassium bromide disks unless otherwise stated. Melting points were measured in open capillaries and are uncorrected. The authors are indebted to Drs. F. N. Hayes, D. G. Ott, and Miss E. Hansbury of the Los Alamos Laboratories for the pulse height measurements.[1] Analyses by Micro Tech Laboratories, Skokie, Ill.

3-(1′-Cyclohexenyl)pyridine. *n*-Butyllithium was prepared from lithium (4.4 g.) and 1-bromobutane (40 g.) in 350 ml. of dry ether. The mixture was cooled in a Dry ice–acetone bath and to it was added 3-bromopyridine (30 g.) and cyclohexanone (28.6 g.). After 3 hr., the reaction mixture was warmed to room temperature, poured onto ice water, and steam distilled to remove reactants. The residue was extracted with ether and the ether extracts dried and distilled to give a crude product, b.p. 266–268°. Refractionation gave 21 g. (77%) of the product, b.p. 98–101°/2 mm. n_D^{25} 1.5683.

Anal. Calcd. for $C_{11}H_{13}N$: C, 82.97; H, 8.23. Found: C, 82.68; H, 8.35.

3-Phenylpyridine. By dehydrogenation with sulfur. Sulfur (4.5 g.) and 3-(1-cyclohexenyl)pyridine (12.0 g.) were heated under reflux for 2 hr. The mixture was distilled to give 4.5 g. (39%) of 3-phenylpyridine, b.p. 273–274°, n_D^{23} 1.6142 (lit.[19] b.p. 117–118°/5 mm.; n_D^{25} 1.6123).

By dehydrogenation over palladized alumina. A Pyrex tube (6 mm. × 40 cm.) was packed with alumina pellets (1 × 3 mm.; 15 g.) on which 0.5 g. of palladium had been precipitated. The tube was heated electrically to 360°. Nitrogen was passed through the tube at a rate of 25 ml./min. (at exit). 3-(1-Cyclohexenyl)pyridine was distilled into the nitrogen stream and the product was condensed at the exit of the tube. Fractionation gave 0.5 g. (50%) of 3-phenylpyridine from 1 g. of 3-(1-cyclohexenyl)pyridine.

(19) C. P. Farley and E. L. Eliel, *J. Am. Chem. Soc.*, **78**, 3481 (1956).

3-Phenylpyridine was also prepared by oxidation of benzo(f)quinoline with permanganate, followed by decarboxylation of the product;[20-22] and by coupling *N*-nitrosoacetanilide with pyridine.[19]

2-Phenylbenzo(f)quinoline. A solution of phenyllithium prepared from 0.15 g. of lithium and 1.6 g. of bromobenzene in 150 ml. of ether was added to a solution of 2.55 g. of benzo(f)quinoline in 150 ml. of dry ether in an atmosphere of nitrogen. The mixture was stirred for 10 hr., and poured into excess cold dilute hydrochloric acid. The ether layer was evaporated and the residue was recrystallized three times from dilute hydrochloric acid to give the hydrochloride of the product, m.p. 215–225° (dec.). The free base (2.4 g.; 80%) was liberated by treating the hydrochloride with dilute aqueous sodium hydroxide and recrystallized from ethanol, m.p. 188–188.5° (lit.[23] m.p. 188°).

2,5-Diphenylpyridine. From 3-phenylpyridine. A solution of phenyllithium in ether (150 ml.) prepared from bromobenzene (2.71 g.) was added to a solution of 3-phenylpyridine (2.50 g.) in dry ether (150 ml.). The mixture was stirred for 24 hr. at room temperature. Water (30 ml.) was added and ether was removed and the residue recrystallized from ethanol to give 2,5-diphenylpyridine (0.95 g.; 26%), m.p. 174–175° (undepressed on admixture with material prepared from 2-phenylbenzo(f)quinoline; see below).

Anal. Calcd. for $C_{17}H_{13}N$: C, 88.28; H, 5.67; N, 6.06. Found: C, 88.09, 88.18; H, 5.79, 5.89; N, 6.12, 6.10.

From 2-phenylbenzo(f)quinoline. Finely divided 2-phenylbenzo(f)quinoline (1.6 g.) was suspended in a solution of sodium hydroxide (0.87 g.) in water (700 ml.). The solution was heated to 90–100°, potassium permanganate (2.26 g.) was added in portions and the suspension was stirred at 90–100° for 4 days. The suspension was filtered and the filtrate was made neutral to phenolphthalein with dilute sulfuric acid and concentrated to 2.5 ml. Ethanol (40 ml.) was added, and the precipitated potassium sulfate was removed by filtration. The solution was evaporated to dryness and the residue was recrystallized from benzene to give 3-(*o*-carboxyphenyl)-6-phenyl-2-carboxypyridine (1.6 g. 85%), m.p. 196° (dec.) (lit.[24] m.p. 196°). pK_a 5.62, pK_b 8.16. Mol. wt.: Calcd., 319; found (by titration), 320.5.

3-(*o*-Carboxyphenyl)-6-phenyl-2-carboxypyridine (1.5 g.) was heated to 200° for 25 min. Carbon dioxide was evolved. The residue was recrystallized from ethanol to give 5-(*o*-carboxyphenyl)-2-phenylpyridine (1.2 g.; 92%), m.p. 195–196° (depressed to 140–151° on admixture with 3-(*o*-carboxyphenyl)-6-phenyl-2-carboxypyridine).

Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76. Found: C, 78.40; H, 4.68.

5-(*o*-Carboxyphenyl)-2-phenylpyridine (0.3 g.) was ground with a large excess of copper dust, and the mixture was heated to redness in a copper test tube. The residue was extracted with benzene. The benzene was evaporated and the residue was recrystallized from ethanol to give 2,5-diphenylpyridine (0.2 g.; 60%), m.p. 174°.

Ultraviolet absorption: λ_{max} 271 mμ (log ε, 4.20), 289.5 mμ (log ε, 4.24). Relative pulse height <0.10.

2-(p-Dimethylaminophenyl)-5-phenylpyridine. A solution of *p*-dimethylaminophenyllithium prepared from *p*-dimethylaminobromobenzene (2 g.) was added to a solution of 3-phenylpyridine in dry ether. The reaction mixture was allowed to stand for 3 days in an atmosphere of nitrogen and was then poured into excess dilute hydrochloric acid. The ether was evaporated and the solution was neutralized with aqueous sodium hydroxide and extracted four times with 50-ml. portions of hot benzene. The benzene was evaporated, and the residue was recrystallized from ethanol to give 2-(*p*-dimethylaminophenyl)-5-phenylpyridine, (0.39 g.; 15%), m.p. 201°.

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.17; H, 6.61. Found: C, 83.12; H, 6.96.

Ultraviolet absorption: λ_{max} 240.5 mμ (log. ε, 3.88), 335 mμ (log ε, 4.32).

Relative pulse height 0.94.

p-Nitrophenylpyridines. A mixture of *p*-nitrophenylpyridines was prepared by the coupling of diazotized *p*-nitroaniline and pyridine using the method previously described.[6] Fractional recrystallization of the hydrochlorides and of the nitrates gave 2-(*p*-nitrophenyl)pyridine (36% yield from *p*-nitroaniline) m.p. 130–131° (lit.[6] m.p. 130–131°) and 3-(*p*-nitrophenylpyridine (15% yield), m.p. 146–147° (lit.[6] m.p. 146–147°). Fractions thought to contain a high proportion of the 4-isomer were combined and converted to the picrates. These were readily separated by fractional recrystallization from acetone into a more soluble picrate, m.p. 157–160° (mainly the 2-isomer; lit.[5] m.p. 168°) and a less soluble picrate, m.p. 225–227° (dec.) (lit.[6] m.p. for picrate of 4-(*p*-nitrophenyl)pyridine, 228–229°). Treatment of the less soluble picrate with aqueous sodium hydroxide gave 4-(*p*-nitrophenyl)pyridine (5% yield from *p*-nitroaniline), m.p. 122–124° (lit.[6] m.p. 122–123°).

p-Aminophenylpyridines. The 2-, 3- and 4-(*p*-nitrophenyl)-pyridines were reduced to the corresponding *p*-aminophenylpyridines with tin and hydrochloric acid,[25] in 86%, 60%, and 40% yields respectively. 2-(*p*-Aminophenyl)pyridine, m.p. 96–97° (lit.[25] m.p. 97–98°); 3-(*p*-aminophenyl)pyridine, m.p. 99–101° with water of crystallization, 116–118° anhydrous (lit.[25] m.p. 102–104°; 116–118°); 4-(*p*-aminophenyl)pyridine, m.p. 232–233° (lit.[25] m.p. 232–234°).

p-Dipyridylbenzenes. From 2-(p-aminophenyl)pyridine. 2-(*p*-Aminophenyl)pyridine (14.5 g.) was dissolved in concentrated hydrochloric acid (55 ml.) and water (25 ml.). The solution was cooled to 0° (some hydrochloride crystallized) and the temperature was kept below 5° while a solution of sodium nitrite (7.0 g.) in water (15 ml.) was added slowly, with stirring. The solution was stirred for 15 min. and added to pyridine (250 ml.) with stirring at such a rate that the temperature of the solution was maintained at 35–40°. The solution was heated to 80° for 30 min., cooled, and poured into cold water (2.5 l.). The resulting suspension was filtered and the solid was washed free from pyridine with cold water and air dried. The product (16 g.), m.p. 110–136°, was dissolved in ethanol (70 ml.). A small amount of insoluble material was discarded. The solution was progressively concentrated and diluted with water to give four fractions of crystalline material, m.p. 150–153° (1.6 g.), 159–163° (0.6 g.), 123–125° (7.8 g.) and 103–108° (1.2 g.): total weight 11.2 g.

The fraction m.p. 159–163° was chromatographed on acid alumina (Woelm, Grade I) using dry benzene as solvent. The chromatogram consisted of several colored and/or fluorescent bands which were eluted with benzene/ethanol mixtures. Ethanol (1%)/benzene eluted a blue fluorescent band; evaporation of the eluate gave an almost colorless, crystalline solid, (14 mg.), m.p. 146–148°. Ethanol (5%)/benzene eluted intermediate colored bands and a yellow-fluorescent band; evaporation of the eluate gave brown tars and semisolids (from the intermediate bands) and a yellow crystalline solid. (50 mg.), m.p. 191–193° (from the fluorescent band). Higher proportions of ethanol eluted further tarry materials.

Chromatography of the other fractions gave similar results but with different proportions of the two crystalline products. The intermediate fractions and the tarry residues were combined and rechromatographed. Tars, and further small amounts of the materials already isolated, were obtained but no additional compounds.

(20) Z. H. Skraup and A. Cobenzyl, *Monatsh.*, **4**, 450 (1884).

(21) Z. H. Skraup and A. Cobenzyl, *Monatsh.*, **4**, 442 (1884).

(22) Z. H. Skaup and A. Cobenzyl, *Monatsh.*, **4**, 456 (1884).

(23) O. Döbner and P. Knutze, *Ann.* **248**, 133 (1888).

(24) R. Ciusa, *Gazz. chim. ital.*, **46**, I, 130 (1916).

(25) R. Forsyth and F. L. Pyman, *J. Chem. Soc.*, 2912 (1926).

Compound (V) m.p. 146–148° (estimated yield 30%) was recrystallized from acetonitrile to give white platelets, m.p. 147–148°.

Anal. Calcd. for $C_{16}H_{12}N_2$: N, 12.06. Found: 12.16.

Ultraviolet absorption. λ_{max} 262 mμ (log ε, 4.34), 295 mμ (log ε, 4.64).

The compound m.p. 191–193° (estimated yield 5%) was recrystallized from toluene, giving *p*-di-(2,4-pyridyl)benzene (VII), m.p. 196–197° (undepressed on admixture with material from 4-(*p*-aminophenyl)pyridine).

Anal. Calcd. for $C_{16}H_{12}N_2$: N, 12.06. Found: 12.23.

Ultraviolet absorption. λ_{max} 255 mμ (shoulder), 290 mμ (log ε, 4.46). Relative pulse height <0.10.

From 3-(p-aminophenyl)pyridine. 3-(*p*-Aminophenyl)pyridine (anhydrous; 5.5 g.) was diazotized and coupled with pyridine as described above for 2-(*p*-aminophenyl)pyridine. The product was recrystallized from aqueous ethanol to give two fractions each having m.p. ~120° (indefinite) (combined weight 4.5 g.). The fractions were combined and the mixture (0.50 g.) was chromatographed as described above. Ethanol (1%)/benzene eluted a pale orange, crystalline solid (0.29 g.; estimated yield 35%), m.p. 126–128.5°. Rechromatography of materials from the remainder of the eluate gave further small amounts of this material but no additional pure compounds. The crystalline product was recrystallized from acetonitrile to give the pure *p*-dipyridylbenzene (VI) as white crystals, m.p. 131.5–132°.

Anal. Calcd. for $C_{16}H_{12}N_2$: N, 12.06. Found: N, 12.04.

Ultraviolet absorption. λ_{max} 260 mμ (shoulder), 290 mμ (log ε, 4.57).

From 4-(p-aminophenyl)pyridine. 4-(*p*-Aminophenyl)pyridine (0.8 g. was diazotized and coupled with pyridine as described above for 2-(*p*-aminophenyl)pyridine. The product (0.6 g.) had m.p. 187–194°. The product (112 mg.) was chromatographed as described above. Ethanol (3%)/benzene eluted an almost white, crystalline solid (51 mg.; estimated yield 24%), m.p. 196–197° (VII) (undepressed on admixture with material from 2-(*p*-aminophenyl)pyridine) with infrared spectrum identical with that of material from 2-(*p*-aminophenyl)pyridine. Rechromatography of materials from the remainder of the eluate gave further small amounts of *p*-di(2,4-pyridyl)benzene and a little higher-melting material. All attempts to obtain a pure compound from this material were unsuccessful.

4-Nitro-4′-(2-pyridyl)biphenyl. Biphenyl (60 g.) was nitrated with concentrated nitric acid at 45°[13] to give 4,4′-dinitrobiphenyl (29 g.; 31%), m.p. 225–230° (lit.[13] m.p. 239–243°). 4,4′-Dinitrobiphenyl (29 g.) was reduced to 4-amino-4′-nitrobiphenyl (13 g.; 52%), m.p. 201–203° (lit.[14] m.p. 198°) with aqueous sodium polysulfide.[14] 4-Amino-4′-nitrobiphenyl (13 g.) was dissolved in glacial acetic acid (80 ml.) and the solution was cooled to 10°. Finely divided sodium nitrite (3.9 g.) was added over 15 min. with vigorous stirring with the temperature below 15°. The solution was stirred for 15 min. and added to pyridine (200 ml.) at such a rate that the temperature was maintained at 35–40°. The solution was heated on a steam bath for 30 min. and poured into water (1500 ml.). The solution was filtered and the solid was washed and air-dried. The product (14.5 g.) was systematically fractionally recrystallized from toluene. The only 4-nitro-4′-pyridylbiphenyl isolated was the 2-isomer (1.9 g.; 11%), m.p. 214–215° (lit.[2] m.p. 213°).

4-(2-Pyridyl)-p-terphenyl. 4-Nitro-4′-(2-pyridyl)biphenyl (1.7 g.) was reduced by stannous chloride in hydrochloric acid[2] to 4-amino-4′-(2-pyridyl)biphenyl (1.1 g.; 73%), m.p. 192–193° (lit.[2] m.p. 191–192°). 4-Amino-4′-(2-pyridyl)biphenyl (1.1 g.) was acetylated with acetic anhydride[2] to give 4-acetamido-4′-(2-pyridyl)biphenyl, (0.9 g.; 70%), m.p. 235–237° (lit.[2] m.p. 236–237°).

4-Acetamido-4′-(2-pyridyl)biphenyl (0.9 g.) was suspended in glacial acetic acid (5 ml.) and acetic anhydride (3 ml.). Anhydrous potassium acetate (1 g.) and phosphorus pentoxide (few mg.) were added. The solution was cooled to 5° and stirred as a mixture of redistilled nitrosyl chloride (0.6 g.) and acetic anhydride (0.6 g.) was added dropwise. The solution was stirred for 15 min. and poured into ice water (50 ml.). The mixture was extracted with benzene (50 ml.), treated with sodium carbonate, and again extracted with benzene (50 ml.). The benzene extracts were combined, washed once with water, and allowed to stand overnight over anhydrous sodium sulfate. The benzene was distilled and the residue (0.8 g.) was chromatographed on acid alumina. Ethanol (2%)/benzene eluted material which was recrystallized from benzene to give 4-(2-pyridyl)-*p*-terphenyl (0.10 g.; 11%). Further recrystallization gave pure material, m.p. 269–270°.

Anal. Calcd. for $C_{23}H_{17}N$: C, 89.86; H, 5.58. Found: C, 89.80; H, 5.72.

Relative pulse height 0.70 at 1.02 g./l. (saturated solution).

2-(p-Biphenylyl)-5-phenylpyridine (IX). The reaction was carried out in a dry box. Lithium (0.14 g.) was suspended in dry ether (200 ml.) in an atmosphere of nitrogen. The suspension was cooled to −65° and 1-bromobutane (1.37 g.) was added dropwise to the stirred mixture. 4-Bromobiphenyl (2.33 g.) was added and the mixture was stirred at −65° for 30 min. 3-Phenylpyridine (1.5 g.) was added and the mixture was allowed to warm to room temperature and stand overnight. Water was added and the mixture was extracted with benzene. The organic layer was removed and concentrated. The product was recrystallized from benzene to give 2-(4-biphenylyl)-5-phenylpyridine (0.5 g.; 17%), m.p. 274–275°.

Anal. Calcd. for $C_{23}H_{17}N$: C, 89.86; H, 5.58. Found: C, 90.09; H, 5.55.

Ultraviolet absorption. λ_{max} 280 mμ (shoulder; log ε, 4.47), 307 mμ (log ε, 4.63).

Relative pulse height 0.41 at 1.8 g./l. (saturated solution).

Note on nomenclature. Compounds I, II, and III have been named as pyridylbiphenyls to provide an element of consistency in this discussion by treating the pyridine rings as substituents where possible. Chemical Abstracts has indexed these as biphenylylpyridines with a cross reference under pyridylbiphenyl. Compounds IV and IX are exceptions named as substituted pyridines to provide simple names. The pyridylterphenyl name for VIII conforms to the principle of naming the compound as a derivative of the largest parent (Chemical Abstracts rule 70). Compounds V, VI, and VII present a special nomenclature problem. They cannot easily be named as substituted pyridines, nor is there any reason for doing so as they are rather obviously disubstituted benzenes. The problem is to indicate in a concise and definitive name the positions of the benzene and pyridine linkages. The name 1-(2-pyridyl)-4-(4-pyridyl)-benzene (for VII) is clear but hardly concise and somewhat labored. 2,2-*p*-Phenylenebispyridine (for V) is concise but the phenylene system is not a commonly used basis for systematic names of di-substituted benzenes, and it also provides no association with the terphenyl concept involved in our present discussion. It has been used in Chemical Abstracts for dipyrrylbenzene with a cross reference. *p*-Di-(2,4-pyridyl)benzene (for VII) is concise and definitive and follows Chemical Abstracts indexing principles for di-substituted benzenes.

Acknowledgment. This research was supported in part by the Atomic Energy Commission under Contract AT-(40-1)-2161 between the University of Louisville and the Atomic Energy Commission. The authors acknowledge this support with gratitude and also express their appreciation to the National Science Foundation for Grant NSF-G4074 which provided a recording ultraviolet spectrophotometer.

LOUISVILLE, KY.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

The Synthesis of 2,2′-Biquinolyls and Related Compounds by Catalytic Dehydrogenation

HENRY RAPOPORT, ROBERT IWAMOTO, AND JAMES R. TRETTER

Received September 30, 1959

Heating a number of quinolines with 5% palladium-on-carbon has led to 2,2′-biquinolyl formation in 11–21% conversions, with most of the unchanged quinolines being recovered. This method for joining two nitrogen-heterocycles at the 2-positions also has been extended to 1,5-naphthyridine and two pyridines. The reaction is quite sensitive to steric factors, as 3-methylquinoline, benzo[h]quinoline, and isoquinoline fail to react.

Quinoline occasionally has been used as a solvent in dehydrogenation reactions. In a recent instance of such a use, we observed the formation of a crystalline compound in too high a yield to have arisen from the material being dehydrogenated. It appeared to result from the reaction of the quinoline with the palladium-on-carbon catalyst. This was confirmed by a parallel reaction employing only quinoline and the catalyst and by identification of the crystalline material as 2,2′-biquinolyl. Neither an impurity in the quinoline nor special activity in the particular catalyst sample were responsible, as the reaction occurred equally well with highly purified quinoline, quinoline recovered from a reaction with palladium-on-carbon, and various samples of commercial catalyst. The facility and high yield with which 2,2′-biquinolyl formation had taken place induced us to examine this reaction for its synthetic possibilities.

There has been considerable interest in 2,2′-biquinolyls because of their specificity as complexing agents for cuprous ion and their sensitivity,[1] which permits detection of copper in one part in 10^8. However, the methods of preparation have been poor and, in some cases, limiting. Condensation of an *o*-aminobenzaldehyde or an *o*-aminophenone with a 2-acylquinoline requires the laborious preparation of intermediates and still gives poor yields.[2] For unsymmetrical 2,2′-biquinolyls, this remains the only reliable method. However, for symmetrical 2,2′-biquinolyls, the best synthesis appeared to be the reductive coupling of Ueda,[3] employing the 2-bromoquinoline, palladium-on-calcium carbonate, hydrazine, and alcoholic potassium hydroxide. Although the yields are poor and vary widely,[4] the product is reliably the 2,2′-compound. A recent application of this method has reported more consistent results.[5] However, the preparation of the intermediate 2-bromoquinoline and the poor yields are still definite drawbacks. The same may be said for the Ullmann-type condensation, in which the yields are extremely poor.[2,4,6] Catalytic dehydrogenation has been invoked for the preparation of 2,2′-biquinolyls with nickel-alumina in a sealed tube[1,6,7] and with a specially prepared pyrophoric nickel catalyst.[8] In these cases, although starting materials are much simpler and are recovered to a large extent, conversions to biquinolyl were 4–5%, and this decreased rapidly with substituted quinolines.

In comparison with the above procedures, the simplicity of the palladium-on-carbon method and the improved yield were quite attractive. A brief study was made of the effect of time of heating, presence or absence of oxygen, and amount of catalyst. There was very little advantage to continue heating beyond 24 hr; the yield was the same in an oxygen or carbon dioxide atmosphere; and 10% by weight of a 5% palladium-on-carbon catalyst was sufficient. These conditions were incorporated into a general procedure which is presented in the experimental section, and which was applied to eleven quinolines and related compounds.

Seven of these compounds formed the corresponding 2,2′-biaryls in the per cent conversions shown in Table I. The actual yields are much higher, as in

TABLE I

2,2′-BIQUINOLYLS AND RELATED COMPOUNDS PREPARED BY CATALYTIC DEHYDROGENATION

Compound	M.P., °	Conversion, %
2,2′-Biquinolyl	196[a]	17
8,8′-Dimethyl-2,2′-biquinolyl	210–211[b]	12
4,4′-Diphenyl-2,2′-biquinolyl	358–360[c]	11
6,6′-Dimethoxy-2,2′-biquinolyl	280–281	21
2,2′-Bi-1,5-naphthyridyl	282–284	8
2,2′-Bipyridyl	70–71[d]	2
4,4′,6,6′-Tetramethyl-2,2′-bipyridyl	144–145	8

[a] Lit.[8] m.p., 193–194°. [b] Lit.[4] m.p., 203–204°. [c] Lit.[2] m.p., 362°. [d] Lit.[8] m.p., 70.5–71.5°.

(1) J. G. Breckenridge, R. W. J. Lewis, and L. A. Quick, *Can. J. Res.*, **17B**, 258 (1939).

(2) F. H. Case and G. Maerker, *J. Am. Chem. Soc.*, **75**, 4920 (1953).

(3) K. Ueda, *J. Pharm. Soc. Japan*, **57**, 180 (1937).

(4) F. H. Case and J. J. Lafferty, *J. Org. Chem.*, **23**, 1375 (1958).

(5) S. Nakano, *J. Pharm. Soc. Japan*, **79**, 310, 314 (1959).

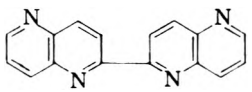
(6) J. G. Breckenridge, *Can. J. Res.*, **28B**, 593 (1950).

(7) J. P. Wibaut, H. D. T. Willink, Jr., and W. E. Nieuwenhuis, *Rec. trav. chim.*, **54**, 804 (1935).

(8) G. M. Badger and W. H. F. Sasse, *J. Chem. Soc.*, 616 (1956).

every case practically all of the uncondensed starting material was recovered, and the material balance was well over 90%. The products were established as the 2,2′-biaryls by elemental analyses and molecular weight determinations, by comparison of ultraviolet spectra and melting points with known compounds, and by complexing with cuprous ion. Complexing occurred in each case except with the sterically-hindered 8,8′-dimethyl-2,2′-biquinolyl and 4,4′,6,6′-tetramethyl-2,2′-bipyridyl.

Of interest is the biaryl (I) which was formed

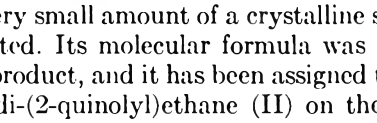


I

from 1,5-naphthyridine, and which gave a copper complex with λ_{max} at 550 mμ. The fact that bipyridyls are formed by this procedure and the possibility that higher temperatures may lead to better conversions are of interest in view of difficulties with present syntheses of bipyridyls.[8,9,10,11]

Three compounds gave no biaryls: 3-methylquinoline, benzo[h]quinoline, and isoquinoline. Each compound presents some steric interference either to complexing with the palladium catalyst or to formation of the biaryl. This absence of reaction indicates the sensitivity of the present method to steric factors.

2-Methylquinoline was subjected to the general procedure to see if coupling would occur to give the 4,4′-biquinolyl. None of this was obtained. However, a very small amount of a crystalline substance was isolated. Its molecular formula was that of a coupled product, and it has been assigned the structure 1,2-di-(2-quinolyl)ethane (II) on the basis of



II

its ultraviolet and infrared absorption. Its ultraviolet absorption maxima were almost identical with those of 2-methylquinoline, except for the absence of some short wavelength fine structure, and the extinction coefficients which were about doubled. In the infrared, 2-methylquinoline, 2,2′-biquinolyl, and compound II all showed bands at 745 cm.$^{-1}$ and 820 cm.$^{-1}$. These are characteristic of four and two adjacent aromatic hydrogens, respectively. There was no absorption in the 900–860 cm.$^{-1}$ range that could be attributed to an isolated aromatic hydrogen.[12]

(9) H. D. T. Willink, Jr. and J. P. Wibaut, *Rec. trav. chim.*, **54**, 275 (1935).

(10) G. T. Morgan and F. H. Burstall, *J. Chem. Soc.*, 20 (1932).

(11) F. H. Burstall, *J. Chem. Soc.*, 1662 (1938).

(12) C. Karr, Jr., P. A. Estep, A. J. Papa, *J. Am. Chem. Soc.*, **81**, 152 (1959).

EXPERIMENTAL[13]

General procedure for the preparation of heterocyclic biaryls. A stirred mixture of the quinoline (or related compound) and 10% by weight of a commercial 5% palladium-on-carbon catalyst was heated under reflux for 24 hr. In all cases, heating was at the boiling point of the compound, except for the following: 4-phenylquinoline was heated at 360°; 6-methoxyquinoline was heated at 265°; and 1,5-naphthyridine was heated at 220°. The mixture was then cooled, 10 parts by volume of chloroform was added, and this mixture was heated to boiling and filtered. Three digests with boiling chloroform (or benzene) were sufficient to remove all adsorbed material from the catalyst. The combined chloroform solutions were then distilled to remove chloroform and to recover unchanged starting material. Chromatography of the residue on alumina (Merck) gave the pure heterocyclic biaryl. Elution was usually accomplished with benzene to which increasing amounts of chloroform were added. In those instances where the starting heterocycle was not sufficiently volatile to be recovered by distillation, it was separated from the bis-compound by sublimation or by chromatography on alumina. The new biaryls prepared by this procedure are:

6,6′-Dimethoxy-2,2′-biquinolyl, m.p. 280–281°; ultraviolet absorption, λ_{max}^{MeOH} 266 mμ (ε 50,000), 309 (12,600), 337 (23,000), 352 (32 000).

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 76.0, H, 5.1, N, 8.9, OCH_3, 19.6. Found: C, 75.9; H, 5.0; N, 9.1; OCH_3, 19.5.

2,2′-Bi-1,5-naphthyridyl, m.p. 282–284°; ultraviolet absorption, λ_{max}^{MeOH} 233 mμ (ε 52,500), 265 (12,000), 275 (13,500) 286 (16,500), 321 (25,000), 333 (25,100).

Anal. Calcd. for $C_{16}H_{10}N_4$: C, 74.4; H, 3.9; N, 21.7; mol. wt., 258. Found: C, 74.7; H, 3.7; N, 21.8; mol. wt., 238.

4,4′,6,6′-Tetramethyl-2,2′-bipyridyl, m.p. 144–145°.

Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.3; H, 7.5; N, 13.2; mol. wt., 212. Found: C, 79.3; H, 7.5; N, 13.2; mol. wt. (Rast), 202.

3-Methylquinoline (heated at its boiling point), isoquinoline (heated at its boiling point), and benzo[h]quinoline (heated at 370°) gave no evidence of biaryl formation and were recovered quantitatively when subjected to the above procedure.

1,2-Di-2-quinolylethane. When 20 g. of 2-methylquinoline was heated with palladium-on-carbon as described in the general procedure above, 18 g. was recovered. Chromatography of the residue on alumina gave crystalline material in the fractions eluted with benzene, and this was recrystallized from methanol. Following sublimation (155°/75 μ), 57 mg. were obtained, melting at 166–167°[14]; ultraviolet absorption,[15] λ_{max}^{MeOH} 314 (ε 7200), 306 (4250), 301 (5500), 294 (4000), 233 (49.500).

Anal. Calcd. for $C_{20}H_{16}N_2$: C, 84.4; H, 5.6; N, 9.9. Found: C, 84.4; H, 5.6; N, 9.9.

BERKELEY, CALIFORNIA

(13) All melting points are corrected. Microanalyses were performed by V. Tashinian, Microchemical Laboratory, University of California, Berkeley.

(14) It is possible that this is the same as the unidentified substance, $C_{20}H_{16}N_2 \cdot H_2O$, melting at 160–162°, obtained from the reaction of 2-methylquinoline and sulfur by W. V. Miller [*Ber.*, **21**, 1827 (1888)].

(15) *Cf.* the ultraviolet absorption of 2-methylquinoline, λ_{max}^{MeOH} 314 mμ (ε 1250), 308 (2500), 301 (3000), 295 (2250), 232 (25,200), 228 (27,500), 224 (27,300).

[CONTRIBUTION FROM THE BIOCHEMICAL RESEARCH LABORATORY, THE DOW CHEMICAL COMPANY]

Phenylnitromethane. Condensation with Pyridine and Quinoline Aldehydes

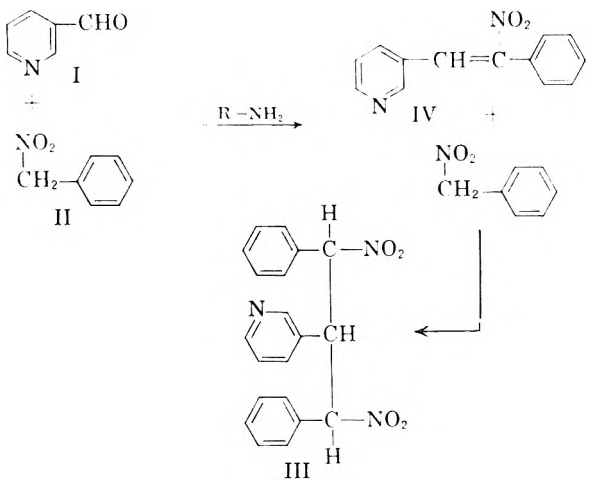
DALE N. ROBERTSON

Received October 21, 1959

The reaction between pyridine-3-carboxaldehyde (I) and phenylnitromethane (II) has been reported to yield 1,3-dinitro-1,3-diphenyl-2-(3-pyridyl)propane (III). Reinvestigation of this reaction has revealed that pyridine and quinoline aldehydes condense with II in a simple aldol manner to give nitroethanols. Dehydration to nitroethylenes, a mandatory intermediate for the dinitropropane III previously reported, could not be accomplished.

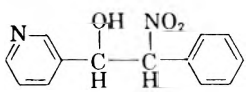
Dornow and Boberg[1] reported that the condensation of pyridine-3-carboxaldehyde (I) with phenylnitromethane (II) gave 1,3-dinitro-1,3-diphenyl-2-(3-pyridyl)propane (III). The assignment of this structure was based on the following elemental analyses: C, 65.65; H, 5.30; N, 11.26. (The theoretical values for structure III, $C_{20}H_{17}O_4N_3$, are: C, 66.10; H, 4.72; N, 11.56. No molecular weight data or infrared spectra were reported.)

The dinitropropane III could only arise by addition of II to the intermediate 1-nitro-1-phenyl-2-(3-pyridyl)-ethylene (IV)[2,3] according to the reaction:



Because of our interest in the α-nitrostilbenes, we attempted to prepare IV *via* the Schiff's base, a method found to be quite reliable with other aromatic aldehydes.[2] In this method, a Schiff's base of an aromatic aldehyde is made to react with phenylnitromethane in glacial acetic acid, giving good yields of α-nitrostilbenes. With a Schiff's base of pyridine-3-carboxaldehyde, only intractable black tars were formed. This led to a reinvestigation of the reaction reported by Dornow and Boberg.[1]

Using *n*-butylamine as catalyst in place of the methylamine in the original work,[1] we were able to isolate a low yield of a white crystalline material melting a few degrees lower than that reported. It was, however, accompanied by large amounts of dark, intractable oils. The infrared spectrum of the white crystals suggested a bonded hydroxyl, pyridine ring, nitro and monosubstituted phenyl. An equivalent weight determination by titration of the pyridine nitrogen (perchloric acid) gave a value of 246.4. The molecular weight of the simple aldol product (V) is 244.25 while that of III is 363.36. The analytical data (C, H, N) also support the simpler structure V.



V

It was found that all three pyridine aldehydes gave excellent yields of adduct when diethylamine or triethylamine was substituted for primary amine catalysts. Quinoline-2-carboxaldehyde gave considerably lower yields. Several other pyridine aldehydes also were employed in the condensation (see Table I).

In contrast to the facile conversion of nitroethanols, in general, to nitroethylenes, the products represented by V could be dissolved in either base or acid and recovered unchanged by neutralization. An attempt to dehydrate one of these adducts to the nitroethylene by heating in acetic acid was unsuccessful, leading again to intractable tars.

It should be pointed out that the lower nitroalkanes often give aldol products with pyridine[4,5] and quinoline aldehydes[6] although the corresponding nitroethylenes are obtained[1,5] at times.

All the compounds of Table I are white solids, quite sensitive to heat (and thus of variable melting point) and are soluble in both dilute acid and alkali.

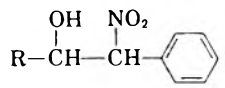
EXPERIMENTAL

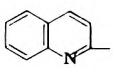
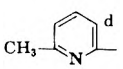
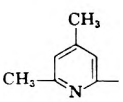
α-(α-Nitrobenzyl)-x-pyridine (and quinoline) methanols. The following general procedure was found to give good yields of quite pure products:

The aldehyde (0.1 mole) and phenylnitromethane (0.1 mole) were mixed in 25 ml. of ethanol or ethyl acetate. A

(1) A. Dornow and F. Boberg, *Ann.*, **578**, 101 (1952).
(2) D. N. Robertson, *J. Org. Chem.*, in press.
(3) D. E. Worrall, *J. Am. Chem. Soc.*, **57**, 2299 (1935).
(4) F. Zymalkowski, *Arch. Pharm.*, **289**, 52 (1956).
(5) A. Burger, M. L. Stein, and J. B. Clements, *J. Org. Chem.*, **22**, 143 (1957).
(6) A. P. Phillips, *J. Am. Chem. Soc.*, **70**, 452 (1948).

TABLE I



R	M.P.[a]	Yield, %	Neutral Equivalent[b] Calcd.	Found	Analyses[c] Carbon Calcd.	Found	Hydrogen Calcd.	Found	Nitrogen Calcd.	Found
	106–107	86.7	244.2	247	63.92	64.52	4.95	4.89	11.47	11.30
	117–117.5	86.7	244.2	247.2	63.92	64.15	4.95	4.81	11.47	11.30
	130–130.5 (dec.)	87.9	244.2	246.4	63.92	64.21	4.95	4.88	11.47	10.48
	132.5–133	38.8	—	—	69.38	69.37	4.79	4.72	9.52	9.33
 [d]	99.5–101	90.0	258.31	259.5	—	—	—	—	—	—
	124–127.5	95.6	272.3	274.8	66.16	66.14	5.92	5.54	—	—
 [d] (bis compound)	144.5–147	80.5	409.5	414.0	—	—	—	—	—	—

[a] Since these compounds are sensitive to heat, the melting points are quite variable, depending on rate of heating, residence time in apparatus, etc. The figures presented should be taken only as guides. [b] By titration with perchloric acid in acetic acid. [c] Infrared spectra were consistent with each formula. [d] Since the neutral equivalents and infrared spectra support these structures, further analyses were not conducted.

few drops of either diethyl- or triethylamine were added and the mixture was allowed to stand. In most cases, the solution warmed spontaneously and crystallization began within a few minutes. Although the reactions appeared to be complete within 1 or 2 hr., they were usually allowed to stand overnight. The products were recovered by filtration, washed with small amounts of alcohol and dried *in vacuo* over phosphorus pentoxide.

Analytical samples were prepared by dissolving the compound in ethyl acetate at room temperature, adding Skellysolve A to turbidity and placing in the deep-freeze at $-17°$ This procedure was necessary because heating slowly decomposed most of the products. (Analytical samples could not be dried at 60°, for example.)

The product from quinoline-2-carboxaldehyde was much more stable and could be recrystallized from hot ethanol–ethyl acetate.

Table I lists the products prepared.

MIDLAND, MICH.

[CONTRIBUTION FROM RADIO-CARBON LABORATORIES]

Studies with Quinolines. II. The Acid-Catalyzed Hydrolysis of Reissert Compounds

JEFFERSON W. DAVIS, JR.

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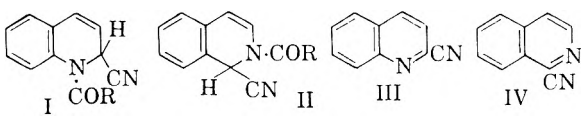
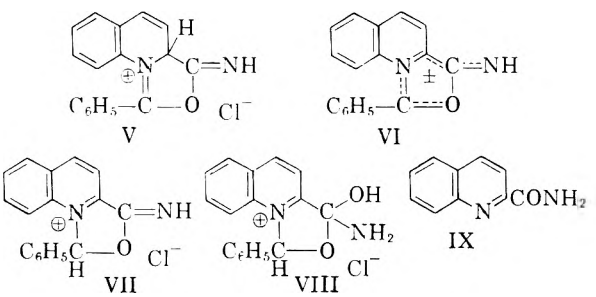
The cyclic imine X has been prepared from 2-benzoyl-1,2-dihydroisoquinaldonitrile, II, on treatment of the latter with hydrobromic acid in acetic acid. The imine was isolated and purified and was found to be stable on treatment with water. The formation of cyclic imines of this type appears to be a general characteristic of Reissert compounds. On decomposition in hydrobromic acid–acetic acid the imine X gives benzaldehyde, isoquinaldamide hydrobromide and the hydrobromide of isoquinaldic acid. On treatment of the hydrobromide of quinaldic acid with thionyl chloride there is loss of hydrogen bromide with formation of the free acid chloride. This route eliminates the necessity of isolating the anhydrous acid.

Reissert compounds or 1-acyl-1,2-dihydroquinaldonitriles, I, 2-acyl-1,2-dihydroisoquinaldonitriles, II, and analogous compounds, when treated with mineral acid, undergo hydrolysis to aldehydes, acid amides, and carboxylic acids. The formation of aldehydes by hydrolysis of these compounds involves a mechanism more complex than the simple hydrolysis of a nitrile to an amide and carboxylic acid. Several mechanisms have been proposed for this unusual behavior of Reissert compounds, but there has been insufficient experimental evidence in support of the several mechanisms predicted by theoretical considerations.



In early studies[1-3] of the mechanism of the acid-catalyzed hydrolysis of Reissert compounds, it was assumed that the nitriles, III and IV, were formed as intermediates which were subsequently hydrolyzed to the amides and carboxylic acids. This assumption was never proved, however, and Cobb and McEwen[4] offered experimental evidence which indicates that the nitrile is not one of the products of the hydrolysis. These authors found that on treatment of I (R = benzoyl) with ethanolic hydrogen chloride no quinaldonitrile could be isolated from the reaction mixture. Similar studies in concentrated hydrochloric acid afforded only benzaldehyde, quinaldamide, quinaldic acid, benzoin quinaldate, and unchanged I. On the other hand, when mole quantities of I and quinaldonitrile were treated in the same manner, 11 to 39% of the nitrile was recovered unchanged. They then proposed a mechanism which excluded the nitrile as an intermediate and which could, on a theoretical basis, explain the formation of all the products isolated from a typical reaction. It was assumed that the Reissert compound I on treatment with hydrochloric acid first gives the cyclic intermediate V which rearranges to VII through the mesoionic intermediate VI. Addition of water to VII gives VIII which then collapses to benzaldehyde and the amide IX.



None of the previous workers were able to isolate in pure form any of the proposed cyclic intermediates.[5] It was this lack of experimental evidence that prompted us to reinvestigate the hydrolysis of Reissert compounds.

In a previous communication[6] we were able to show that a Reissert compound I (R = benzoyl) on treatment with hydrobromic acid in acetic acid gives good yields of benzaldehyde and quinaldic acid. We have repeated this reaction with 2-benzoyl-1,2-dihydroisoquinaldonitrile, II (R = benzoyl), with similar results and were able to isolate in 95% yield the hydrobromide analog of one of the cyclic intermediates proposed by Cobb and McEwen.[4] This intermediate or Reissert imine

(1) W. E. McEwen and R. N. Hazlett, *J. Am. Chem. Soc.*, **71**, 1949 (1949).

(2) M. Colonna, *Gazz. chim. ital.*, **82**, 503 (1952).

(3) C. G. Swain and W. A. Sheppard, Abstracts of papers presented at ACS National Meeting, Cincinnati, Ohio, March 29 to April 7, 1955, P40N.

(4) R. L. Cobb and W. E. McEwen, *J. Am. Chem. Soc.*, **77**, 5042 (1955).

(5) McEwen and co-workers did, however, obtain unstable yellow precipitates which could not be purified and which decomposed with water to give benzaldehyde and quinaldamide. Haworth and Perkin obtained an orange compound when a chloroform solution of 2-benzoyl-6,7-dimethoxy-1,2-dihydroquinaldonitrile was treated with hydrogen chloride. This orange substance gave benzaldehyde and 6,7-dimethoxyisoquinaldamide upon steam distillation [R. D. Haworth and W. H. Perkin, *J. Chem. Soc.*, 1434 (1925)].

(6) J. W. Davis Jr., *J. Org. Chem.*, **24**, 1691 (1959).

X[7] may be crystallized from hot alcohol and does not decompose on treatment with hot or cold water. It can be isolated with ease in a high state of purity. Upon decomposition it gives benzaldehyde, isoquinaldamide hydrobromide XI, and isoquinaldic acid hydrobromide XII.

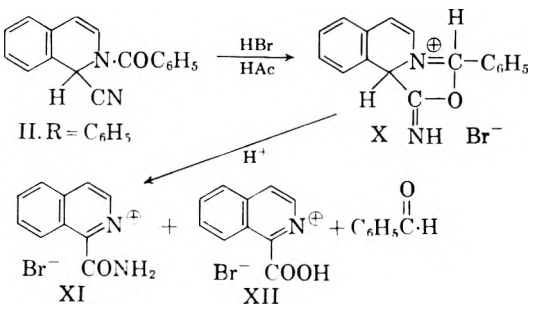
When 2-benzoyl-1,2-dihydroisoquinaldonitrile, II (R = benzoyl), is added to a mixture of hydrobromic acid in acetic acid there is an intermediate color change from colorless to bright yellow which gradually changes to deep orange over a period of about 5 minutes. By this time the suspended Reissert compound has completely dissolved. Some minutes later the imine X begins to separate and is complete within 2 to 3 minutes. If the imine is allowed to remain in contact with the acid medium, an exothermic reaction takes place, converting it to the amide hydrobromide, the acid hydrobromide, and benzaldehyde.

The catalytic formation of this cyclic imine X appears to be instantaneous. If the temperature is maintained at 20°, the rate of reaction seems to depend on the solubility of the Reissert compound in the reaction medium; its subsequent precipitation may be compared to crystallization from a supersaturated solution. The breakdown of the imine X to benzaldehyde and the acid amide hydrobromide evolves heat and is favored by the catalytic medium of hydrobromic acid in acetic acid. No Reissert compound could be isolated from the mother liquors and the odor of benzaldehyde was absent. When the mother liquors were placed in the deep freeze at −10° for 24 hours some isoquinaldamide hydrobromide crystallized. We may assume that this amide hydrobromide was derived from a small amount of the imine which remained in solution since isoquinaldamide hydrobromide is much less soluble in the reaction medium than the cyclic imine X and would have been removed in the original filtration. The odor of benzaldehyde was apparent.[8]

When hydrochloric acid in acetic acid was used as the hydrolysis medium, the color changes and the time for complete solution were the same as in the case of hydrobromic acid in acetic acid. There was no odor of benzaldehyde or immediate precipitation of the imine hydrochloride. Addition of excess water did hot precipitate any unchanged Reissert compound. When the reaction mixture was allowed to stand overnight at room temperature, crystals were formed and there was still no evidence of the presence of benzaldehyde.[9]

The formation of Reissert imines from Reissert compounds appears to be a general reaction and under the proper conditions, particularly when acetic acid is used as solvent, only one equivalent of mineral acid is necessary. The experimental evidence presented below indicates that the acid-catalyzed hydrolysis of Reissert compounds proceeds as follows: Reissert compound → Reissert imine → acid amide + aldehyde + acid.

Or in the example studied here



When the hydrobromides of quinaldic and isoquinaldic acid are treated with thionyl chloride there is loss of hydrogen bromide with formation of the free acid chlorides. This route to the acid chlorides is preferred since a purer product is obtained and the necessity of passing through the anhydrous acids is eliminated.

The quinaldyl radical reacts readily with primary and secondary amino groups to give highly crystalline derivatives.[6,10] The isoquinaldyl radical may be used in like manner.

EXPERIMENTAL[11]

2-Benzoyl-1,2-dihydroisoquinaldonitrile, II. This compound was prepared according to the procedure of Reissert as modified by Padbury and Lindwall.[12] The yield from isoquinoline[13] was approximately 50% after two crystallizations from absolute ethanol. The product melted at 125–126°.

Reissert imine X. *Action of hydrobromic acid–acetic acid on* II. Ten g. of 2-benzoyl-1,2-dihydroisoquinaldonitrile, II (R = benzoyl), as prepared above were suspended in 100 ml. of glacial acetic acid and the mixture stirred vigorously while cooled in a water bath at 20°. Ten ml. of 47% hydrobromic acid were added. After about 5 min. all of the solid had dissolved and the solution was dark orange. The stirring

(7) Since this appears to be a general reaction leading to a new series of compounds, for convenience we will call them "Reissert imines."

(8) The imine will decompose quantitatively when treated with the sulfuric acid solution of 2,4-dinitrophenylhydrazine, giving benzaldehyde 2,4-dinitrophenylhydrazone, the acid amide and acid.

(9) The isolation of the several mineral acid salts of Reissert compounds derived from quinoline, isoquinoline, ring-substituted quinolines, and ring-substituted isoquinolines will be presented in a future communication.

(10) The application of the several ring-substituted acid chlorides, particularly the 2- and 5-nitro derivatives, to the identification of primary and secondary amino compounds will be presented at a later date. It is interesting to note that some of the amide derivatives of quinoline inhibit the growth of Ehrlich Ascites tumor in mice with prolongation of life. Of particular interest was quinaldylalanine which showed a T/C of 0.09 (unpublished data).

(11) All melting points are uncorrected. The analyses were performed by Dr. Elek of Los Angeles, Calif., and Drs. Weiler and Strauss of Oxford, England.

(12) J. J. Padbury and H. G. Lindwall, *J. Am. Chem. Soc.*, **67**, 1268 (1945).

(13) The isoquinoline was obtained from Eastman Kodak and melted at 26–27°.

was continued and after about 3 min. the imine X began to separate. Stirring was continued for several minutes more after which the bright yellow crystals were collected on a glass centered funnel and washed with glacial acetic acid until the washings were almost colorless. The crystals were washed with ether and dried in vacuum over sodium hydroxide. The product weighed 12.5 g. and melted at 158–160°. On recrystallization from hot methanol there was obtained 9.0 g. of pale yellow prismatic needles which melted at 159–160°. A recrystallized sample was dried in vacuum over phosphorus pentoxide at 80° for 24 hr.

Anal. Calcd. for $C_{17}H_{15}ON_2HBr$.C, 59.65; H, 4.09; Br, 23.39; N, 8.18. Found: C, 59.70; H, 4.01; Br, 23.31; N, 8.21.

Action of hydrobromic acid–acetic acid on the Reissert imine X. A 13.4-g. sample of the imine was suspended in 10 ml. of 48% hydrobromic acid in 10 ml. of glacial acetic acid. the flask was set up to reflux and heated on a steam bath for 10 min. On cooling, 50 ml. of acetone was added and the crystals were collected and washed with acetone. On air drying the product weighed 9.0 g. The filtrate and washings were combined (Solution A) and worked up as described below. The 9 g. of material was suspended in 75 ml. of hot methanol and water added until all had dissolved. On refrigeration overnight 3 g. of light yellow crystals was obtained which melted at approximately 260°. [The mother liquors were saved (Solution B).] On recrystallization from 75% acetic acid or ethanol–isopropyl ether approximately 2.5 g. of colorless needles was obtained which melted at 272–273°. The analytical sample melted at 275–276°.

Anal. Calcd. for $C_{10}H_8ON_2Br$. C, 47.43; H, 3.55; Br, 31.59; N, 11.07. Found: C, 47.56; H, 3.88; Br, 31.10; N, 11.38.

This compound was found to be identical with the hydrobromide of isoquinaldamide. It sublimes at 250° without decomposition and when treated with aqueous ammonia gives isoquinaldamide which melts at 167–168°.

The mother liquors (Solution B) were evaporated to dryness to give approximately 6 g. of a light yellow solid. This was recrystallized from 85% acetic acid to give almost colorless needles which melted at 199–200°. A recrystallized sample dried over phosphorus pentoxide at 80° for 24 hr. was analyzed.

Anal. Calcd. for $C_{10}H_9O_2BrN$. C, 47.10; H, 3.14; N, 5.51; Br, 31.40. Found: C, 47.32; H, 3.32; N, 5.47; Br, 30.81. This was found to be identical with the hydrobromide of isoquinaldic acid. It may be sublimed at about 100° and 1 mm. pressure.

The original acetone-acid mother liquors (Solution A) were steam distilled. From the distillate was isolated an 85% yield of redistilled benzaldehyde.[14]

Action of water on the Reissert imine X. One g. of the cyclic imine X was suspended in 25 ml. of water and the mixture stirred for 30 min. There was no evidence of decomposition or odor of benzaldehyde. The crystals were collected by filtration and dried in a desiccator under vacuum. About 90% of the material was recovered and had a melting point of 159–160° identical with that of the starting imine X. A mixture of the two gave the same melting point. The same reaction was repeated with refluxing for 30 min. with similar results.

Isoquinaldic acid from isoquinaldic acid hydrobromide. Due to the difference in solubility of quinaldic acid and isoquinaldic acid, the latter could not be isolated in comparable yields as previously described for quinaldic acid.[6] The following procedure was therefore used for the isolation:

Ten g. of isoquinaldic acid hydrobromide (crystallized from a 1:1 mixture of 48% hydrobromic acid and glacial acetic acid) was dissolved in 20 ml. of water and a slight excess of concentrated ammonium hydroxide added. The resulting solution was boiled to remove excess ammonia and after cooling adjusted to *p*H5 with hydrochloric acid. The mixture was evaporated under reduced pressure and the residue extracted with hot benzene. On concentration and cooling isoquinaldic acid crystallized. The yield of recrystallized acid melting at 159–160° was 5.8 g. or approximately 85%.

Quinaldyl chloride from quinaldic acid hydrobromide. Ten g. of quinaldic acid hydrobromide[15] were suspended in 100 ml. of thionyl chloride[16] contained in an apparatus set up to reflux and protected from moisture by means of a calcium chloride tube. The flask was warmed gently at first, the temperature being gradually increased so that hydrogen chloride passed smoothly through the top of the condenser. After the hydrobromide had dissolved, the solution was refluxed for an additional 0.5 hr. (total 3.5 hr.). The thionyl chloride was removed under reduced pressure and the pale yellow crystals were taken up in approximately 50 ml. of hot anhydrous ether. On cooling in the refrigerator overnight clusters of pale yellow needles were obtained which melted at 95–96°. A mixed melting point with an authentic sample was essentially the same. The conversion is quantitative but only when the acid hydrobromide is anhydrous. When the hydrated form is used approximately 25% of the material does not dissolve in ether. This is probably due to the formation of the acid chloride hydrochloride. The same result occurs when the free hydrated acid is used to prepare the acid chloride.

VAN NUYS, CALIF.

(14) A dark oily material remained in the flask after completion of the steam distillation. This material has been described previously [see ref. 1. Also see A. Reissert, *Ber.*, **38**, 3415 (1905)].

(15) Dried in a vacuum oven at approximately 100° for 3 hr.

(16) Distilled from linseed oil.

[CONTRIBUTION FROM THE ORGANIC RESEARCH DIVISION OF THE U. S. VITAMIN AND PHARMACEUTICAL CORPORATION]

Guanamines.[1] III. Perfluoroalkylguanamines and Related Compounds

SEYMOUR L. SHAPIRO, VINCENT A. PARRINO, AND LOUIS FREEDMAN

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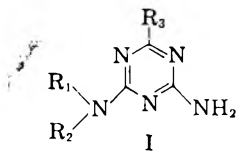
A series of guanamines of type I has been synthesized for pharmacological evaluation. The ultraviolet absorption spectra of a selected series of these compounds have been determined and are discussed.

Our investigation of guanamine derivatives[1] is extended to triazines of type I which have been



I

R_3 = —CF_3, —C_2F_5, —C_3F_7, —$CFCl_2$, —$CHBr_2$

prepared for pharmacological study,[2] particularly as anti-bacterial[3] and anti-viral agents.[4] The compounds which have been prepared[5,6,7] are described in Table I.

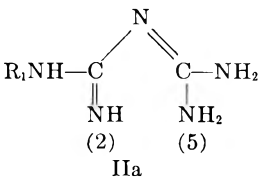
The synthesis of the required guanamines I was effected by reaction of the biguanide[8] with the appropriate ethyl ester.

While reaction of phenyl biguanide with ethyl trichloroacetate gave virtually only I, R_3 = OH, R_1 = C_6H_5—, R_2 = H and merely traces of I, R_3 = —CCl_3, R_1 = C_6H_5—, R_2 = H, it is relevant that none of the variants of R_3 employed in this study gave any of I, R_3 = OH compounds.[9]

Distinctions in the nature of the reactivity of ethyl trichloroacetate and ethyl trifluoroacetate have been noted by others.[10]

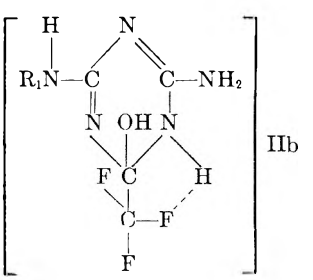
In this system the selectivity of reactivity of the ethyl trichloroacetate may be a function of steric factors.

From other studies[11] it would appear that the active species for the biguanide in methanol would be associated with a form IIa which could react with



IIa

the ester $R_3COOC_2H_5$ at N^2 or N^5 to give the acylated intermediate. Either acylated form in turn undergoes nucleophilic attack by the alternative nitrogen with proton transfer to give IIb (R_3 = —CF_3)[12] which permits *trans* elimination of water



IIb

and isolation of I, R_3 = CF_3.

In turn, the ester R_3 = —CCl_3 could give the transition state intermediate IIc with elimination of chloroform and isolation of I, R_3 = OH.

(1) (a) Paper I of this series, S. L. Shapiro, V. A. Parrino, K. Geiger, S. Kobrin, and L. Freedman, *J. Am. Chem. Soc.*, **79**, 5064 (1957); (b) paper II, S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3996 (1959).

(2) A. F. Lindenstruth, J. H. Fellman, and C. A. VanderWerf, *J. Am. Chem. Soc.*, **72**, 1886 (1950).

(3) H. M. Walborsky, M. Baum, and D. F. Loncrini, *J. Am. Chem. Soc.*, **77**, 3637 (1955).

(4) W. Cutting and A. Furst, *Antibiotics & Chemotherapy*, **8**, 441 (1958).

(5) A variety of papers and patents have described 2,4,6-trisperhaloalkyltriazines; (a) E. T. McBee, O. R. Pierce, and R. O. Bolt, *Ind. Eng. Chem.*, **39**, 391 (1947); (b) E. Ghigi, *Gazz. chim. ital.*, **71**, 641 (1941); (c) D. D. Coffman, U. S. Patent **2,442,995** (June 8, 1948); (d) G. W. Rigby, U. S. Patent **2,484,528**, (Oct. 11, 1949); (e) T. R. Norton, *J. Am. Chem. Soc.*, **72**, 3527 (1950); (f) T. L. Cairns, A. W. Larchar, and B. C. McKusick, *J. Am. Chem. Soc.*, **74**, 5633 (1952); (g) E. Kober and C. Grundmann, *J. Am. Chem. Soc.*, **81**, 3769 (1959).

(6) For I. R_1 = C_6H_5, R_2 = H, R_3 = —CCl_3, see S. L. Shapiro and C. G. Overberger, *J. Am. Chem. Soc.*, **76**, 97 (1954).

(7) Since the completion of our work, W. F. Cockburn and R. A. B. Bannard, *Can. J. Chem.*, **35**, 1285 (1957), have reported on several analogs of I (see Table I).

(8) The biguanides used as initial reactants have been previously described; (a) S. L. Shapiro, V. A. Parrino, E. Rogow, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3725 (1959); (b) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3728 (1959).

(9) (a) A. Kreutzberger, *J. Am. Chem. Soc.* **79**, 2629 (1957) observed that the —CCl_3 group attached to the triazine ring is readily removed as chloroform in nucleophilic displacements using ammonia, amines, water or ethanol, with ethanol being the most powerful nucleophile; (b) S. Birtwell and G. J. Stacey, U. S. Patent **2,830,052** (April 8, 1958), obtained guanamines of the class R_3 = —CCl_3 upon reaction of biguanides with trichloroacetic anhydride.

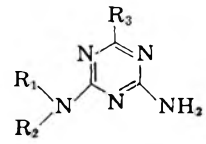
(10) (a) M. M. Joullié, *J. Am. Chem. Soc.*, **77**, 6662 (1955); (b) M. M. Joullié and A. R. Day, **76**, 2990 (1954), found that ethyl trichloroacetate reacts with secondary amine to give the urethane with elimination of chloroform.

(11) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 2220 (1959).

(12) For somewhat similar hydrogen bonding in chloral hydrate, see B. Stehlík and A. Tháč, *Chem. Zvesti*, **3**, 164 (1949) [*Chem. Abstr.*, **44**, 7218° (1950)].

TABLE I

GUANAMINES



No.	R_1	R_2	M.P.[a]	RS[b]	Yield, %	Formula	Analyses[c] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
	R_3 = —$CFCl_2$											
1	CH_3—	CH_3—	187–190	A	68	$C_6H_8Cl_2FN_5$	30.0	30.2	3.4	3.5	29.2	29.2
2	C_3H_5—[d]	H	105–107	A	64	$C_7H_8Cl_2FN_5$	33.4	33.3	3.2	3.2	27.8	28.0
3	*i*-C_5H_{11}—	H	132–134	B	32	$C_9H_{14}Cl_2FN_5$	38.3	38.6	5.0	5.0	24.8	25.0
4	—$(CH_2)_5$—		159–162	A	20	$C_9H_{12}Cl_2FN_5$	38.6	38.8	4.3	4.4	25.0	24.8
5	C_6H_{11}—[e]	H	133–135	A	85	$C_{10}H_{14}Cl_2FN_5$	41.8	42.0	4.8	5.1	23.8	24.0
6	$C_6H_5CH_2CH_2$—	H	118–120	A	66	$C_{12}H_{12}Cl_2FN_5$	45.6	45.8	3.8	4.0	22.2	22.0
7	C_6H_5—	H	178–179	A	42	$C_{10}H_8Cl_2FN_5$	41.7	41.8	2.8	2.9	24.3	24.0
8	2-CH_3—C_6H_4—	H	179–182	B	27	$C_{11}H_{10}Cl_2FN_5$	43.7	44.3	3.3	3.5	23.2	23.0
9	3-CH_3—C_6H_4—	H	119–125	B	8	$C_{11}H_{10}Cl_2FN_5$	43.7	44.3	3.3	3.5	23.2	23.2
10	4-CH_3—C_6H_4—	H	153	A	58	$C_{11}H_{10}Cl_2FN_5$	43.7	43.7	3.3	4.5	23.2	23.2
11	2,3-di-CH_3—C_6H_3—	H	178–180	A	12	$C_{12}H_{12}Cl_2FN_5$	45.6	45.8	3.8	3.7	22.2	22.3
12	2,4-di-CH_3—C_6H_3—	H	211–212	A	27	$C_{12}H_{12}Cl_2FN_5$	45.6	45.9	3.8	3.9	22.2	22.0
13	2,5-di-CH_3—C_6H_3—	H	152–163	C	22	$C_{12}H_{12}Cl_2FN_5$	45.6	46.0	3.8	4.0	22.2	21.7
14	2,6-di-CH_3—C_6H_3—	H	207–209	D	30	$C_{12}H_{12}Cl_2FN_5$	45.6	45.5	3.8	4.3	22.2	21.7
15	2-C_2H_5—C_6H_4—	H	144–145	C	38	$C_{12}H_{12}Cl_2FN_5$	45.6	46.1	3.8	3.9	22.2	22.2
16	—C_6H_4—CH_2—CH_2—[f]		211–213	A	38	$C_{12}H_{10}Cl_2FN_5$	45.9	46.2	3.2	3.4	22.3	22.4
17	2-CH_3—C_6H_4—	C_2H_5—	95– 99	C	42	$C_{13}H_{14}Cl_2FN_5$	47.3	47.4	4.3	4.1	21.2	21.2
18	4-CH_3—C_6H_4—	C_2H_5—	143–144	A	26	$C_{13}H_{14}Cl_2FN_5$	47.3	47.2	4.3	4.4	21.2	21.2
19	3-Cl—C_6H_4—	H	165–168	A	29	$C_{10}H_7Cl_3FN_5$	37.2	37.5	2.2	2.5	21.7	22.3
20	3-Br—C_6H_4—	H	166–168	C	32	$C_{10}H_7BrCl_2FN_5$	32.7	33.2	1.9	2.5	19.1	18.9
21	2-CH_3—3-Cl—C_6H_3—	H	172–173	A	17	$C_{11}H_9Cl_3FN_5$	39.3	40.0	2.7	2.7	20.8	20.2
22	2-CH_3—4-Cl—C_6H_3—	H	179–181	A	23	$C_{11}H_9Cl_3FN_5$	39.3	39.5	2.7	3.0	20.8	21.1
23	2-CH_3—5-Cl—C_6H_3—	H	168–170	E	16	$C_{11}H_9Cl_3FN_5$	39.3	39.1	2.7	2.1	20.8	21.0
24	2-CH_3—4-Br—C_6H_3—	H	182–184	A	27	$C_{11}H_9BrCl_2FN_5$	34.7	35.1	2.4	2.6	18.4	18.2
25	3,4-di-Cl—C_6H_3—	H	171–172	A	30	$C_{10}H_6Cl_4FN_5$	33.6	33.9	1.7	1.8	19.6	19.3
26	2-CH_3—5-OH—C_6H_3—	C_2H_5—	231–233	E	29	$C_{13}H_{15}Cl_2FN_5O$	45.0	45.2	4.4	4.5		
27	2,5-di-CH_3O—C_6H_3—	H	184–185	A	17	$C_{12}H_{12}Cl_2FN_5O_2$	41.4	41.8	3.5	3.5	20.1	20.5
28	R_3 = —CF_3 CH_3—	CH_3—	154–156	C	50	$C_6H_8F_3N_5$					33.8	33.8
29	C_3H_5—[d]	H	116–118	C	36	$C_7H_8F_3N_5$	38.4	38.5	3.7	4.1	32.0	32.0
30[g]	—$(CH_2)_5$—		156–158	A	40	$C_9H_{12}F_3N_5$	43.7	43.9	4.9	5.5	28.3	28.0
31[h]	C_6H_{11}—[e]	H	157–161	A	65	$C_{10}H_{14}F_3N_5$	46.0	46.4	5.4	5.6	26.8	26.9
32	$C_6H_5CH_2CH_2$—	H	159–161	C	65	$C_{12}H_{12}F_3N_5$	50.9	51.4	4.3	4.5	24.7	24.8
33	C_6H_5—	H	183–185	B	27	$C_{10}H_8F_3N_5$					27.4	28.0
34	3-CH_3—C_6H_4—	H	150–152	C	32	$C_{11}H_{10}F_3N_5$	49.1	49.3	3.7	4.2	26.0	26.1

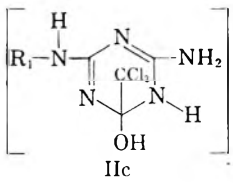
TABLE I (*Continued*)

No.	R_1	R_2	M.P.[a]	RS[b]	Yield, %	Formula	Analyses[c] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
35	4-CH_3—C_6H_4—	H	185–187	A	44	$C_{11}H_{10}F_3N_5$	49.1	49.4	3.7	4.1	26.0	25.7
36	2,3-di-CH_3—C_6H_3—	H	203–205	A	34	$C_{12}H_{12}F_3N_5$					24.7	25.0
37	2,4-di-CH_3—C_6H_3—	H	219–221	A	36	$C_{12}H_{12}F_3N_5$	50.9	51.2	4.3	4.5	24.7	25.0
38	2,6-di-CH_3—C_6H_3—	H	222–224	A	32	$C_{12}H_{12}F_3N_5$	50.9	51.2	4.3	4.3	24.7	23.5
39[f]	2-C_2H_5—C_6H_4—	H	172–173	C	34	$C_{12}H_{12}F_3N_5$	50.9	51.0	4.3	4.4	24.7	24.7
40	2-CH_3—C_6H_4—	C_2H_5—	89–97	C	44	$C_{13}H_{14}F_3N_5$	52.5	52.9	4.7	5.4	23.6	24.0
41	4-CH_3—C_6H_4—	C_2H_5—	136–138	A	18	$C_{13}H_{14}F_3N_5$	52.5	53.2	4.7	4.9	23.6	23.7
42	3-Cl—C_6H_4—	H	166–169	C	42	$C_{10}H_7ClF_3N_5$	41.5	41.8	2.4	2.6	24.2	24.2
43	3-Br—C_6H_4—	H	149–151	C	20	$C_{10}H_7BrF_3N_5$					21.0	20.8
44	2-CH_3—5-Cl—C_6H_3— R_3 = —C_2F_5	H	207–209	A	23	$C_{11}H_6ClF_3N_5$					23.1	23.0
45	CH_3—	CH_3—	178–180	A	40	$C_7H_8F_5N_5$	32.7	33.1	3.1	3.4	27.2	27.2
46	C_3H_5—[d]	H	112–114	C	48	$C_8H_8F_5N_5$	35.7	35.7	3.0	3.5	26.0	25.8
47	—$(CH_2)_5$—		130–131	A	51	$C_{10}H_{12}F_5N_5$					23.6	23.9
48[j]	$C_6H_5CH_2CH_2$—	H	106–108	C	45	$C_{13}H_{12}F_5N_5$	46.8	47.2	3.6	4.0	21.0	20.8
49	C_6H_5—	H	184–185	B	39	$C_{11}H_8F_5N_5$	43.3	43.2	2.6	2.9	22.9	23.2
50[k]	3-CH_3—C_6H_4—	H	159–161	A	28	$C_{12}H_{10}F_5N_5$	45.1	45.4	3.2	3.2	21.9	22.0
51	4-CH_3—C_6H_4—	H	180–181	A	38	$C_{12}H_{10}F_5N_5$					21.9	22.2
52	2,3-di-CH_3—C_6H_3—	H	176–182	A	22	$C_{13}H_{12}F_5N_5$	46.8	47.3	3.6	4.2	21.0	21.0
53[l]	2,4-di-CH_3—C_6H_3—	H	175–176	C	21	$C_{13}H_{12}F_5N_5$	46.8	47.0	3.6	4.0	21.0	21.0
54	2,5-di-CH_3—C_6H_3—	H	150–153	C	24	$C_{13}H_{12}F_5N_5$	46.8	47.0	3.6	4.0	21.0	21.0
55[m]	2,6-di-CH_3—C_6H_3—	H	190–191	A	10	$C_{13}H_{12}F_5N_5$	46.8	46.7	3.6	4.1	21.0	21.1
56	2-CH_3—C_6H_4—	C_2H_5—	109–111	C	43	$C_{14}H_{14}F_5N_5$	48.4	48.5	4.1	4.4	20.2	20.2
57	4-CH_3—C_6H_4—	C_2H_5—	143–145	A	28	$C_{14}H_{14}F_5N_5$	48.4	48.6	4.1	4.5	20.2	19.7
58	3-Cl—C_6H_4—	H	117–119	C	31	$C_{11}H_7ClF_5N_5$					20.6	21.0
59	3-Br—C_6H_4—	H	131–134	C	29	$C_{11}H_7BrF_5N_5$					18.2	17.8
60	2-CH_3—4-Cl—C_6H_3— R_3 = —C_3F_7	H	166–169	D	43	$C_{12}H_9ClF_5N_5$					19.8	20.1
61	CH_3—	CH_3—	151–153	C	54	$C_8H_8F_7N_5$	31.3	31.7	2.6	2.8	22.8	22.8
62	C_3H_5—[d]	H	101–103	C	47	$C_9H_8F_7N_5$	33.9	34.4	2.5	3.1	21.9	21.8
63	—$(CH_2)_5$—		136–137	A	49	$C_{11}H_{12}F_7N_5$	38.1	38.4	3.5	4.3	20.2	19.7
64	C_6H_{11}—[e]	H	65–68	A	55	$C_{12}H_{14}F_7N_5$	39.9	40.3	3.9	4.1	19.4	19.2
65	$C_6H_5CH_2CH_2$—	H	112–114	A	31	$C_{14}H_{12}F_7N_5$	43.9	43.9	3.2	3.1	18.3	17.9
66	C_6H_5—	H	122–124	B	29	$C_{12}H_8F_7N_5$	40.6	40.8	2.3	2.5	19.7	20.2
67[n]	3-CH_3—C_6H_4—	H	105–107	A	19	$C_{13}H_{10}F_7N_5$					19.0	18.9
68[o]	2,3-di-CH_3—C_6H_3—	H	158–159	B	29	$C_{14}H_{12}F_7N_5$	43.9	44.3	3.2	3.6	18.3	18.2
69	2,6-di-CH_3—C_6H_3—	H	185–188	D	22	$C_{14}H_{12}F_7N_5$	43.9	44.5	3.2	3.4	18.3	18.4
70	2-CH_3—C_6H_4—	C_2H_5—	96–98	C	30	$C_{15}H_{14}F_7N_5$	45.3	45.5	3.6	3.8	17.6	17.8
71	4-CH_3—C_6H_4—	C_2H_5—	112–114	A	27	$C_{15}H_{14}F_7N_5$	45.3	45.3	3.6	3.7	17.6	17.7
72	3-Cl—C_6H_4—	H	132–134	C	49	$C_{12}H_7ClF_7N_5$	37.0	37.0	1.8	2.3	18.0	18.2
73	3-Br—C_6H_4—	H	129–130	C	36	$C_{12}H_7BrF_7N_5$					16.1	15.9
74	2-CH_3—4-Cl—C_6H_3—	H	122–124	D	25	$C_{13}H_9ClF_7N_5$	38.7	38.7	2.2	2.9	17.3	17.2
75	2-CH_3—5-Cl—C_6H_3— R_3 = —$CHBr_2$	H	151–153	C	31	$C_{13}H_9ClF_7N_5$	38.7	38.9	2.2	2.3	17.4	17.0
76	CH_3—	CH_3—	196–198	E	56	$C_6H_9Br_2N_5$	23.2	23.5	2.9	3.4	22.5	22.6

TABLE I (*Continued*)

No.	R_1	R_2	M.P.[a]	RS[b]	Yield, %	Formula	Analyses[c] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
77	C_3H_5—[d]		145–147	A	60	$C_7H_9Br_2N_5$	26.0	26.3	2.8	2.6	21.7	22.0
78	—$(CH_2)_5$—		184	A	54	$C_9H_{13}Br_2N_5$	30.8	30.3	3.7	4.0	20.0	19.9
79	$C_6H_5CH_2CH_2$—	H	114–116	F	52	$C_{12}H_{13}Br_2N_5$	37.2	37.7	3.4	3.8	18.1	17.7
80	C_6H_5—	H	165–168	A	38	$C_{10}H_9Br_2N_5$	33.5	33.7	2.5	2.6	19.5	19.7
81	3-CH_3—C_6H_4—	H	183–185	A	23	$C_{11}H_{11}Br_2N_5$					18.8	18.9
82	2,3-di-CH_3—C_6H_3—	H	179–180	A	32	$C_{12}H_{13}Br_2N_5$	37.2	37.6	3.4	3.7	18.1	18.2
83	2,4-di-CH_3—C_6H_3—	H	183–185	A	4	$C_{12}H_{13}Br_2N_5$	37.2	37.2	3.4	3.7	18.1	18.2
84	2,6-di-CH_3—C_6H_3—	H	227–228	E	5	$C_{12}H_{13}Br_2N_5$	37.2	37.4	3.4	3.8	18.1	17.8
85[p]	2-C_2H_5—C_6H_4—	H	173–174	A	25	$C_{12}H_{13}Br_2N_5$	37.2	37.3	3.4	3.6	18.1	18.3
86	2-CH_3—C_6H_4—	C_2H_5—	133–136	C	40	$C_{13}H_{15}Br_2N_5$	38.9	39.4	3.8	3.8	17.5	17.0
87	4-CH_3—C_6H_4—	C_2H_5—	142–144	A	26	$C_{13}H_{15}Br_2N_5$	38.9	39.4	3.8	4.5	17.5	16.9
88[q]	3-Cl—C_6H_4—	H	146–148	A	17	$C_{10}H_8Br_2ClN_5$					17.8	18.3
89	2-CH_3—4-Cl—C_6H_3—	H	175–176	A	27	$C_{11}H_{10}Br_2ClN_5$					17.2	17.5

[a] Melting points are not corrected. [b] RS = recrystallizing solvent: A = acetonitrile; B = benzene; C = acetonitrile-water; D = isopropyl alcohol; E = propanol; F = ethanol. [c] Analyses by Weiler and Strauss, Oxford, England. [d] C_3H_5— = allyl. [e] C_6H_{11}— = cyclohexyl. [f] —$C_6H_4CH_2CH_2$— with attached *N* is 1-indolinyl. [g] Ref. 7 reports m.p. 160°. [h] Ref. 7 reports m.p. 165–168°. [i] The initially isolated compound was an equimolar complex of compound 39 and the reactant biguanide, m.p. 133–135° (benzene). *Anal.* Calcd. for $C_{22}H_{27}F_3N_{10}$: C, 54.1; H, 5.6; N, 28.7. Found: C, 54.3; H, 5.5; N, 29.2. On treatment with boiling water the product (insoluble) is obtained. [j] The picrate melted 155–156° (propanol). *Anal.* Calcd. for $C_{19}H_{15}F_3N_8O_7$: C, 40.6; H, 2.7; N, 19.9. Found: C, 40.3; H, 3.1; N, 20.0. [k] Initially isolated as an equimolar complex with reactant biguanide, m.p. 129–135° (benzene). Not obtained analytically pure. Upon treatment with boiling water the biguanide component dissolved (and was identified as the dipicrate) and the insoluble portion dried and recrystallized as shown in the table afforded the product. [l] Equimolar complex with biguanide, m.p. 168–170° (acetonitrile) (see footnote *k*). [m] Equimolar complex with biguanide, m.p. 167–168° (acetonitrile). *Anal.* Calcd. for $C_{23}H_{27}F_9N_{10}$: C, 51.3; H, 5.1; N, 26.0. Found: C, 51.8; H, 5.5; N, 26.3 (see footnote *i*). [n] Equimolar complex with biguanide, m.p. 93–97° (benzene). *Anal.* Calcd. for $C_{22}H_{23}F_7N_{10}$; C, 47.2; H, 4.1. Found: C, 47.9; H, 4.7 (see footnote *k*). [o] Equimolar complex with biguanide, m.p. 134–137° (benzene). *Anal.* Calcd. for $C_{24}H_{27}F_7N_{10}$: N, 23.8. Found: N, 23.2 (see footnote *k*). [p] Equimolar complex with the reactant biguanide, m.p. 125–135° (benzene) (see footnote *k*). [q] An acceptable carbon-hydrogen analysis was not obtained. When a picrate derivative was made, it apparently dissociated on attempted recrystallization from water.



IIc

Paralleling the oxyalkylguanamine study,[8b] this series also showed molar complexes with the product I and the reactant biguanide (compounds 50, 53, 55, 67, 68, 85). The formation of such complexes was confined to R_1 = *ortho*- substituted or 3-methylphenyl. However, all variants of R_3 with the exception of R_3 = —$CFCl_2$ gave such complexes. These complexes were readily dissociated into the constituent biguanide and guanamine by boiling with water.

A number of effects are indicated by the ultraviolet absorption data (Table II), particularly in relation to spectra of triazines previously established.[1a,13]

When R_1 is phenyl, R_2 is hydrogen and R_3 is varied as perfluoroalkyl, the spectra parallel R_3 = —CH_2Cl while R_3 = —CCl_2F is virtually the same as R_3 = $CHCl_2$.[13] In turn, I as above, R_3 = —$CHBr_2$ shows a non-specific absorption suggestive of neither aniline type nor triazine type spectra.[1a]

Trial with molecular models indicates with selected conformations that *ortho* substituents on the R_1 phenyl group can interact sterically with the halogens on the R_3 group. In the instance where R_3 contains bromine even the *ortho* hydrogens of the R_1 phenyl group will interact, and consequently the phenyl group assumes a position noncoplanar with the triazine ring with the dibromomethyl compounds.

Another interesting effect is the bathochromic shift noted relative to R_3 = H[1a] using the R_3 substituents of this series with the alkylaminoguanamines. A shift of approximately 12 mμ is noted with the β-phenethyl compounds and approximately 10 mμ with the cyclohexyl compound. Moreover, a bathochromic effect is noted with the R_1R_2 substituted compounds in this series as, for example, in the piperidino structures (numbers 4, 30, 47, 63) and the dimethylamino structures (1, 45, 61) compared to the mono-substituted such as the allyl (2, 29) or the β-phenethyl (6, 32, 48, 65) and the cyclohexyl compounds (31, 64). While the extinction coefficients are relatively the same and also parallel those where R_3 = hydrogen, the λ_{max} for the di-substituted amino derivatives shows a bathochromic effect of approximately 5 mμ.

An additional effect is shown by the three characteristic spectral patterns with aryl structures:

1) Those which parallel the unsubstituted phenyl group with relatively hypsochromic absorption maxima and high extinction coefficients and which provide no steric hindrance to the coplanarity of the anilino group with the triazine ring.

2) Those showing essentially a shoulder type of absorption having a partial steric hindrance between the anilino group and the triazine ring. These include the structures throughout wherein R_1 is *o*-tolyl, 2,3-dimethylphenyl, *N*-ethyl; *p*-tolyl, and *o*-ethylphenyl (with the exception of compound 56).

3) Those with well defined specific absorption maxima, hypsochromic and hyperchromic to the R_1-alkyl substituted compounds with structures conventionally considered to have high steric hindrance about the anilino nitrogen.[8a] These include

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA[a,b]

No.[c]	λ max,[d] mμ	ε × 10^{-3}	No.[c]	λ max,[d] mμ	ε × 10^{-3}
1	282	3.33	42	253	18.5
				273–284	13.6
2	278	3.63			
			45	280	3.4
4	229	28.7			
	285	3.52	47	228	27.1
				282	3.48
6	278	3.74			
			48	275	4.03
7	255	20.4			
			49	254	18.5
8	267–287	3.32			
			51	254	19.1
10	254	19.2			
			52	263–275	6.1
11	260–280	6.01			
			55	272	4.72
14	270	4.35			
			56	274	4.51
15	n.s.a.[e]				
			58	251	18.2
17	276	4.56		276–282	11.7
19	255	20.6	61	280	3.46
	276–282	11.7			
			63	229	22.7
29	272	3.89		283	3.11
30	227	27.7	64	276	3.72
	280	3.8			
			65	278	4.01
31	217	28.5			
	272	3.69	66	254	18.5
32	273	4.0	68	258–278	6.32
33	254	18.3	69	272	4.79
35	255	17.7	70	272	4.52
	275–285	11.8			
			71	262–284	5.67
36	265–278	2.97			
			72	252	18.7
38	268	4.85		272–286	10.9
39	260–273	8.5	80	280–300	7.72
40	269	4.62	85	240–270	4.83
41	262–272	6.32	86	281	4.25

[a] The spectra were measured in methanol using a Beckman Model DK ultraviolet recording spectrophotometer. [b] The authors wish to thank M. Blitz and his staff for establishing the ultraviolet spectra. [c] The number corresponds to the compound number of Table I. [d] Where a range is shown, the data are for a shoulder and the ε value has been calculated at the center of the shoulder range. [e] n.s.a. = non-specific absorption.

(13) C. G. Overberger and S. L. Shapiro, *J. Am. Chem. Soc.*, 76, 1855 (1954).

compounds where R_1 = 2,6-dimethylphenyl (compounds 14, 38, 55, 69) and *N*-ethyl, *o*-tolyl (compounds 17, 40, 70, 86) as well as compound 56 mentioned above. Here, it is likely that there is no interaction between the substituted phenyl group, its attached nitrogen and the triazine ring and the noted spectrum would be largely a function of triazine absorption.[14]

The anti-bacterial and anti-fungal studies have been hampered by the relatively poor solubility of the compounds of Table I in aqueous systems at physiological *p*H values.

(14) For related observations, see (a) H. Lumbroso and R. Dabard, *Bull. soc. chim. France*, 749 (1959); (b) A. Arcoria, H. Lumbroso and R. Passerini, *Bull. soc. chim. France*, 754 (1959); (c) S. L. Shapiro, I. M. Rose, F. C. Testa, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 6498 (1959).

EXPERIMENTAL

Guanamines of Table I. These were prepared by the same general procedure.

A solution of 0.025 mole of the biguanide hydrochloride (or nitrate) in 25 ml. of methanol was treated with 24 ml. (0.05 mole) of 23% sodium methoxide in methanol followed by 0.025 mole of ester. The reaction mixture was maintained at 20° for 24–48 hr. and then decanted in 60 ml. of water. After 72 hr., the formed precipitate of product was separated, dried and recrystallized.

In those instances where analyses indicated that the isolated material was a complex with the reactant biguanide (compounds 50, 53, 55, 67, 68, 85), this complex was dissociated by a 2–3 hr. reflux in water. The biguanide dissolved in the hot water, and the insoluble guanamine was separated and recrystallized.

Acknowledgement. The authors wish to thank R. Levinton for the data on the anti-bacterial activity.

YONKERS 1, N. Y.

[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES OF THE U. S. VITAMIN AND PHARMACEUTICAL CORPORATION]

Guanamines.[1] IV. Pyridylguanamines

SEYMOUR L. SHAPIRO, VINCENT A. PARRINO, AND LOUIS FREEDMAN

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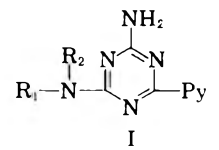
A series of 2-amino-4-substituted amino-6(2-, 3- and 4-pyridyl)-*s*-triazines has been synthesized and examined for pharmacological activity. Significant activity as antiinflammatory, analgesic, and diuretic agents has been noted with selected compounds.

Our investigations of guanamines with pharmacological activity are extended to pyridylguanamines of the type I.[2]

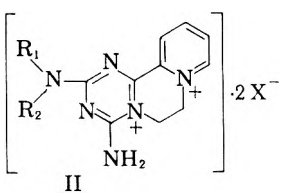


I

Py = 2-, 3-, and 4-pyridyl
R_1 = alkyl, alkenyl, aryl, substituted aryl
R_2 = hydrogen, alkyl
R_1R_2N = heterocyclic structures

The synthesis of the guanamines (Table I) was effected by reaction of the substituted biguanide in methanol with the appropriate pyridine carboxylic acid ester under sodium methoxide catalysis. Yields of product I were considerably better when R_1R_2N— was derived from aliphatic amines than from aryl amines. This may be associated with the formation of complexes between the product and the reactant biguanide,[1b,1c] and one such complex was isolated in this series. In selected instances (with arylbiguanides), the only isolable product was the nicotinic or isonicotinic acid salt of the biguanide.

Structures such as I, Py = 2-pyridyl, suggested chelation with iron and other metallic ions,[2d,3] and attempted preparation of bisquanternary structures of type II, as herbicides.[4]



II

The attempt to convert I, Py = 2-pyridyl, to the corresponding bisquaternary salt with ethylene dibromide yielded only unchanged reactant.

(1) For previous papers in this series, see (a) S. L. Shapiro, V. A. Parrino, K. Geiger, S. Kobrin, and L. Freedman, *J. Am. Chem. Soc.* **79**, 5064 (1957); (b) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3996 (1959); (c) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Org. Chem.*, **25**, 379 (1960).

(2) Compounds of type I have not been previously reported. For compounds having more than one pyridyl nucleus on the triazine ring, see (a) S. Saure, *Chem. Ber.*, **83**, 335 (1950); (b) H. J. Kahn, V. A. Petrow, R. Wien, and J. Harrison, *J. Chem. Soc.*, 858 (1945); (c) P. B. Russel and G. H. Hitchings, *J. Am. Chem. Soc.*, **72**, 4922 (1950); (d) F. H. Case and E. Koft, *J. Am. Chem. Soc.*, **81**, 905 (1959); for pyridylamino-*s*-triazine compounds, see (d) J. T. Thurston, U. S. Patent **2,474,194** (June 21, 1949); (e) W. O. Foye and A. E. Buckpitt, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 385 (1952).

(3) G. Maerker and F. H. Case, *J. Am. Chem. Soc.*, **80**, 2745 (1958).

(4) R. J. Fielden, R. F. Homer, and R. L. Jones, U. S. Patent **2,823,987** (Feb. 18, 1958).

TABLE I

PYRIDYLGUANAMINES,[h,j] I

No.	R_1	R_2	M.P., °C.[a,b]	Yield, %	Formula	Analyses[c] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
					Py = 3-pyridyl						
1	CH_3—	CH_3—	200–202[b1]	43	$C_{10}H_{12}N_6$					38.9	38.8
2	C_2H_5—[d]	H	148–149	44	$C_{11}H_{12}N_6$					36.8	37.2
3	*i*-C_5H_{11}—	H	120–123	45	$C_{13}H_{18}N_6$	60.4	60.3	7.0	7.0	32.5	32.6
4	—$(CH_2)_5$—		164–166	51	$C_{13}H_{16}N_6$	60.9	60.8	6.3	6.4	32.8	32.8
5	C_6H_{11}—[e]	H	155–157	43	$C_{14}H_{18}N_6$	62.2	62.2	6.7	6.8	31.1	30.8
6	$C_6H_5CH_2CH_2$—	H	154–155	45	$C_{16}H_{16}N_6$	65.7	65.6	5.5	5.8	28.8	28.6
7	C_6H_5—	H	217–218	19	$C_{14}H_{12}N_6$	63.6	63.6	4.6	4.7	31.8	31.9
8[f]	2-CH_3—C_6H_4	H									
9	3-CH_3—C_6H_4—	H	216–218[b2]	18	$C_{15}H_{14}N_6$	64.7	64.8	5.1	5.2	30.2	29.8
10	4-CH_3—C_6H_4—	H	200–201[b3]	35	$C_{15}H_{14}N_6$	64.7	64.8	5.1	4.8	30.2	30.4
11	2,3-di-CH_3—C_6H_3—	H	209–210[b4]	28	$C_{16}H_{16}N_6$					28.8	28.8
12	2,4-di-CH_3—C_6H_3—	H	194–195	27	$C_{16}H_{16}N_6$	65.7	65.7	5.5	5.6	28.8	28.7
13	2,5-di-CH_3—C_6H_3—	H	182–192[b5]	4	$C_{16}H_{16}N_6$	65.7	65.8	5.5	5.9	28.8	28.6
14	2,6-di-CH_3—C_6H_3—	H	204–205	31	$C_{16}H_{16}N_6$	65.7	65.5	5.5	5.6	28.8	28.8
15	2-C_2H_5—C_6H_4—	H	162–163	32	$C_{16}H_{16}N_6$	65.7	65.2	5.5	5.7	28.8	28.8
16	—$C_6H_4CH_2CH_2$—[g]		203–204[b2]	16	$C_{16}H_{14}N_6$	66.2	66.6	4.9	4.9	29.0	28.6
17	2-CH_3—C_6H_4—	C_2H_5—	146–148	37	$C_{17}H_{18}N_6$	66.6	66.9	5.9	5.9	27.4	27.0
18	4-CH_3—C_6H_4	C_2H_5—	183–185	31	$C_{17}H_{18}N_6$	66.6	67.0	5.9	6.1		
19	3-Br—C_6H_4—	H	213–215[b1]	19	$C_{14}H_{11}BrN_6$	49.0	48.7	3.2	3.7	24.5	25.0
20	2-CH_3-4-Cl—C_6H_3—	H	178–180	31	$C_{15}H_{13}ClN_6$	57.6	57.2	4.2	4.1		
21	2-CH_3-5-Cl—C_6H_3—	H	184–186	24	$C_{15}H_{13}ClN_6$	57.6	57.8	4.2	4.3	26.9	27.2
22	2,5-di-CH_3O—C_6H_3—	H	209–211	10	$C_{16}H_{16}N_6O_2$	59.3	59.2	5.0	5.0	25.9	26.2
					Py = 1 pyridyl						
23	CH_3—	CH_3—	229–231[b1]	45	$C_{10}H_{12}N_6$	55.5	55.7	5.6	6.0	38.9	38.5
24	C_2H_5—[d]	H	150–152	52	$C_{11}H_{12}N_6$	57.9	58.0	5.3	4.9		
25	*i*-C_5H_{11}—	H	155–156	45	$C_{13}H_{18}N_6$	60.4	60.1	7.0	6.8		
26	—$(CH_2)_5$—		170–173	58	$C_{13}H_{16}N_6$	60.9	60.9	6.3	6.2	32.8	33.0
27	C_6H_{11}—[e]	H	186–187	42	$C_{14}H_{18}N_6$	62.2	61.8	6.7	6.5		
28	$C_6H_5CH_2CH_2$—	H	173–174[b1]	50	$C_{16}H_{16}N_6$	65.7	65.5	5.5	5.8	28.8	29.0
29	C_6H_5—	H	211–213	40	$C_{14}H_{12}N_6$	63.6	63.8	4.6	4.5	31.8	32.2
30	3-CH_3—C_6H_4	H	208–210[b3]	41	$C_{15}H_{14}N_6$	64.7	64.8	5.1	5.3	30.2	30.0
31	4-CH_3—C_6H_4—	H	233–234[b3]	21	$C_{15}H_{14}N_6$	64.7	64.5	5.1	5.4	30.2	30.0
32	2,3-di-CH_3—C_6H_3—	H	183–187	9	$C_{16}H_{16}N_6$	65.7	65.4	5.5	5.7	28.8	28.8
33	2,4-di-CH_3—C_6H_3—	H	186–188	30	$C_{16}H_{16}N_6$	65.7	65.3	5.5	5.3		
34	2,5-di-CH_3—C_6H_3—	H	146–188	23	$C_{16}H_{16}N_6$	65.7	65.3	5.5	5.6	28.8	28.7
35	2,6-di-CH_3—C_6H_3—	H	202–203	10	$C_{16}H_{16}N_6$	65.7	65.9	5.5	5.5	28.8	28.4
36	2-C_2H_5—C_6H_4—	H	213–214	31	$C_{16}H_{16}N_6$	65.7	66.0	5.5	5.4	28.8	28.8
37	3-CH_3CHOH—C_6H_4—	H	189–190	12	$C_{16}H_{16}N_6O$	62.3	62.2	5.2	5.0		
38	—$(C_6H_4CH_2CH_2)$—[g]		230–231[b3]	22	$C_{16}H_{14}N_6$	66.2	66.1	4.9	5.0	29.0	29.2
39	2-CH_3—C_6H_4—	C_2H_5—	220–221[b3]	39	$C_{17}H_{18}N_6$	66.6	66.9	5.9	5.5	27.4	27.2

TABLE I (*Continued*)

No.	R_1	R_2	M.P. °C.[a,b]	Yield %	Formula	Analyses[c] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
40[f]	4-CH_3—C_6H_4—	C_2H_5—	170–171[b,r]	21	$C_{17}H_{18}N_6$	66.6	66.9	5.9	5.9	27.4	27.0
41	3-Cl—C_6H_4—	H	213–215[b,s]	22	$C_{14}H_{11}ClN_6$	56.3	56.4	3.7	3.7	28.1	28.0
42	3-Br—C_6H_4—	H	233–235[b,s]	25	$C_{14}H_{11}BrN_6$	49.0	48.7	3.2	3.5	24.5	24.6
43	2-CH_3-4-Cl—C_6H_3—	H	228–229[b,t]	29	$C_{15}H_{13}ClN_6$	57.6	57.7	4.2	4.1	26.9	27.2
44	2-CH_3-5-Cl—C_6H_3—	H	234–235[b,s]	26	$C_{15}H_{13}ClN_6$	57.6	57.7	4.2	4.4	26.9	27.1
45	2,5-di-CH_3O—C_6H_3—	H	238–239[b,s]	8	$C_{16}H_{16}N_6O_2$	59.3	59.4	5.0	4.9	25.9	25.7
				Py = 2-pyridyl							
46	CH_3—	CH_3—	238–240	43	$C_{10}H_{12}N_6$	55.5	55.5	5.6	5.8	38.9	38.8
47	*n*-C_5H_{11}—	H	148–150	62	$C_{13}H_{18}N_6$	60.4	60.9	7.0	6.9	32.5	32.7
48	C_6H_5—	H	234–235	30	$C_{14}H_{12}N_6$	63.6	64.1	4.6	4.7	31.8	31.6
49	2 CH_3—C_6H_4—	H	176–178	34	$C_{15}H_{14}N_6$	64.7	64.8	5.1	4.8	30.2	30.6
50	2,4-di-CH_3—C_6H_3—	H	189–191	29	$C_{16}H_{16}N_6$	65.7	65.2	5.5	5.7	28.8	29.1
51	2-CH_3—C_6H_4—	C_2H_5—	206–208	51	$C_{17}H_{18}N_6$	66.6	67.0	5.9	5.8	27.4	27.4
52	*p*-Cl—C_6H_4—	H	244–246	24	$C_{14}H_{11}ClN_6$	56.3	56.3	3.7	3.7	28.1	28.0
53	*p*-Cl—C_6H_4—	C_2H_5—	215–217	42	$C_{16}H_{15}ClN_6$	58.8	59.4	4.6	4.5	25.7	26.0
54	3-Br—C_6H_4—	H	183–184	29	$C_{14}H_{11}BrN_6$	49.0	49.4	3.2	3.5	24.5	24.2
55	5-Cl-2,4-di-CH_3O—C_6H_2—	H	246–250[b,s]	21	$C_{16}H_{15}ClN_6O_2$	53.6	53.9	4.2	4.4	23.4	24.0

[a] Melting points are not corrected. [b] Recrystallizing solvent is acetonitrile unless otherwise shown. [b,1] Ethanol. [b,2] Methanol. [b,3] Propanol. [b,4] Isopropyl alcohol. [b,5] Benzene. [b,6] Water. [b,7] Acetic acid–water. [c] Analyses by Weiler and Strauss, Oxford, England. [d] C_3H_5 = Allyl. [e] C_6H_{11} = Cyclohexyl. [f] Compound 8, R_1 = 2-CH_3—C_5H_4, gives compound biguanide complex, m.p. 141–145° (benzene). *Anal.* Calcd. for $C_{24}H_{27}N_{11}$: C, 61.4; H, 5.8; N, 32.8. Found: C, 60.7; H, 6.1; N, 31.9. The compound was identified by isolation of the picrate. [g] —$C_6H_4CH_2CH_2$— with attached nitrogen gives 1-indolino group. [h] The following compounds were characterized as their monopicrates:

Comp. No.	M.P., °C.[a,b]	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
2	220[b,3]	$C_{17}H_{15}N_9O_7$	44.6	44.6	3.3	3.0	27.6	27.6
8	209–211	$C_{21}H_{17}N_9O_7$	49.7	49.6	3.4	3.4	24.8	25.0
12	212	$C_{22}H_{19}N_9O_7$	50.7	51.0	3.7	3.9		
24	233[b,6]	$C_{17}H_{15}N_9O_7$	44.6	44.6	3.3	3.2	27.6	27.6

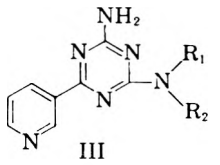
[i] It is of interest that recrystallization from aqueous acetic acid does not yield the acetic acid salt. The basicity of the compound is evidently too low to form acetic acid salts in aqueous media. [j] In the attempted preparation of the subject compounds, in the following instances the product isolated was the nicotinic acid salt of the reactant biguanide:

R_1	M.P., °C.[a,b]	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
3-Cl—C_6H_4—	188–189[b,3]	$C_{14}H_{15}ClN_6O_2$	50.2	50.5	4.5	4.3	25.1	25.2
2-CH_3-4-Br—C_6H_3—	192–195	$C_{16}H_{17}BrN_6O_2$	45.8	45.5	4.4	4.4		
3,4-di-Cl—C_6H_3—	228–250[b,3]	$C_{14}H_{14}Cl_2N_6O_2$	45.5	45.4	3.8	3.9		
2-CH_3-4-Br—C_6H_3—[k]	194–198[b,4]	$C_{15}H_{17}BrN_6O_2$	45.8	45.8	4.4	4.4	21.4	21.4

[k] Isonicotinic acid salt.

The 2-pyridyl guanamines gave colored solutions or precipitates with ferrous ion, whereas the 3- and 4-pyridyl compounds did not.

Since pyridylguanamines can be envisioned as derivatives of nicotinamide and isonicotinamide with the triazine ring supplying the carboxamide type function,[5] as shown for III,



III

a variety of pharmacological effects associated with these pyridine derivatives was evaluated.

No systematic pharmacological response was noted which would permit an analysis of structure *vs.* activity,[6] although in general, the most active structures were found with the alkylamino derivatives of I, Py = 3- and 4-pyridyl. Upon evaluation[7] the following compounds showed antiinflammatory activity: 7 (15 units/g.), 26 (4 units/g.); analgesic activity: 27 (33% at 75 mg./kg.), 28 (83% at 330 mg./kg.). Compounds 2 and 24 showed diuretic action in rats, and also lowered blood pressure significantly. Compound 17 had 4+ anticonvulsant activity associated with a negative Evipal sleeping time response.

(5) F. C. Schaefer, J. R. Dudley and J. T. Thurston, *J. Am. Chem. Soc.*, **73**, 3004 (1951).

(6) For pharmacological study of 5-(4-pyridyl)-3-amino-1,2,4-triazols, see K. Biemann and H. Bretschneider, *Monatsch. Chem.*, **89**, 603 (1958).

(7) The following screening techniques applied have been described. (a) Antiinflammatory activity: S. L. Shapiro, H. Soloway, and L. Freedman: *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 333 (1957); (b) analgesic: C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954); (c) anticonvulsant activity and Evipal sleeping time: S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 1648 (1958); also ref. 1b; (d) diuretic: see ref. 1a; (e) blood pressure: S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 2743 (1958).

EXPERIMENTAL

Reactants. The biguanides utilized in this study have been described.[8] Ethyl picolinate was prepared in 58% yield, b.p. 118–122° (14 mm.), following the procedure described for ethyl nicotinate.[9]

Pyridylguanamines of Table I. The compounds of Table I were prepared by the same general procedure. A solution of 0.025 mole of the biguanide hydrochloride (or nitrate) in 25 ml. of methanol was treated with 24 ml. (0.05 mole) of 23% sodium methoxide in methanol followed by 0.025 mole of the pyridine carboxylic acid ester. The reaction mixture was maintained at 20° for 24–48 hr. and then decanted into 60 ml. of water. After 72 hr., the precipitate was separated, dried, and recrystallized.

Color reactions. Ferrous ion (200 mg./l.)[10] gave brown solutions with compounds 46 and 47, and purple precipitates with compounds 48 and 52. Compound 53 did not react under these test conditions and may have been too insoluble. The 2-pyridylguanamines having an alkylamino substituent give a different color response from those with the arylamino substituent.

The related compounds (1, 2, 7, 18, 23, 29, 24, 40) in the 3- and 4-pyridyl series gave no color with ferrous ion under these conditions.

With cupric ion (500 mg./l.) a brown color was noted with compound 46, and when the hydroxylamine hydrochloride solution was not added, a green color was obtained. Compound 52 under similar conditions gave a brown and green precipitate, respectively.

Acknowledgment. The authors are indebted to Dr. G. Ungar and his staff for the pharmacological screening of the compounds.

YONKERS 1, N. Y.

(8) (a) S. L. Shapiro, V. A. Parrino, E. Rogow, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3725 (1959); (b) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3728 (1959).

(9) H. Gilman and H. S. Broadbent, *J. Am. Chem. Soc.*, **70**, 2755 (1948).

(10) The procedure used was adapted from *Official Methods of Analysis of the Association of Official Agricultural Chemists*, Association of Official Agricultural Chemists, Washington, D. C., 8th Ed., 1955, p. 208; using 1 ml. of test solution, 0.1 ml. of hydroxylamine hydrochloride solution, 0.5 ml. of acetate buffer solution and about 2 mg. of the pyridylguanamine, and heating to boiling.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

A Convenient Synthesis of *t*-Alkyl Esters of Amino Acids[1a]

ARNULF VOLLMAR AND MAX S. DUNN

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The preparation of *t*-alkyl esters of glycine, alanine and phenylalanine *via* the corresponding azido derivatives is described and some of the characteristics of the compounds are pointed out.

A convenient synthesis of *t*-alkyl esters of amino acids, desired for certain kinetic and microbiological investigations, is reported in this paper. Standard procedures for the preparation of amino acid esters of primary and secondary alcohols are well known and have been reviewed recently,[1b] but amino acid esters of *t*-alcohols are less readily accessible because of the lability of *t*-alcohols in acid media. Amino acid esters of *t*-alcohols should be of interest in peptide synthesis in view of their ready hydrolysis under mild acid conditions.

The *t*-butyl and trichloro-*t*-butyl esters of *N*,*N*-

dimethylglycine have been obtained through amination of the corresponding chloroacetates with dimethylamine[2,3]; Sheehan[4,5] prepared *t*-butyl 4-carboxy-5,5-dimethyl-α-amino-2-thiazolidine, an intermediate in the synthesis of penicillin by hydrazinolysis of the protective phthalyl group.

In the present work it was practicable to introduce the amino group by the hydrogenolytic reduction of azides, a method first described by Bertho and Maier,[6] who obtained glycine ethyl ester in 80% yield by the hydrogenolysis of ethyl azidoacetate with platinum oxide. More recently, Bretschneider *et al.*[7] prepared *O*-ethyl serine ethyl ester by this method. The bromo carbonic ester derivatives, required for the synthesis of azido carbonic esters, were prepared as colorless liquids by acylating *t*-alcohols with bromoacetyl bromide and α-bromopropionyl bromide. Minor acid-catalysed decomposition sometimes occurred during distillation of the esters, especially the high boiling *t*-amyl esters. Under such circumstances the *t*-esters were washed with potassium carbonate solution to remove traces of acids. Decomposition was minimal when the distillation was carried out at low pressure. The *t*-butyl ester of α-bromo-β-phenylpropionic acid was prepared by the addition of isobutylene to the acid.[8]

The azido derivatives, prepared by refluxing the bromo esters with sodium azide in aqueous acetone, distilled smoothly to give colorless liquids. These products may be stored without apparent change in the refrigerator but become yellow within a few days at room temperature. As alkyl azides[9] act to lower the blood pressure, azido esters may possess similar toxic properties.

The *t*-alkyl esters of amino acids, obtained by catalytic reduction of the azido group, were isolated in high yields, usually as the hydrochlorides. These salts melt at relatively high temperatures and are virtually non-hygroscopic. This is in contrast to the *n*-butyl, isobutyl, *n*-amyl, and isoamyl ester hydrochlorides of glycine[10] and alanine,[11] which are strongly deliquiescent, apparently because of coordination with water molecules.[12] It was advantageous to isolate glycine *sec*-butyl ester as the non-hygroscopic oxalate rather than the hygroscopic hydrochloride.

The azido esters showed characteristic infrared absorption at 2120 cm.$^{-1}$ and 1345–1353 cm.$^{-1}$ because of the asymmetrical and symmetrical vibrations of the N_3 group.[13]

Branched alkyl groups of alkanes show splitting of the band correlated with the methyl symmetrical deformation modes.[14] *t*-Butyl has two bands at 1397 and 1370 cm.$^{-1}$, 3,3-dimethylpropyl at 1384 and 1367 cm^{-1}.[15] In close accord with these results obtained from the alkanes the *t*-alkyl esters absorbed in the same range. The *t*-butyl esters absorb at 1393 and 1367 cm.$^{-1}$, the intensity of the second band being about twice as much as the first; the *t*-amyl esters absorb at 1383 and 1368 cm.$^{-1}$ with less intensity differences and can be distinguished thereby from the *t*-butyl esters.

Aqueous solutions of *t*-alkyl esters of amino acid hydrochlorides turn acid on standing a few hours at room temperature and this hydrolysis is accelerated by heating the solutions. The main products are alkenes and *t*-alcohols. *t*-Butyl alcohol was identified by its boiling point, refractive index, and 3,5-dinitrobenzoate as a product of the hydrolysis of glycine *t*-butyl ester hydrochloride.

Gordon *et al.*[16,17] studied the aminolysis of several series of esters varying the alkyl ester group. They found a decreasing reaction rate in the order of *n*-butyl, isobutyl, *sec*-butyl, and *t*-butyl and attributed that result to the increasing electron release effects as well as to steric hindrance. As the self-condensation of free amino acid esters[18,19] leading to peptide esters is also an ester aminolysis a similar order could be expected for the stability toward condensation. Glycine *t*-butyl ester is fairly stable when stored at 26°. After one week the refractive index had not changed and only traces of

(1) (a) Paper No. 131. This work was supported by grants from the American Cancer Society, the National Tuberculosis Association, the United States Public Health Service and the University of California. (b) Theodor Wieland *et al.*, "Methoden der organischen Chemie" (Houben-Weyl), ed. Eugen Mueller, Vol. XI/2, 4. Aufl., Thieme Verlag Stuttgart, 1958, p. 355.

(2) R. Wolffenstein, A. Loewy, and M. Bachstez, *Chem. Ber.*, **48**, 2035 (1915).

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TABLE I

PHYSICAL CONSTANTS AND ELEMENTARY ANALYSIS OF *t*-ALKYL ESTERS OF AMINO ACIDS AND RELATED COMPOUNDS

	B.P./Mm.	n_D^{25}	Yield, %	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
sec-Butyl bromoacetate[a]	80.5/17	1.4450	72	$C_6H_{11}BrO_2$	36.94	36.81	5.68	5.84		
t-Butyl bromoacetate[a]	62–63/12	1.4425	78	$C_6H_{11}BrO_2$	[b]					
t-Amyl bromoacetate[a]	84/16; 36/1	1.4486	74	$C_7H_{13}BrO_2$	40.21	40.08	6.27	6.17		
t-Butyl α-bromopropionate	62/13	1.4374	71	$C_7H_{13}BrO_2$	40.21	40.00	6.27	6.31		
t-Amyl α-bromopropionate	86–86/16; 36/1	1.4440	67	$C_8H_{15}BrO_2$	43.06	43.11	6.77	6.57		
sec-Butyl azidoacetate	89/17	1.4343	88	$C_6H_{11}N_3O_2$	45.84	45.93	7.05	6.97	26.73	26.54
t-Butyl azidoacetate	72–73/13; 79–80/18	1.4332	95	$C_6H_{11}N_3O_2$	45.84	45.56	7.05	7.04	26.73	26.49
t-Amyl azidoacetate	92/16; 44/1	1.4389	94	$C_7H_{13}N_3O_2$	49.10	49.04	7.65	7.41	24.54	24.63
t-Butyl α-azidopropionate	73/14	1.4251	91	$C_7H_{13}N_3O_2$	49.10	48.91	7.65	7.74	24.54	24.78
t-Amyl α-azidopropionate	92–93/17; 44/1	1.4327	93	$C_8H_{15}N_3O_2$	51.87	51.96	8.16	7.98		
sec-Butyl glycine oxalate	139° (m.p.)		71	$C_{14}H_{28}N_2O_8$	47.71	47.59	8.01	7.95		
t-Butyl glycinate	57/13; 68/21	1.4222	81	$C_6H_{13}NO_2$	54.93	55.17	9.99	9.81	10.68	10.96
t-Butyl glycinate hydrochloride	136° (m.p.)[c]		89	$C_6H_{14}ClNO_2$	42.98	42.92	8.41	8.38	8.35	8.47
t-Butyl glycinate oxalate	156° (m.p.)		76	$C_{14}H_{28}N_2O_8$	47.71	47.93	8.01	7.98		
t-Amyl glycinate	80.5/17; 35/1	1.4291	86	$C_7H_{15}NO_2$	57.90	57.86	10.41	10.44	9.64	9.54
t-Amyl glycinate hydrochloride	121° (m.p.)[c]		88	$C_7H_{16}ClNO_2$	46.28	46.24	8.87	8.71	7.71	7.91
t-Butyl DL-alaninate	58/13	1.4155	85	$C_7H_{15}NO_2$	57.90	58.08	10.41	10.57	9.64	9.88
t-Butyl DL-alaninate hydrochloride	144° (m.p.)[c]		90	$C_7H_{16}ClNO_2$	46.28	46.54	8.87	8.88	7.71	7.89
t-Amyl DL-alaninate	80.5/17	1.4235	83	$C_8H_{17}NO_2$	60.34	60.21	10.76	10.70		
t-Amyl DL-alaninate hydrochloride	135° (m.p.)[c]		89	$C_8H_{18}ClNO_2$	49.09	48.95	9.27	9.17	7.16	7.37

[a] Lachramatory. [b] See ref. 21. [c] The ester hydrochloride melts with decomposition with liberation of alkene and formation of residual amino acid hydrochloride.

peptides were revealed by paper chromatography. On the other hand the index of refraction of glycine isobutyl ester increased appreciably in a few hours, and the peptides formed after two days approximated those observed for a sample of glycine *t*-butyl ester stored for four months.

EXPERIMENTAL[20a]

Reagents. Bromoacetyl bromide, α-bromopropionyl bromide, *t*-butyl alcohol, *sec*-butyl alcohol, and *t*-amyl alcohol were Eastman's products. The alcohols were purified by fractional distillation. Dimethylaniline was dried over potassium hydroxide and distilled. Skelly B boiled at 60–70°.

t-Butyl bromoacetate. In a three-neck flask, fitted with a stirrer, a calcium chloride tube and a dropping funnel were placed 124 g. (1.02 mol.) dimethyl aniline, 74 g. (1 mol.) *t*-butyl alcohol and 165 ml. ether. A 200-g. sample (0.99 mol.) of bromoacetylbromide was run into the stirred solution within 1 hr. while the flask was cooled in an ice bath. Stirring was continued for 4 hr. at room temperature. The crystallized dimethylaniline hydrobromide was dissolved by addition of 150 ml. of water; the ether layer was treated with three 40-ml. portions of 10% sulfuric acid, then with sodium bicarbonate solution and water. The organic phase was dried over sodium sulfate and filtered. The ether was distilled through a Vigreux column and the ester was fractionated at reduced pressure. A 152-g. sample (78%) of colorless *t*-butyl bromoacetate, boiling at 69–70.5°/17–18 mm. was obtained. For the preparation of the *t*-amyl esters the ether was removed at slightly reduced pressure. The distillation of the *t*-amyl ester was carried out with the vacuum oil pump.

t-Butyl azidoacetate. To 39 g. (0.6 mol.) sodium azide in 150 ml. 60% (v/v) acetone were added 78 g. (0.4 mol.) *t*-butyl bromoacetate. Two phases were formed. The mixture was refluxed on a steam bath for 14 hr. The acetone was removed through a column. The oil was dissolved in 100 ml. ether and the aqueous phase was extracted with two 70-ml. portions of ether. The combined ether solutions were dried over anhydrous sodium sulfate and filtered. The ether was distilled through a column. Fractionation gave 60 g. (95%) azido ester, boiling at 79–80.5°/18 mm.

Glycine t-butyl ester hydrochloride. A 23.6-g. sample (0.15 mol.) of *t*-butyl azidoacetate, 200 ml. methanol, and 500 mg. palladium-charcoal (5% palladium) were placed in a 1 l. three-neck flask equipped with a condenser and a gas dispersion tube with fritted cylinder. Hydrogen was passed through the solution at room temperature for 10 hr., the mixture being stirred magnetically. The filtered solution was adjusted to *p*H 5.0 by slow addition of methanolic hydrogen chloride, the acidity being measured with a *p*H meter. The solution was evaporated under reduced pressure, 400 ml. ether added and the crystalline material stored overnight in the refrigerator. The product was filtered, washed with ether and dried over sulfuric acid in a desiccator; yield, 21.6 g. (90%). The hydrochloride can be recrystallized from cold chloroform-ether, chloroform-Skelly B or ethanol-ether.

Glycine t-butyl ester. A 16.7-g. sample (0.1 mol.) of glycine *t*-butyl ester hydrochloride was dissolved in 30 ml. methanol. Triethylamine 10.2 g. (0.1 mol.) and 400 ml. ether were added. After standing overnight in the refrigerator, the tri-

(20) (a) Each synthesis is typical of that used to prepare the compounds listed in Table I. (b) R. Grewe, *Chem. Ber.*, **76**, 1081 (1943).

ethylamine hydrochloride was filtered, the ether distilled through a Vigreux column, and the ester fractionated at reduced pressure; yield, 10.7 g. (81%), b.p. 68°/21 mm. Liberation of the amino acid ester by passing dry ammonia through the suspension of the hydrochloride in ether also gave satisfactory yields.

t-Butyl hippurate (benzoyl glycine t-butyl ester). A 3.35-g. sample of glycine *t*-butyl ester hydrochloride was dissolved in 10 ml. of water; a solution of 2.0 g. sodium hydroxide in 10 ml. of water was added, the mixture was cooled with ice, and 2.8 g. benzoyl chloride was added while the mixture was shaken. The crystalline material which separated was dissolved in 50 ml. of benzene. The benzene layer was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Addition of Skelly B immediately caused crystallization of a colorless substance. After standing at low temperature for some hours, the crystalline material was filtered and dried; yield, 3.5 g. (74%), m.p. 109–110°. The substance crystallizes well from hot Skelly B.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.49; H, 7.37; N, 6.11.

The same compound was obtained by reaction of hippuryl chloride and *t*-butyl alcohol in the presence of pyridine, by the silver salt method (*t*-butyl bromide and silver hippurate) and by ester interchange of methyl hippurate with *t*-butyl alcohol and sodium *t*-butoxide. However, the yields never exceeded 30% by any of these methods.

t-Amyl hippurate. Preparation was analogous to the *t*-butyl ester. Yield, 76%; m.p. 76–77°, recrystallized from Skelly B.

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68. Found: C, 67.28; H, 7.75.

Benzoyl-DL-alanine-t-butyl ester. Preparation was analogous to the glycine derivative. Yield, 68%, m.p. 99°, recrystallized from Skelly B.

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68. Found: C, 67.70; H, 7.59.

DL-Phenylalanine t-butyl ester hydrochloride. A 50-g. sample of α-bromo-β-phenylpropionic acid, obtained from bromobenzylmalonic acid[20b] by decarboxylation, was dissolved in 50 ml. of ether. The solution was placed in a 250 ml. pressure bottle, chilled in an ice bath, and 2.5 ml. of concentrated sulfuric acid and 50 ml. of liquid isobutylene were added. The mixture was shaken at room temperature for 7 hr., cooled before opening the bottle, and transferred to a separatory funnel containing a solution of 34 g. sodium hydroxide in 125 g. water, 130 g. ice, and 50 ml. of ether. The mixture was shaken vigorously, the ether layer was separated, and the aqueous phase was extracted twice with 70-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate. The isobutylene and the ether were distilled through a Vigreux column, and the solvents were removed at 20 mm. and a bath temperature not exceeding 50°. The 48 g. of slightly yellow-colored oil obtained was used without further purification.

A 38.7-g. sample of the ester was dissolved in 100 ml. of acetone. This solution was added to a mixture of 19 g. sodium azide in 50 ml. of water and the mixture was refluxed for 20 hr. The acetone was removed by distillation and the remaining oil was worked up in the usual way. The fractionation gave 30.4 g. (90%) of the azido ester as a colorless oil, boiling near 112° at 1 mm.; $n_D^{25} = 1.4976$.

Anal. Calcd. for $C_{13}H_{17}N_3O_2$: C, 63.13; H, 6.92; N, 16.99. Found: C, 62.96; H, 7.03; N, 17.04.

A 12.3 g. sample (0.05 mol.) of the azide was dissolved in 300 ml. of methanol and hydrogenated as described before. The solution was adjusted to *p*H 4.9 with methanolic hydrogen chloride and evaporated under reduced pressure. Addition of ether gave 10.9 g. (85%) of the hydrochloride as colorless needles; m.p. near 228–230° (dec.).

Anal. Calcd. for $C_{13}H_{19}NO_2 \cdot HCl$: C, 60.57; H, 7.82; N, 5.43. Found: C, 60.52; H, 7.72; N, 5.56.

The benzoyl derivative of the ester was obtained in a yield of 79%; m.p. near 84°. It can be recrystallized from Skelly B.

Anal. Calcd. for $C_{20}H_{23}NO_3$: C, 73.81; H, 7.12. Found: C, 73.86; H, 7.05.

Infrared-Spectra. Infrared data were obtained by measuring the absorption of 10% solutions of the esters in chloroform with a Perkin-Elmer Model 21 Spectrophotometer.

NOTE ADDED IN PROOF: Since this work was completed two communications on t-butyl esters of amino acids[22] and its acyl derivatives[23] have appeared.

LOS ANGELES 24, CALIF.

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[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

1,2,5-Trisubstituted Pyrroles of Pharmacologic Interest

R. RIPS, CH. DERAPPE, AND N. P. BUU-HOÏ

Received September 9, 1959

A large number of 2,5-disubstituted pyrroles bearing an aromatic or a heterocyclic substituent in position 1 have been prepared, most of them for evaluation of their antispasmodic activity.

In previous papers, we have recorded the pronounced antispasmodic activity of several 2,5-dimethyl- and 2-methyl-5-phenyl- pyrroles bearing in position 1 an alkoxyphenyl group.[1] These compounds, especially 1-(2-β-diethylaminoethoxyphenyl)-2-methyl-5-phenylpyrrole (I), showed a musculotropic spasmolytic activity several times greater than that of papaverine, although their neurotropic spasmolytic potency was generally considerably less than that of atropine. Spasmolytic activity has also been encountered in a number of 2,5-disubstituted 1-pyridylpyrroles,[2] although to a lesser degree. These various observations prompted the synthesis of further members of

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(2) N. P. Buu-Hoï, R. Rips, and R. Cavier, *J. Med. Pharm. Chem.*, in press.

TABLE I

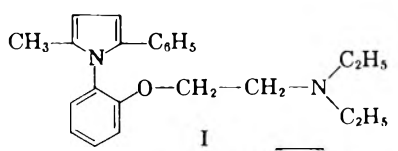
1,2,5-TRISUBSTITUTED PYRROLES WITH A NITROGEN HETEROCYCLIC SUBSTITUENT

Pyrrole	Formula	M.P., °C.	B.P., °C.	Analyses Calcd. C	H	N	Found C	H	N
1-(2-Pyridyl)-2,5-dimethyl-[a]	$C_{11}H_{12}N_2$	—	151–152/15 mm.	—	—	—	—	—	—
1-(2-Pyridyl)-2-methyl-5-phenyl-	$C_{16}H_{14}N_2$	97	215/18	82.0	6.0	11.9	82.1	6.0	11.9
1-(2-Pyridylmethyl)-2,5-dimethyl-[b]	$C_{12}H_{14}N_2$	53	152–153/14			15.0			15.1
1-(2-Pyridylmethyl)-2-methyl-5-phenyl-[c]	$C_{17}H_{16}N_2$	78	213/14			11.3			11.3
1-(2-Pyridylmethyl)-2,5-diphenyl-	$C_{22}H_{18}N_2$	143	261/14			9.0			9.3
1-(3-Pyridylmethyl)-2,5-dimethyl-	$C_{12}H_{14}N_2$	61	174/17			15.0			15.0
1-(3-Pyridylmethyl)-2-methyl-5-phenyl-[d]	$C_{17}H_{16}N_2$	77	221–222/17			11.3			11.2
1-(3-Pyridylmethyl)-2,5-diphenyl-[e]	$C_{22}H_{18}N_2$	145	266/18			9.0			9.1
1-(4-Pyridylmethyl)-2,5-dimethyl-[f]	$C_{12}H_{14}N_2$	75	182/18			15.0			15.2
1-(4-Pyridylmethyl)-2-methyl-5-phenyl-[g]	$C_{17}H_{16}N_2$	82	224–225/18			11.3			11.4
1-(4-Pyridylmethyl)-2,5-diphenyl-[h]	$C_{22}H_{18}N_2$	171	267–268/14			9.0			9.1
1-(6-Methyl-2-pyridylmethyl)-2,5-dimethyl-	$C_{13}H_{16}N_2$	61	148–150/12			14.0			14.0
1-(6-Methyl-2-pyridylmethyl)-2-methyl-5-phenyl-	$C_{18}H_{18}N_2$	100	210–212/13			10.6			10.5
1-(6-Methyl-2-pyridylmethyl)-2,5-diphenyl-	$C_{23}H_{20}N_2$	106	258–260/13			8.6			8.5
1-Picolinoylamino-2,5-dimethyl-	$C_{12}H_{13}N_3O$	151	218/17	67.0	6.1	19.5	66.8	6.4	19.7
1-Nicotinoylamino-2-methyl-5-phenyl-	$C_{17}H_{15}N_3O$	163	282–284/14	73.6	5.5	15.2	73.8	5.7	15.2
1-Nicotinoylamino-2,5-diphenyl-	$C_{22}H_{17}N_3O$	248	316–318/14	77.9	5.1	12.4	77.8	5.5	12.4
1-Isonicotinoylamino-2-methyl-5-phenyl-	$C_{17}H_{15}N_3O$	185	279/13	73.6	5.5	15.2	73.6	5.7	15.2
1-Isonicotinoylamino-2,5-diphenyl-	$C_{22}H_{17}N_3O$	260	—	77.9	5.1	12.4	77.9	5.1	12.6
1-[5-(1,3,4-Triazolyl)]-2,5-dimethyl-	$C_8H_{10}N_4$	203	263/18			34.6			34.4
1-[5-(1,3,4-Triazolyl)]-2-methyl-5-phenyl-	$C_{13}H_{12}N_4$	198	215/15			25.0			24.7

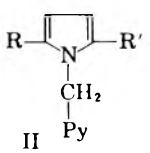
[a] *Cf.* N. P. Buu-Hoï, *J. Chem. Soc.*, 2882 (1949); the hydrochloride had m.p. 127°. [b] Hydrochloride, m.p. 175–176°. [c] Hydrochloride, m.p. 165°. [d] Hydrochloride, m.p. 149–150°. [e] Hydrochloride, m.p. 174–175°. [f] Hydrochloride, m.p. 175°. [g] Hydrochloride, m.p. 150°. [h] Hydrochloride, m.p. 140°.

both categories of pyrroles for pharmacological evaluation.

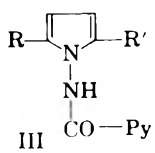
The Knorr-Paal condensation[3] of hexane-2,5-dione, phenacylacetone, and 1,2-dibenzoylethane with the three isomeric picolylamines and 2-aminomethyl-6-methylpyridine was affected with excellent yields in all instances. The characteristics of the reaction products obtained (Formula II) are listed in Table I, along with the Knorr-Paal condensation-products (Formula III) of the same γ-diketones with the hydrazides derived from the three isomeric pyridinecarboxylic acids. It is to be noted that both hexane-2,5-dione and phenacyl-



I

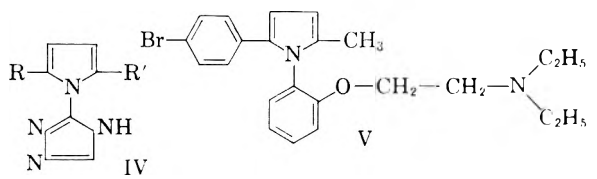


II



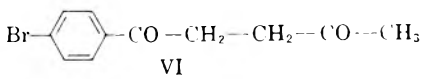
III

acetone readily yielded pyrroles with 2-aminopyridine, although Bishop,[4] using a different technique, was unable to condense hexane-2,5-dione with 2-aminopyridine. Our technique was also applied with success to the condensation of the above γ-diketones with more complex heterocyclic amines, such as 5-amino-1,3,4-triazole which gave compounds of Formula IV.



IV V

In order to investigate the influence of the introduction of a bromine atom on spasmolytic activity in compound I, 1-(2-β-diethylaminoethoxyphenyl)-2-methyl-5-*p*-bromophenylpyrrole (V) was prepared. Its synthesis involved a Friedel-Crafts condensation of levulinic acid chloride with bromobenzene to give *p*-bromophenacylacetone (VI) whose Knorr-Paal condensation with *o*-aminophenol yielded 1-*o*-hydroxyphenyl-2-methyl-5-*p*-



VI

bromophenylpyrrole; alkylation of this last with β-diethylaminoethyl chloride afforded the required basic ether V. For assessing the effect of the replacement of the ether linkage in compound I by a thioether bond, 1-(2-β-diethylaminoethylthiophenyl)-2-methyl-5-phenylpyrrole (VII) was synthesized in the usual way, from 1-*o*-mercaptophenyl-2-methyl-5-phenylpyrrole. Lastly, a basic ester of a pyrrole acid, namely the β-diethylamino-

(3) L. Knorr, *Ann.*, **236**, 313 (1886); C. Paal, *Ber.*, **18**, 2254 (1885).

(4) W. S. Bishop, *J. Am. Chem. Soc.*, **67**, 2261 (1945).

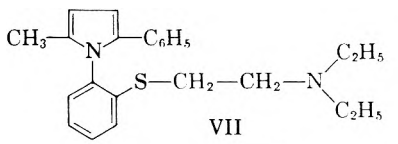
TABLE II

2,5-DISUBSTITUTED 1-ARYLPYRROLES

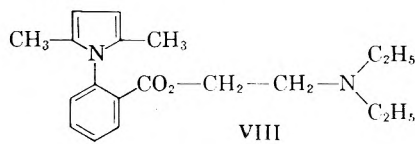
Pyrrole	Formula	M.P., °C.	B.P., °C.	Analyses Calcd. C	Calcd. H	Found C	Found H
1-(2-Mercaptophenyl)-2-methyl-5-phenyl-[a]	$C_{17}H_{15}NS$	91	212/14 mm.	76.9	5.7	77.0	5.7
1-(2-Mercaptophenyl)-2,5-diphenyl-[a]	$C_{22}H_{17}NS$	139	258/14	80.7	5.2	80.7	5.2
1-(5-Hydroxy-1-naphthyl)-2-methyl-5-phenyl-[b]	$C_{21}H_{17}NO$	157	—	84.2	5.7	83.9	5.8
1-(3-Hydroxy-2-naphthyl)-2-methyl-5-phenyl-[b]	$C_{21}H_{17}NO$	118	—	84.2	5.7	84.2	5.7
1-(7-Hydroxy-2-naphthyl)-2-methyl-5-phenyl-[b]	$C_{21}H_{17}NO$	162	285–287/11	84.2	5.7	83.7	5.7
1-(2-Hydroxyphenyl)-2-methyl-5-(4-bromophenyl)-[b]	$C_{17}H_{14}BrNO$	144	245/11	62.2	4.3	62.6	4.5
1-(2-Carboxyphenyl)-2-methyl-5-phenyl-[c]	$C_{18}H_{15}NO_2$	187	255/17	78.0	5.5	77.8	5.6
1-(2-Carboxyphenyl)-2,5-diphenyl-[c]	$C_{23}H_{17}NO_2$	252	296/15	81.4	5.1	81.3	5.0

[a] Crystallization from cyclohexane. [b] Crystallization from a mixture of benzene and cyclohexane. [c] Crystallization from acetic acid.

ethyl ester of 1-*o*-carboxyphenyl-2,5-dimethylpyrrole (VIII) was prepared; this acid, obtained by



VII



VIII

Knorr-Paal condensation of hexane-2,5-dione with anthranilic acid, is included in Table II along with other new 2,5-disubstituted 1-arylpyrroles prepared in the course of this work.

Preliminary experiments show compounds V and VII to possess a musculotropic spasmolytic activity greater than papaverine hydrochloride when tested in the perfused rat duodenum against spasms induced by barium chloride; compound VIII proved to be only slightly active in the same test.

EXPERIMENTAL

Knorr-Paal reactions. The condensation of the various γ-diketones with aromatic and heterocyclic primary arylamines was performed in every instance without a catalyst, by heating the mixture for 15 min. to 1 hr. to above 100°, until steam had ceased to evolve. An excess of the diketone was used, and the reaction product was in most cases separated by vacuum fractionation; in the other cases, direct crystallization was effected. Yields ranged from 35% (condensations with aminonaphthols) to 90% (condensations with low-boiling amines). Recrystallizations were from benzene or cyclohexane in the case of pyridyl-substituted pyrroles, and from cyclohexane or acetic acid in the case of aryl-substituted pyrroles.

p-Bromophenacylacetone (VI). To 58 g of levulinic acid was added 62.5 g. of thionyl chloride (both freshly redistilled), in small portions with stirring, and the mixture was heated at 50° for 1 hr.; the excess thionyl chloride was distilled off, and the residue vacuum-fractionated, giving 46.5 g. of a colorless liquid, b.p. 80°/15 mm. To a well stirred suspension of 55 g. of aluminum chloride in 300 ml. of bromobenzene, the foregoing chloride was added dropwise; the mixture was kept at room temperature for 15 min., then heated at 65° for 1 hr., and left overnight at room temperature. After decomposition with ice and hydrochloric acid, the organic layer was collected, washed with water, then with 5% aqueous sodium hydroxide, and dried over sodium sulfate. The bromobenzene was distilled off *in vacuo*, and the residue fractionated, giving a 60% yield of *p*-bromophenacylacetone, b.p. 180°/13 mm., crystallizing from cyclohexane in shiny colorless needles, m.p. 85°.

Anal. Calcd. for $C_{11}H_{11}BrO_2$: C, 51.8; H, 4.4. Found: C, 51.8; H, 4.4.

1-(2-β-Diethylaminoethoxyphenyl)-2-methyl-5-p-bromophenylpyrrole (V). To a solution of 11.5 g. of 1-(2-hydroxyphenyl)-2-methyl-5-(4-bromophenyl)pyrrole and 2.5 g. of sodium hydroxide in 50 ml. of ethanol, 8 g. of freshly distilled β-diethylaminoethyl chloride was added portionwise with stirring; once the reaction had subsided, the mixture was refluxed for 1 hr. The ethanol was then distilled off, water added, and the reaction product taken up in chloroform; the organic layer was washed with water and dried over sodium sulfate. The residue from evaporation of the solvent afforded on vacuum fractionation, 10 g. of a viscous yellow oil, b.p. 253–255°/11 mm.

Anal. Calcd. for $C_{23}H_{27}BrN_2O$: C, 64.7; H, 6.4; N, 6.6. Found: C, 64.5; H, 6.4; N, 6.7.

The corresponding *hydrochloride*, prepared by treating the free base in ethereal solution with the equimolar amount of hydrogen chloride, crystallized from ethanol benzene in colorless prisms, m.p. 156°.

1-(2-β-Diethylaminoethylthiophenyl)-2-methyl-5-phenylpyrrole (VII). Prepared similarly from 1-*o*-mercaptophenyl-2-methyl-5-phenylpyrrole, this ether was a viscous yellow oil which could not be distilled without decomposition, and which yielded a *hydrochloride*, crystallizing from ethanol-ether in colorless prisms, m.p. 135°.

Anal. Calcd. for $C_{23}H_{29}ClN_2S$: C, 68.9; H, 7.2. Found: C, 68.6; H, 7.5.

β-Diethylaminoethyl ester of 1-o-carboxyphenyl-2,5-dimethylpyrrole (VIII). This ester, obtained from the sodium salt of the corresponding acid (prepared from 6 g. of the acid and 1.1 g. of sodium hydroxide) and 4 g. of β-diethylaminoethyl chloride, was a pale yellow oil, b.p. 217°/17 mm., n_D^{17} 1.5432; yield: 5.2 g.

Anal. Calcd. for $C_{19}H_{26}N_2O_2$. C, 72.6; H, 8.3; N, 8.9. Found: C, 72.3; H, 8.3; N, 9.2.

The corresponding *hydrochloride* crystallized from ethanol-ether in fine colorless prisms, m.p. 121°.

PARIS (VE), FRANCE

[CONTRIBUTION FROM THE DEPARTMENT OF PATHOLOGY, THE GEORGETOWN UNIVERSITY MEDICAL CENTER]

Hypotensive Agents. XII. The *Exo* and *Endo* Isomers of *N*-Dimethylaminoethyl-4-methyl-4,7-*endo*-oxyperhydroisoindole Bis-methonium Cation[1,2]

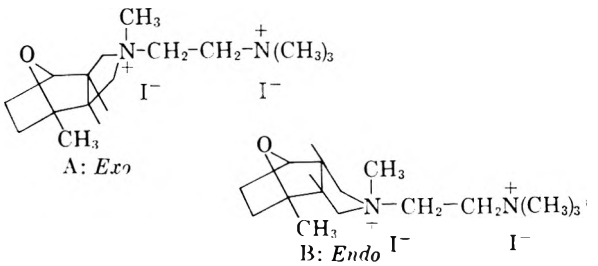
LEONARD M. RICE[3] AND CHARLES H. GROGAN[4]

Received June 12, 1959

In studying the structure-activity relationship of bis-quaternary ammonium salts in lowering blood pressure, the compound *exo-cis*-*N*-dimethylaminoethyl-4-methyl-4,7-*endo*-oxyperhydroisoindole bis-methonium cation was found to be a very potent agent and nontoxic. The *endo-cis* stereoisomer was synthesized and its activity in this respect was essentially the same as that of the previously reported *exo-cis* derivative.

It has been demonstrated that the bis-methonium salt of *N*-dimethylaminoethyl-4-methyl-4,7-*endo*-oxyperhydroisoindole, our code H-2, is a very potent hypotensive agent both in animals and man[5] with an extremely large therapeutic index.[6] In the various series of symmetrical and unsymmetrical quaternary ammonium compounds prepared previously by us[7] and others, mainly Cavallito and co-workers,[8] changing the size of the cationic group greatly influenced the pharmacological activity. We have recently shown[9] that changing the bridging within the ring system making up the cationic group, a change in the molecular size and shape, greatly influenced the usefulness of the resultant compounds as hypotensive agents.

Examination of the structure of H-2, shows that there are two forms of this compound depending on the position of the pyrrolidine ring with respect to the oxygen atom in space. These are shown by the structures A and B. In practice the *exo* isomer, A, is generally represented as having the pyrrolidine ring and oxygen atom on the same side of the plane and the *endo* form, B, as having them on the opposite sides. It was felt that this type of space-structure relationship might furnish another means of obtaining additional information on structure-activity relationships. With these facts in mind, we have now prepared the *exo* and *endo* isomers of H-2 and compared their pharmacological activity.



The synthesis of the desired *exo* and *endo* isomers was carried out by first preparing the phthalic anhydrides of the proper configuration. When maleic anhydride and 2-methyl furan are condensed according to the method of Alder and Backendorf,[10] the resultant Δ^4-monoene adduct, I, has the *exo* configuration. Woodward and Baer[11] have shown this to be the case with maleic anhydride and furan. On hydrogenation of I, the *exo-cis* perhydrophthalic anhydride, II, is obtained. Condensation of diethyl acetylene-1,2-carboxylate with 2-methyl furan based on the procedures of Alder and Rickert,[12] Alder and Backendorf[10] and Diels and Olsen[13] yields the $\Delta^{1,4}$-diene adduct, III. This adduct on hydrogenation absorbed one mole of hydrogen and yielded the Δ^1-cyclohexene,[12,14] IV. On saponification the corresponding acid, V, was obtained. On further hydrogenation of V, one mole of hydrogen was absorbed and the *endo-cis* perhydrophthalic acid, VI, was obtained. This acid was converted to the corresponding anhydride, VII, on treatment with acetyl chloride and acetic anhydride.

The Δ^4-acid from I differed from the Δ^1-acid, V. The anhydride, VII, in view of the work of Woodward and Baer,[11] is thus the *endo* form, although the opposite assignment was applied by earlier German workers.[10,12]

The anhydrides II and VII were treated with dimethylaminoethylamine as previously described[5] to yield the amic acids which were cyclized to the

(1) Presented in part before the Medicinal Chemistry Division, American Chemical Society, 134th National Meeting, Chicago, Ill., Sept., 1958.

(2) Supported by a research grant from the Geschickter Fund for Medical Research, Inc.

(3) Present Address: Wyeth Institute for Medical Research, Radnor, Pa.

(4) Present Address: National Institutes of Health, Bethesda 14, Md.

(5) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, **75**, 4911 (1953).

(6) C. H. Grogan and L. M. Rice, U. S. Patent **2,784,199**, March 5, 1957.

(7) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **24**, 7 (1959).

(8) C. J. Cavallito, A. P. Gray, and T. B. O'Dell, *Arch. intern. pharmacodynamie*, **101**, 38 (1955).

(9) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **23**, 844 (1958).

(10) K. Alder and K. H. Backendorf, *Ann.*, **535**, 101 (1938).

(11) R. B. Woodward and H. Baer, *J. Am. Chem. Soc.*, **70**, 1161 (1948).

(12) K. Alder and H. F. Rickert, *Ber.*, **70**, 1354 (1957).

(13) O. Diels and S. Olsen, *J. prakt. chem.*, **156**, 185 (1940).

(14) O. Diels and K. Alder, *Ann.*, **490**, 251 (1931).

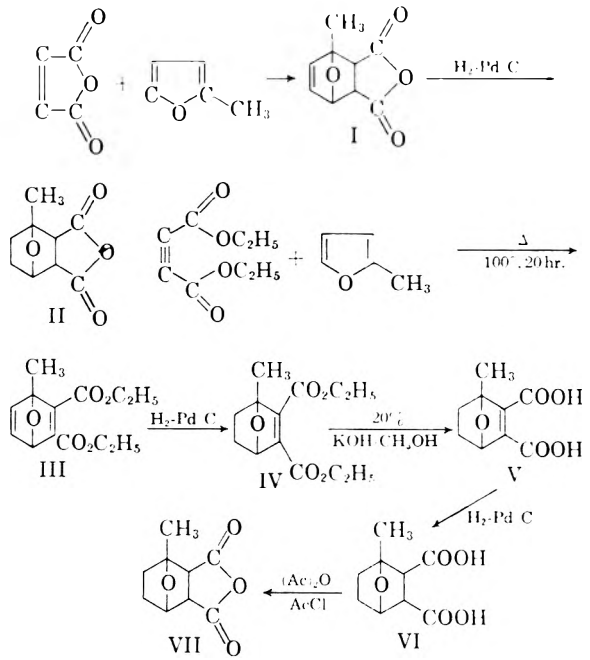
TABLE I

ANALYTICAL DATA

Compound	Analysis											
	Carbon, %		Hydrogen, %		Nitrogen, %		Oxygen, %		Chlorine, %		Iodine, %	
	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Exo imide	61.88	61.74	7.99	8.07	11.10	11.12	—	—	12.28	12.38[a]	—	—
Endo imide	61.88	61.67	7.99	7.74	11.10	11.15	19.02	19.03	12.28	12.21[a]	—	—
Exo base	69.60	69.38	10.78	10.61	12.49	12.19	—	—	23.86	23.94[b]	—	—
Endo base	69.60	69.50	10.78	10.61	12.49	12.69	7.13	7.14	23.86	23.78[b]	—	—
Exo H-2	35.45	35.34	5.95	5.82	5.51	5.45	—	—	—	—	49.94	49.90
Endo H-2	35.45	35.40	5.95	5.71	5.51	5.45	—	—	—	—	49.94	49.84

[a] Imide hydrochloride. [b] Base dihydrochloride.

corresponding imides. These were in turn reduced with lithium aluminum hydride to yield the desired isoindole bases from which derivatives were prepared.



A comparison of the melting points of the derivatives of the *exo* and *endo* forms is shown in Table II. Except in the case of the starting anhydrides and the base dihydrochlorides they are nearly identical. However, a marked depression of the melting points was obtained in all cases on mixing the isomeric forms.

Although there was little doubt from the analytical data, (Table I) that the materials were pure and, as shown by the mixed melting points, (Table II) different, additional evidence was obtained from the infrared spectra and x-ray diffraction patterns of the crystalline dimethonium salts. The infrared spectra of each stereoisomeric form, although generally similar, exhibited distinct differences. The spectra were obtained in potassium bromide pellets using a Perkin Elmer Model 221 spectrophotometer. The multiplicity of frequencies associated with single bond C–N, C–C, and C–O stretching modes, and the large influence of the environment on them, renders them less useful in identifying structural units than in the identification of particular molecules. With these facts in mind, the major differences between 7 and 13 μ are summarized. The *exo* form had absorption bands at 7.09M, 8.12M, 9.19W, 10.55W, 11.64S and 12.20μW which did not occur in the spectrum of the *endo* form. The *endo* form had bands at 7.53-WW, 7.70W, 8.64W, 10.08S and 11.80μS which did not occur in the *exo* spectrum. In addition there were significant shifts in corresponding bands with accentuation or attenuation throughout the spectra. The two bands 7.53μWW and 7.61μW of the *endo* form were replaced by a single 7.61μS band in the *exo* spectrum and the very weak band at 7.97μ of the *endo* form was resolved into a very weak doublet at 7.94μ and 7.99μ in the *exo* form.

TABLE II

Compound	Melting Point °		
	Exo	*Endo*	Mixed *exo-endo*
Anhydride	105–106	87	68–70
Imide·HCl	260	261–262	247
Isoindole·2 HCl	237	213–214	205–208
Isoindole·2 CH_3I	233–234	233–234	220–222

The x-ray diffraction patterns, kindly obtained for us by Dr. Herman Noelther of the Celanese Corporation of America, also showed distinct differences in structure.

These two *exo* and *endo* isomeric forms of H-2 when evaluated as hypotensive agents in dogs[15] displayed, as far as we were able to discern, almost identical activity. Hence it has been shown that this change in shape in the molecule of the very active hypotensive agent, H-2, from *exo* to *endo* produced little or no change in toxicity or pharmacological activity.

EXPERIMENTAL

Exo-cis-3-methyl-3,6-endo-oxyhexahydrophthalic anhydride. Maleic anhydride, 49 g. (0.50 mole) was mixed in anhydrous ether solution with 41.1 g. (0.50 mole) of 2-methyl furan and let stand two days. The ether was removed *in vacuo* and the resultant Δ^4 adduct hydrogenated in ethyl acetate at room

(15) W. E. O'Malley, G. Winkler, L. M. Rice, and C. F. Geschickter, *J. Am. Pharm. Assoc. Sci. Ed.*, **46**, 346 (1957).

temperature over 5% palladium on charcoal. The catalyst was filtered and the solvent removed *in vacuo*. The desired anhydride was obtained in colorless blocks in nearly quantitative yield, m.p. 99–101°. Recrystallization from benzene or ethyl acetate raised the m.p. to 105–106°. The unrecrystallized material is suitable for subsequent steps without further purification. The Δ^4 adduct cannot be recrystallized with heating as it decouples.

Endo-cis-3-methyl-3,6-endo oxyhexahydrophthalic anhydride. Acetylene-1,2-diethyl carboxylate, 85 g. (0.50 mol.) and 2-methyl furan, 41.1 g. (0.50 mol.) were heated together at 100° for 20 hr. without solvent essentially as described[12,13,14] for furan and homologs. At the end of this period, all volatile products were removed by heating *in vacuo* at 70–80°. The adduct, a reddish brown oil, shown to be a $\Delta^{1,4}$ *endo*-oxycyclohexadiene[12] in the case of furan and acetylene-1,2-diethyl carboxylate, was hydrogenated in acetone with 5% palladium-charcoal to yield the Δ^1-adduct which was saponified with 20% methanolic potassium hydroxide to the free acid. This was obtained by evaporation to dryness on the water bath and extraction of the residue with two 200-ml. portions of ether. The ether was stripped and the resultant Δ^1-acid hydrogenated in methanol with 5% palladium-charcoal to yield the saturated acid. This was converted to the *endo-cis* anhydride by treatment with acetic anhydride containing 10% acetyl chloride and melted at 77–80° after distillation of excess reactants. Recrystallization from benzene, ethyl acetate, or acetone-ligroin raised the melting point to 87°.

Imides. The dimethylaminoethylimides of both anhydrides were prepared as previously described[5] by direct reaction of molar equivalents of the anhydrides and dimethylaminoethylamine without solvent. The imides were isolated as colorless oils boiling in the range 120–130°/0.2 mm. Imide hydrochlorides were prepared in isopropyl alcohol with alcoholic-hydrochloric acid. The boiling points of the imides and the melting points of their hydrochlorides were essentially identical (see Table II).

Isoindoles. The *exo-cis* and *endo-cis* isoindoles from the above imides were prepared[5] by reduction of 25.2 g. (0.10 mol.) quantities of the imides in anhydrous ether with lithium aluminum hydride and isolated by vacuum distillation. They were converted into dihydrochlorides and dimethiodides. Again the boiling points of the isoindoles, 100–105°/0.2 mm., and the melting points of the dimethonium salts were identical. The melting points of the dihydrochloride salts, however, differed considerably (see Table II).

FALLS CHURCH, VA.

[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. XXII.[2] Reactions of Orthoesters with 4,5-Diaminopyrimidines

JOHN A. MONTGOMERY AND CARROLL TEMPLE, JR.

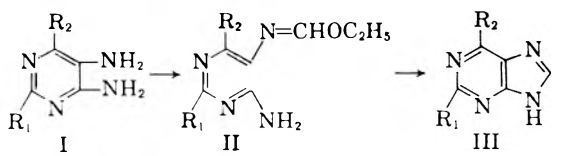
Received August 17, 1959

The usefulness of the reactions of triethyl orthoformate, triethyl orthoacetate, and triethyl orthopropionate with 4,5-diaminopyrimidines for the preparation of purines is discussed.

The preparation of chloropurines by the reaction of chloro-4,5-diaminopyrimidines with triethyl orthoformate–acetic anhydride[3] and with diethoxymethyl acetate (prepared from triethyl orthoformate and acetic anhydride)[4] has previously been reported from these laboratories.

In contrast to the behavior of 4,5-diamino-2-(or -6-)chloropyrimidine and 4,5-diamino-2,6-dichloropyrimidine, the reaction of 4,5-diaminopyrimidine with triethyl orthoformate–acetic anhydride gave 4,5-diacetamidopyrimidine[5] as the principal product and only a small amount of the expected purine. The reaction of 4,5-diaminopyrimidine and acetic anhydride alone also produced 4,5-diacetamidopyrimidine,[5] whereas 4,5-diamino-2-chloropyrimidine and acetic anhydride alone gave only the monoacetylated product, 5-acetamido-4-amino-2-chloropyrimidine. Apparently a chlorine atom in the 2 or the 6 position (or both) of the pyrimidine ring determines the course of the orthoester–acetic anhydride reaction.

Since hypoxanthine is readily formed from 4,5-diamino-6-pyrimidinol by merely refluxing the pyrimidine with formic acid, it seemed that treatment of the pyrimidine or one of its salts with triethyl orthoformate alone might also produce hypoxanthine. This surmise proved to be true, since the pyrimidine, its sulfate, and its hydrochloride gave hypoxanthine in good yield on refluxing with triethyl orthoformate, although the reaction mixture was heterogeneous in each case. The free pyrimidine



I II III

$CH_3COOC(OC_2H_5)=CHC(CH_3)(OC_2H_5)_2$

IV

$CH_3COOC(R)(OC_2H_5)_2$

V

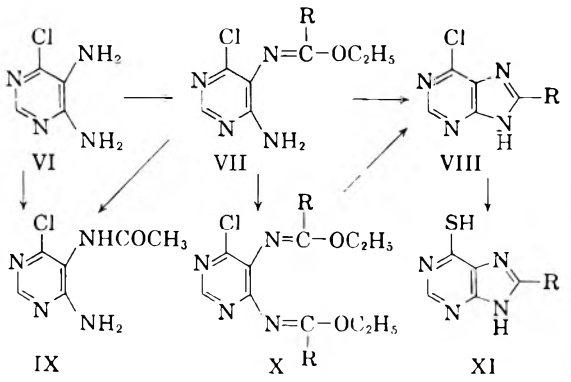
(1) Affiliated with the Sloan-Kettering Institute for Cancer Research. This work was supported by the Cancer Chemotherapy National Service Center (Contract No. SA-43-ph-1740) and by the C. F. Kettering Foundation.

(2) Part XXI. T. P. Johnston, C. L. Kussner, and L. B. Holum, *J. Org. Chem.*, **25**, 399 (1960).

(3) J. A. Montgomery, *J. Am. Chem. Soc.*, **78**, 1928 (1956).

(4) (a) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **79**, 5238 (1957); (b) J. A. Montgomery and L. B. Holum, *J. Am. Chem. Soc.*, **80**, 404 (1958).

(5) D. J. Brown, *J. Appl. Chem.*, **7**, 109 (1957).



and diethoxymethyl acetate gave a homogeneous solution which yielded hypoxanthine on heating.

These results led us to reinvestigate the action of triethyl orthoformate alone on the chloro-4,5-diaminopyrimidines. The data now indicate that reaction takes place without acetic anhydride and that, in the case of the 2- and the 6-chloro-4,5-diaminopyrimidines, it is an intermediate such as II(R_1=Cl, R_2=H; R_1=H, R_2=Cl) which is formed; whereas 4,5-diamino-2,6-dichloropyrimidine is converted to 2,6-dichloropurine (III, R_1=R_2=Cl). In all cases the reaction is slow; however, the addition of formic acid or mixed alkane sulfonic acid to the reaction mixture increased the rate of all three reactions and also caused the 2- and the 6-chloro-4,5-diaminopyrimidines to be converted to the corresponding purines. A comparison of the results with diethoxymethyl acetate and ethyl orthoformate is shown in Table I.

TABLE I

Purine	% Yield: Diethoxymethyl Acetate	% Yield: Ethyl Orthoformate
6-Chloro-	75, 52[a]	53[b]
2-Chloro-	79[a]	64[b], 74[c]
2,6-Dichloro	89[d]	42, 78[c]
Hypoxanthine	48	75

[a] Using two equivalents of diethoxymethyl acetate in triethyl orthoformate. [b] Catalyst: mixed alkane sulfonic acid. [c] Catalyst: formic acid. [d] Ref. 4b.

Refluxing 4,5-diaminopyrimidine (I, R_1=R_2=H) with triethyl orthoformate alone gave 4-amino-5-(ethoxymethyleneamino)pyrimidine (II, R_1=R_2=H). Heating I(R_1=R_2=H) or II(R_1=R_2=H) in diethoxymethyl acetate converted them to purine; fusion at 180° also converted II (R_1=R_2=H) to purine.

Other experiments have shown that the usefulness of the orthoester ring closure for the preparation of purines is limited by lack of solubility of many 4,5-diaminopyrimidines in the medium and by the cost of the reagents. Its advantages are confined to the preparation of the chloropurines which cannot be prepared by other ring closure procedures because of concomitant hydrolysis of the chlorine atoms.

In an effort to extend the orthoester cyclization to the preparation of 8-alkylpurines, the reaction of triethyl orthoacetate and of triethyl orthopropionate with 4,5-diamino-6-chloropyrimidine was studied. Taylor[6] has reported the preparation of 2,8-dimethylhypoxanthine and, more recently, Prasad, Noell, and Robins[7] the preparation of 6,8-dimethylpurine by the use of triethyl orthoacetate and acetic anhydride. Since Post and Erickson[8] found that the reaction of triethyl orthoacetate and acetic anhydride gave IV instead of the methyl analog of diethoxymethyl acetate (V, R=CH_3), no attempts were made to prepare this compound or the ethyl analog (V, R=C_2H_5). Instead, the original orthoester-acetic anhydride cyclization procedure[3] was followed. 6-Chloro-8-methylpurine[9] and 6-chloro-8-ethylpurine were obtained from these reactions, but the yields were low. These low yields can probably be attributed to the predominance of side reactions. Our experimental evidence indicates that one of the side reactions is the acetylation of the pyrimidine (VI → IX) or the reaction of acetic anhydride with the initial product from the pyrimidine and the orthoester (VII → IX). In any case, it is doubtful whether acetic anhydride plays the same role in the reactions of triethyl orthoacetate and triethyl orthopropionate that it does in the reactions of triethyl orthoformate.[3,8]

In view of the success experienced in the acid-catalyzed reactions of triethyl orthoformate and the chloro-4,5-diaminopyrimidines mentioned above, this procedure was attempted with triethyl orthopropionate. The results were unexpected in that, instead of 6-chloro-8-ethylpurine (VIII, R=C_2H_5), a mixture of 4-amino-6-chloro-5-(1-ethoxypropylideneamino)pyrimidine (VII, R=C_2H_5) and 6-chloro-4,5-bis(1-ethoxypropylideneamino)pyrimidine (X, R=C_2H_5) was obtained.

Other experiments showed that 4,5-diamino-6-chloropyrimidine heated with triethyl orthopro-

(6) E. C. Taylor, in G. E. W. Wolstenholme and C. M. O'Connor, eds., "The Chemistry and Biology of Purines" (A Ciba Foundation Symposium), J. and A. Churchill, Ltd., London, 1957, p. 20.

NOTE ADDED IN PROOF: Dr. Taylor has informed the authors of two papers in press describing this work in detail: E. C. Taylor and C. C. Cheng, *J. Org. Chem.*, **25**, 148 (1960) and E. C. Taylor, E. Richter, and J. E. Loeffler, *J. Org. Chem.*, in press.

(7) R. N. Prasad, C. W. Noell, and R. K. Robins, *J. Am. Chem. Soc.*, **81**, 193 (1959).

(8) H. W. Post and E. R. Erickson, *J. Org. Chem.*, **2**, 260 (1937).

(9) Recently prepared by Koppel and Robins by another method.[10]

(10) H. C. Koppel and R. K. Robins, *J. Org. Chem.*, **23**, 1457 (1958).

pionate alone at 95–100° for two hours produced VII(R = C_2H_5) in good yield, and some 6-chloro-8-ethylpurine. Further heating of VII(R = C_2H_5) in triethyl orthopropionate at reflux temperature converted it to X(R = C_2H_5) (at 100° this conversion is slow). Heating VII(R = C_2H_5) in triethyl orthopropionate at 100° for one hour after the addition of a drop of formic acid also produced X(R = C_2H_5). Heating VII(R = C_2H_5) in triethyl orthopropionate for three hours after the addition of an equivolume of acetic anhydride produced a new compound whose ultraviolet absorption spectrum indicated that it was 5-acetamido-4-amino-6-chloropyrimidine (IX).

As expected, dry fusion of both VII(R = C_2H_5) and X(R = C_2H_5) produced 6-chloro-8-ethylpurine. Although better results were obtained with VII than with X, the yield from the former compound was only 36%. Attempts were made to improve the yield of the purine by the use of solvents. Heating the pyrimidine in *N*,*N*-dimethylformamide gave none of the desired purine; however, the use of dimethyl sulfoxide resulted in a 32% yield of the purine—about the same as by the dry fusion method. In later, large-scale runs the use of dimethyl sulfoxide was superior to the dry fusion.

The reaction of 4,5-diamino-6-chloropyrimidine and triethyl orthoacetate was very similar to the reaction of this pyrimidine with triethyl orthopropionate in that both the mono-(VII, R = CH_3) and disubstituted (X, R = CH_3) pyrimidines were formed; however, less of the disubstituted product was found in this case.

The identity of this latter compound (X, R = CH_3) was inferred from its ultraviolet and infrared absorption spectra; it was not isolated and purified. The 4-amino-6-chloro-5-(1-ethoxyethylideneamino)pyrimidine was converted to 6-chloro-8-methylpurine by dry fusion as in the case of 6-chloro-8-ethylpurine, but the yield was even lower (13%).

The 6-chloropurines were converted to the corresponding 6-purinethiols (XI, R = CH_3[10] and C_2H_5) in the usual manner,[4,11] since this work is a part of a study to determine the effect of substitution on the anticancer activity of 6-chloropurine and 6-purinethiol.

EXPERIMENTAL

The ultraviolet absorption spectra were determined in aqueous solution with a Beckman DK-2 spectrophotometer, but the optical densities at the maxima were determined with a Beckman DU. The infrared spectra were determined in pressed potassium bromide discs with a Perkin-Elmer model 21 spectrophotometer. Melting points were determined on a Kofler Heizbank and are corrected.

Purine. A solution of 4,5-diaminopyrimidine (500 mg.) in diethoxymethyl acetate (5 ml.) was heated at 120° for 1 hr. and then evaporated to dryness *in vacuo*. Volatile impurities were removed by dissolving the residue in methanol and evaporating the solution *in vacuo*. The brown solid obtained was dried *in vacuo* over phosphorus pentoxide: yield, 540 mg.; m.p., 190–194°. This material, a mixture of purine and 9(7)-acetylpurine, was recrystallized from a 3:1 mixture of ethyl acetate and toluene (200 ml.) using Norit treatment. The yield of recrystallized purine was 445 mg. (82%); m.p., 212–214° (lit.[12] 212–213°).

A small amount of material obtained from the mother liquor from the recrystallization was identified as 9(7)-acetylpurine by a comparison of its infrared spectrum with that of an authentic sample (see below).

9(7)-Acetylpurine. A suspension of purine (500 mg.) in acetic anhydride (3 ml.) was heated on a hot plate for several minutes. The solution was chilled, and the solid that deposited was collected by filtration and dried *in vacuo* over phosphorus pentoxide: yield, 175 mg.; m.p., 167–168° with sublimation.

Spectral Data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1: 261 (6.9); *p*H 7: 263 (7.9); *p*H 13: 271 (7.7); C_2H_5OH: 264 (7.3). $\bar{\nu}$ in $cm.^{-1}$: 3050, 3000, 2940, and 2910 (CH); 1730 (C=O of active acetyl); 1595, 1570 and 1495 (C=C, C=N); 1400, 1330, 1300, 1275, 960, 800 and 715 (strong unassigned bands).

Anal. Calcd. for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.56. Found: C, 51.80; H, 3.86; N, 34.41.

Dilution of the acetic anhydride filtrate with 1:1 ether-Skellysolve C (b.p. 85°–105°) (100 ml.) gave an additional 135 mg. of 9(7)acetylpurine; m.p., 166–167°. Total yield, 310 mg. (46%).

5-Acetamido-4-amino-2-chloropyrimidine. A suspension of 4,5-diamino-2-chloropyrimidine (700 mg.) in acetic anhydride (15 ml.) slowly became homogeneous when warmed at 40°, and then a white flocculent precipitate deposited. After standing overnight the solution was filtered and the solid that was collected was washed with absolute ethanol and dried *in vacuo* over phosphorus pentoxide: yield, 740 mg. (82%); m.p., 209–211°.

Recrystallization of the crude material (260 mg.) from propanol (8 ml.) gave a white solid: yield, 145 mg.; m.p., 214–215°.

Spectral Data. λ_{max} in mμ ($\epsilon \times 10^{-3}$); *p*H 1: 240–270 (broad); *p*H 7: 235.5 (8.86), 280.5 (5.48); *p*H 13: 251.5 (broad) (7.14), 283.5 (6.75).

Anal. Calcd. for $C_6H_7ClN_4O$: C, 38.60; H, 3.78; N, 30.00. Found: C, 38.69; H, 4.12; N, 29.89.

4-Amino-5-(ethoxymethyleneamino)pyrimidine (II, R_1 = R_2 = *H*). A suspension of 4,5-diaminopyrimidine (500 mg.) in triethyl orthoformate (25 ml.) was heated on a hot plate for 5 min., the solution cooled, and the crystals that deposited collected by filtration, washed with Skellysolve C (25 ml.) and dried *in vacuo* over phosphorus pentoxide: yield, 360 mg.; m.p., 130°.

Spectral data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 7: 252 (8.20), 284 (6.30); *p*H 13: 258 (8.4), 283 (6.6). $\bar{\nu}$ in cm^{-1}: 3380 and 3320 (NH); 2960 and 2920 (CH); 1640 (exocyclic C=N); 1630 (NH); 1585 and 1500 (C=C, C=N); 930 and 910 (ring CH).

Anal. Calcd. for $C_7H_{10}N_4O$: C, 50.60, H, 6.03; N, 33.70. Found: C, 50.81; H, 6.14; N, 33.92.

An additional 140 mg. of impure product was obtained from the triethyl orthoformate filtrate. The total yield was 500 mg. (66%).

Reaction of 4,5-diamino-6-chloropyrimidine with triethyl orthopropionate (A). A mixture of 4,5-diamino-6-chloropyrimidine (5.0 g.) and triethyl orthopropionate (100 ml.) containing a small amount of 98% formic acid (about 0.5 ml.) was heated with stirring at 100° for 15 min. The light yellow solution was heated at 100° for an additional 2 hr., and evaporated under diminished pressure to a semi-solid,

(11) A. Bendich, P. J. Russell, and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6037 (1954).

(12) A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).

The light brown solid, *4-amino-6-chloro-5-(1-ethoxypropylideneamino)pyrimidine*, (VII, R = C_2H_5), was collected by filtration, washed with Skellysolve C (15 ml.), and dried *in vacuo* over phosphorus pentoxide: yield, 2.73 g. (34.5%); m.p., 128° (solidifies and remelts 135°). The ultraviolet spectrum indicates that this material decomposes to 4,5-diamino-6-chloropyrimidine in 0.1*N* hydrochloric acid.

Spectral Data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1: 269 (6.4), 306 (8.1); *p*H 7: 250 (7.2), 284 (6.9); *p*H 13: 250 (7.25), 284 (6.95). $\bar{\nu}$ in cm.$^{-1}$: 3400, 3330, and 3210 (NH); 2990, 2950 and 2920 (aliphatic CH); 1660 (exocyclic C=N); 1630 (NH); 1560 and 1540 (C=C, C=N); 1470 and 1375 (aliphatic CH).

Anal. Calcd. for $C_9H_{13}ClN_4O$: C, 47.20; H, 5.68; N, 24.50. Found: C, 47.22; H, 5.65; N, 24.18.

The combined filtrate and wash were evaporated to dryness *in vacuo*, giving a brownish liquid, *6-chloro-4,5-bis(1-ethoxypropylideneamino)pyrimidine* (X, R = C_2H_5); yield, 6.86 g. (63.5%). The ultraviolet spectrum indicates that this material decomposes to 4,5-diamino-6-chloropyrimidine in 0.1*N* hydrochloric acid.

Spectral Data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1: 265 (6.9), 307 (6.2); *p*H 7: 250 (6.45), (8.7); *p*H 13: 250 (6.45), 287 (8.7). $\bar{\nu}$ in cm.$^{-1}$: 2990, 2960 and 2920 (aliphatic CH); 1670 (broad) (exocyclic C=N); 1540 and 1520 (C=C, C=N); 1470 and 1370 (aliphatic CH).

Distillation of this material (6.86 g.) *in vacuo* (0.1–0.05 mm.) gave a light brown liquid (5.8 g.). The ultraviolet and infrared spectra were practically identical with those given above.

Anal. Calcd. for $C_{14}H_{21}ClN_4O_2$: C, 53.70; H, 6.72; N, 17.90. Found: C, 53.71; H, 6.41; N, 17.50.

(*B*). A mixture of 4,5-diamino-6-chloropyrimidine (0.51 g.) and triethyl orthopropionate (25 ml.) was heated with stirring at 95–100° for 2 hr. A small amount of unchanged 4,5-diamino-6-chloropyrimidine was removed by filtration and the filtrate evaporated to dryness *in vacuo*. The solid residue was triturated with Skellysolve C (5 ml.), and then collected by filtration and dried *in vacuo* over phosphorus pentoxide: yield, 0.60 g. (75%); m.p., 128° (solidifies and remelts at 134–135°). The ultraviolet spectrum of this material was identical with that of *4-amino-6-chloro-5-(1-ethoxypropylideneamino)pyrimidine* (VII, R = C_2H_5).

Impure *6-chloro-8-ethylpurine* (*0.24 g.*) was obtained by evaporation of the Skellysolve filtrate described above.

6-Chloro-8-ethylpurine (VIII, R = C_2H_5) (A). A melt of 4-amino-6-chloro-5-(1-ethoxypropylideneamino)pyrimidine (1.00 g.) was heated in a beaker at 155–160° for 45 min. The resulting gum was extracted with three 100-ml. portions of hot benzene, and the combined extracts evaporated to dryness *in vacuo*: yield, 0.250 g.; m.p., 167° dec.

An additional amount of solid was obtained by extracting an aqueous solution of the residue from the benzene extraction with ether (100 ml.). Sublimation of the combined solids at 135° (0.1 mm.) gave 290 mg. (36%) of 6-chloro-8-ethylpurine; m.p., 170–172° dec. (when heated from 150°).

Spectral Data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1: 232 (3.86), 238 (3.93), 265 (11.2); *p*H 7: 270 (11.0); *p*H 13: 277 (11.8.) $\bar{\nu}$ in cm.$^{-1}$: 3060 (heterocyclic CH); 2995 and 2940 (aliphatic CH); 2800–2400 (acidic H); 1610, 1585 and 1520 (C=C, C=N); 1450 (aliphatic CH); 1380 (C—CH_3); 1235 and 1220 (unassigned).

Anal. Calcd. for $C_7H_7ClN_4$: C, 46.00; H, 3.84; N, 30.70. Found: C, 46.04; H, 3.88; N, 30.60.

(*B*). A solution of 280 mg. of 4-amino-6-chloro-5-(1-ethoxypropylideneamino)pyrimidine in dimethyl sulfoxide (2 ml.) was heated at 140° for 1 hr. The solution was then diluted with water (10 ml.) and extracted with three 20-ml. portions of ether. After being dried, the combined ether extracts were evaporated to dryness *in vacuo* and the residue sublimed at 140° (0.5–0.3 mm.) to give 70 mg. of 6-chloro-8-ethylpurine: m.p., 168° dec. (rapid heating from 150°). The ultraviolet and infrared spectra of this solid were practically identical with those given in (*A*) above.

4-Amino-6-chloro-5-(1-ethoxyethylideneamino)pyrimidine (VII, R = CH_3). A mixture of 4,5-diamino-6-chloropyrimidine (1.00 g.) and triethyl or thioacetate (60 ml.) was heated with stirring at 100–105° for 15 min., giving a yellow solution. The solution was evaporated to dryness *in vacuo*, the residue triturated with Skellysolve C, and the light brown solid collected by filtration and dried *in vacuo* at 80°: yield, 1.17 g. (79.5%); m.p., 144°. The ultraviolet spectrum indicates that this material decomposes to 4,5-diamino-6-chloropyrimidine in 0.1*N* hydrochloric acid.

Spectral data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1: 269 (6.6), 306 (8.7); *p*H 7: 249 (7.3), 283 (7.0); *p*H 13: 249 (7.3), 283 (7.0). $\bar{\nu}$ in cm.$^{-1}$: 3320 and 3150 (NH); 2970, 2920 and 2845 (aliphatic CH); 1660 (C=N); 1640 (NH); 1560 and 1550 (C=C, C=N); 1450 and 1380 (C—CH_3).

Anal. Calcd. for $C_6H_{11}ClN_4O$: C, 44.70; H, 5.12; N, 26.10. Found: C, 44.79; H, 5.08; N, 26.04.

The Skellysolve C filtrate was evaporated to dryness to give a small amount of brownish liquid. The ultraviolet and infrared spectra indicated that this material was impure *6-chloro-4,5-bis(1-ethoxyethylideneamino)pyrimidine*, since the spectra were very similar to those of 6-chloro-4,5-bis(1-ethoxypropylideneamino)pyrimidine.

6-Chloro-8-methylpurine[9] (VIII, R = CH_3) (A). A melt of 4-amino-6-chloro-5-(1-ethoxyethylideneamino)pyrimidine (1.10 g.) was heated in a sublimation tube at 150–155° for 1.5 hr. The resulting residue was then subjected to sublimation at the same temperature under reduced pressure. After a small amount of impure starting material was collected, the residue was sublimed at 180–185° to give a white solid; yield, 190 mg. This material decomposed at *ca.* 200°.

This sample was further purified by dissolving it in warm 2*N* sodium hydroxide (2 ml.) and extracting the cooled, neutralized solution with three 20-ml. portions of chloroform. Evaporation *in vacuo* of the combined extracts gave a white solid: yield, 110 mg. (13%); m.p., 225–227° dec. (rapid heating from 200°; lit,[10] 212–213°).

Spectral data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1: 264 (11.0); *p*H 7: 269 (10.6); *p*H 13: 277 (10.6). $\bar{\nu}$ in cm.$^{-1}$; 2940 and 2870 (aliphatic CH); 1610, 1570, and 1520 (C=C, C=N); 1440 and 1380 (C—CH_3); 1340, 1220, and 1000 (unassigned).

Anal. Calcd. for $C_6H_5ClN_4$: C, 42.70; H, 2.97; N, 33.25. Found: C, 42.50; H, 3.12; N, 33.47.

(*B*). A mixture of 4,5-diamino-6-chloropyrimidine (2.00 g.) and triethyl orthoacetate (100 ml.) was heated with stirring at 95–100° for 20 min., and the resulting solution evaporated to dryness *in vacuo*. The residue was heated at 155° for 1.5 hr., and the resulting gum was treated with boiling water. After removal of the insoluble residue, the aqueous filtrate was evaporated to dryness, giving a solid residue which was sublimed at 180° *in vacuo*. This material (0.78 g.) on recrystallization from benzene gave impure 6-chloro-8-methylpurine; yield, 0.50 g.; m.p., 213–215° dec. (taken fast from 200°). This material was used, without further purification, for the preparation of 8-methyl-6-purinethiol.[10]

8-Ethyl-6-purinethiol (XI, R = C_2H_5). A solution of crude 6-chloro-8-ethylpurine (760 mg.) in propanol (10 ml.) containing thiourea (350 mg.) was refluxed for 4 hr., evaporated to dryness, and the residue dissolved in hot water (30 ml.). Concentration of the aqueous solution in a stream of nitrogen deposited hydrated 8-ethyl-6-purinethiol: yield, 370 mg. (48%); m.p., >260°.

Spectral data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1: 227 (11.6); 327 (18.8); *p*H 7: 232 (10.9); 324 (19.4); *p*H 13: 234 (15.4); 309 (19.5). $\bar{\nu}$ in cm.$^{-1}$: 3000–2300 (aliphatic CH); 2800–2400 (acidic H); 1615, 1580, 1540, and 1500 (C=C, C=N); 1470 and 1375 (C—CH_3); 1340 and 1190 (unassigned).

Anal. Calcd. for $C_7H_8N_4S \cdot {}^1/_3H_2O$: C, 45.16; H, 4.66; N, 30.15. Found: C, 45.17; H, 4.73; N, 29.79.

The above material did not lose its water of crystallization after being dried *in vacuo* over phosphorus pentoxide. Anhydrous 8-ethyl-6-purinethiol was obtained by dissolving the hydrated material in hot methyl isobutyl ketone, and evaporating the solution to dryness *in vacuo*.

Anal. Calcd. for $C_7H_{14}N_4S$: C, 46.66; H, 4.48; N, 31.10; Found: C, 46.37; H, 4.45; N, 30.60.

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BIRMINGHAM, ALA.

[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. XXI. Nitrosated Sulfonamides Related to Myleran

THOMAS P. JOHNSTON, CONRAD L. KUSSNER, AND LEE B. HOLUM

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A number of *N,N'*-polymethylenebis[*N*-nitrosomethanesulfonamide]'s and *N,N'*-dimethyl-*N,N'*-dinitrosoalkanedisulfonamides, structurally related to the anticancer agent Myleran and isomeric Myleran, respectively, have been prepared by the nitrosation of the corresponding bissulfonamides. In contrast, the nitrosation of simple *N*-substituted methanesulfonamides gave unstable products.

Current interest in the anticancer activity exhibited by 1-methyl-3-nitro-1-nitrosoguanidine[2,3] and particularly by 1-methyl-1-nitrosourea[3] against Leukemia L1210 in mice has focused attention on other *N*-nitroso compounds, such as *N*-nitrososulfonamides,[4] that have the common property of undergoing basic decomposition to give diazomethane. In the search for possible new anticancer agents containing a methyl-*N*-nitrosoamino group, a logical approach would appear to be the replacement of the functional group of known anticancer agents by a nitrosated function of the type described above. On the basis of structural similarity to the tetramethylene ester of methanesulfonic acid (Myleran), the synthesis and screening of certain bifunctional aliphatic nitrososulfonamides (Table I) were undertaken. Myleran belongs to a class of alkylating agents first reported as effective agents in the chemotherapy of neoplastic diseases by Haddow and Timmis[5] in 1953.

The following types of isomeric bisnitrososulfonamides have been prepared by the nitrosation of the corresponding bis-sulfonamides (see Table I): (1) *N,N'*-dimethyl-*N,N'*-dinitrosoalkanedisulfonamides (IIIa, b, c) and (2) *N,N'*-polymethylenebis-[*N*-nitrosomethanesulfonamide]'s (IVa,b,c). These nitrosations were performed by treating formic acid solutions of the bis-sulfonamides Ia, b, c and IIa, b, c with aqueous sodium nitrite solution. Pure samples of the bisnitrososulfonamides of each class are relatively stable solids when kept cool and dry; some have been stored for several months without appreciable decomposition. One mode of decomposition was observed when a sample of *N,N'*-tetramethylenebis[*N*-nitrosomethanesulfonamide] (VIb) was stored for six months at room temperature with no special precaution to keep it anhydrous: denitrosation to the corresponding bis-sulfonamide IIb occurred (*cf.* the thermal denitrosations of *N*-nitrosomethanesulfonanilide and *N*-nitroso-*p*-toluenesulfonanilide described by de Boer[6]). The liquid nitrosates derived from *N*-methyl[7]-, *N*-benzyl- and *N*-(*p*-chlorobenzyl)methanesulfonamides (VIa, b) are too unstable to permit isolation of pure products. The bisnitrososulfonamides IIIb and IVb were subjected to thermal decomposition in chlorobenzene by a procedure similar to that employed by de Boer in his study of the decomposition of *N*-methyl-[6] and other *N*-alkyl-*p*-toluenesulfonamides.[8] Compound IIIb evolved nitrogen smoothly at 90°, and relatively pure dimethyl 1,4-butanedisulfonate crystallized from the cooled reaction mixture, whereas IVb evolved nitrogen slowly at 85°, but the reaction product separated as an acidic brown oil, indicating that the tetramethylene ester of methanesulfonic acid apparently formed underwent excessive decomposition (m.p.[9] of pure Myleran, 116°).

The intermediate alkanedisulfonyl chlorides used to prepare the *N,N'*-dimethylalkanedisulfonamides Ia, b, c were also converted by treatment with sodium methoxide into the corresponding dimethyl

(1) Affiliated with Sloan-Kettering Institute. This work was supported by funds from the National Institutes of Health, Contract No. SA-43-ph-1740, and from the C. F. Kettering Foundation. Part XX, J. A. Montgomery and K. Hewson, *J. Am. Chem. Soc.*, **82**, 463 (1960).

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(4) T. J. de Boer and H. J. Backer, *Rec. trav. chim.*, **73**, 229 (1954); *Org. Syntheses*, **34**, 96 (1954).

(5) A. Haddow and G. M. Timmis, *Lancet*, **264**, 207 (1953).

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(7) Method of preparation similar to that described by J. N. Baxter, J. Cymerman-Craig, and J. B. Willis, *J. Chem. Soc.*, 669 (1955) except that benzene was the solvent; yield, 80%; b.p., 132–134°/1 mm.

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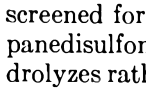
TABLE I

BISSULFONAMIDES, BISNITROSOSULFONAMIDES, BISSULFONATES AND METHANESULFONAMIDES

Compound (No.)	Yield, %	Recrystn. Solvent[a]	M.P.°, [b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Bissulfonamides: A. $CH_3NHO_2S(CH_2)_nSO_2NHCH_3$								
n = 3(Ia)	67[c]	A	120	$C_6H_{14}N_2O_4S_2$	26.07	25.83	6.13	6.21
n = 4(Ib)	70[d]	A	177	$C_6H_{16}N_2O_4S_2$	29.49	29.54	6.60	6.22
n = 5(Ic)	77[d]	A	148	$C_7H_{18}N_2O_4S_2$	32.54	32.44	7.02	6.81
B. $CH_3SO_2NH(CH_2)_nNHO_2SCH_3$								
n = 3(IIa)	32[c]	B	115	$C_5H_{14}N_2O_4S_2$	26.07	26.35	6.13	6.00[e]
n = 4(IIb)	40[d]	B	134	$C_6H_{16}N_2O_4S_2$	29.49	29.49	6.60	6.60
n = 5(IIc)	44[c]	A	110	$C_7H_{18}N_2O_4S_2$	32.54	32.86	7.02	7.14[f]
Bisnitrososulfonamides: A. $CH_3N(NO)O_2S(CH_2)_nSO_2N(NO)CH_3$								
n = 3(IIIa)	52[d]	C	108[g]	$C_5H_{12}N_4O_6S_2$	20.83	21.09	4.20	4.28
n = 4(IIIb)	76[d]	D	142[g]	$C_6H_{14}N_4O_6S_2$	23.83	23.84	4.67	4.71[h]
n = 5(IIIc)	69[d]	C	87[g]	$C_7H_{16}N_4O_6S_2$	26.58	26.81	5.10	5.10
B. $CH_3SO_2N(NO)(CH_2)_nN(NO)O_2SCH_3$								
n = 3(IVa)	52[d]	B[i]	77[g]	$C_5H_{12}N_4O_6S_2$	20.83	20.99	4.20	4.50
n = 4(IVb)	65[d]	B	114[g]	$C_6H_{14}N_4O_6S_2$	23.83	24.13	4.67	4.71[j]
n = 5(IVc)	49[d]	C	94[g]	$C_7H_{16}N_4O_6S_2$	26.58	26.59	5.10	5.36
Bissulfonates: $CH_3OO_2S(CH)_nSO_2OCH_3$								
n = 3(Va)	46[d]	E, F	46–47[k]	$C_5H_{12}O_6S_2$	25.85	25.92	5.21	5.20
n = 4(Vb)	54[d]	B	90	$C_6H_{14}O_6S_2$	29.26	29.44	5.73	5.72
n = 5(Vc)	52[d]	B	51–52	$C_7H_{16}O_6S_2$	32.29	32.26	6.20	6.15
Methanesulfonamides: CH_3SO_2NRR'								
R = H, R′ = $C_6H_5CH_2$ (VIa)	84[d]	G	65	$C_8H_{11}NO_2S$	51.86	52.01	5.99	6.00[l]
R = H, R′ = p-$ClC_6H_4CH_2$ (VIb)	70[d]	A	134	$C_8H_{10}ClNO_2S$	43.73	43.39	4.59	4.50
R = R′ = p-$ClC_6H_4CH_2$ (VIc)	61[c]	H	124	$C_{15}H_{15}Cl_2NO_2S$	52.33	52.45	4.39	4.56
NRR′ =  (VId)	25[c]	H	136	$C_5H_{11}NO_2S_2$	33.13	32.98	6.12	6.20

[a] A, water; B, methyl alcohol; C, tetrahydofuran–petroleum ether pair; D, tetrahydrofuran; E, propyl alcohol; F, ethyl ether; G, benzene–petroleum ether pair; H, isopropyl alcohol. [b] M.p.'s >60° determined on a Kofler Heizbank; <60°, in a capillary. [c] Based on a recrystallized product. [d] Based on crude product of m.p. within 4° of that of the pure product. [e] Calcd.: N, 12.17; found: N, 12.17. [f] Calcd.: N, 10.85; found: N, 10.68. [g] Melts with decomposition (gas evolution). [h] Calcd.: S, 21.21; found: S, 21.38. [i] Solvent C equally effective. [j] Calcd.: S, 21.21; found: S, 21.60. [k] Lit.[10] m.p. 45°. [l] Calcd.: N, 7.39; found: N, 7.69.

alkanedisulfonates Va, b, c, which are isomeric with Myleran or homologs of Myleran. Geiseler and Kuschmiers[10] recently reported the preparation of one of these esters, dimethyl 1,3-propanedisulfonate (Va), by the methylation of the disulfonic acid with diazomethane. These compounds are bifunctional alkylating agents of a type not previously screened for anticancer activity. Dimethyl 1,3-propanedisulfonate is somewhat water-soluble and hydrolyzes rather rapidly in aqueous solution.

The preparation of *N*-(*p*-chlorobenzyl)methanesulfonamide (VIc) was initially attempted by the *p*-chlorobenzylation of methanesulfonamide in dimethylformamide in the presence of potassium carbonate; the product isolated was the dialkylated product, *N*,*N*-di(*p*-chlorobenzyl)methanesulfonamide (VIc), which could be obtained in good yield from such a procedure designed to give dialkylation. When bis(2-chloroethyl) sulfide was the alkylating agent, cycloalkylation resulted to give 4-(methylsulfonyl)thiamorpholine (VIc), which can be recrystallized from dilute sodium hydroxide solution—a fact that substantiates the assigned structure.

Further substantiation of the structure of the cycloalkylated product VIc is found in a comparison of the characteristic infrared absorption bands of a selected group of the sulfonamides described in this paper (Table II): the absence of NH stretching absorption bands around 3200 cm.$^{-1}$ distinguishes an *N*,*N*-disubstituted sulfonamide from unsubstituted and *N*-monosubstituted sulfonamides. The broadness of the NH stretching band shown by methanesulfonamide is indicative of a much greater degree of hydrogen bonding than is the case with *N*-monosubstituted sulfonamides which show relatively sharp NH absorption bands around 3275 cm.$^{-1}$ The intense bands associated with the asymmetrical and symmetrical stretching vibrations of the sulfonyl group in sulfonamides are the strongest bands in the spectrum of each compound of Table II. These observations are in substantial agreement with

(10) G. Geiseler and R. Kuschmiers, *Chem. Ber.*, 91, 1881 (1958).

those previously reported concerning the spectra of methanesulfonamide and related compounds.[11]

TABLE II
CHARACTERISTIC INFRARED ABSORPTION BANDS OF SULFONAMIDES IN THE SOLID STATE[a]

Compound	νNH (cm.$^{-1}$)	νSO_2N (cm.$^{-1}$) Asymmetric S—O Stretching	νSO_2N (cm.$^{-1}$) Symmetric S—O Stretching
$CH_3SO_2NH_2$	3500–3000(m)[b]	1320(s)	1150(s)
Ic	3280}, 3245} (m-s)	1320(s)	1120(s)
IIc	3280(m-s)	1300(s)	1140}, 1125} (s)
VIc	...	1325(s)	1150(s)
VId	...	1325(s)	1150(s)

[a] Perkin-Elmer Model 21 spectrophotometer, sodium chloride prism, potassium bromide disk technique used. [b] (m), Medium; (s), strong; }, doublet.

Preparations of the compounds described in this paper are summarized in Table I; typical procedures are given in the Experimental section.

EXPERIMENTAL

1,5-Pentanedisulfonyl chloride.[12] This procedure is an adaptation of that described by Autenrieth and Bölli[13] for the preparation of 1,3-propanedisulfonyl chloride. A mixture of 20 g. (0.087 mole) of 1,5-dibromopentane, 24 g. (0.19 mole) of sodium sulfite and 45 ml. of water was heated under reflux for 7 hr. The resulting solution was filtered hot and evaporated to dryness under reduced pressure. The residue (41 g.), further dried at 115°, was ground fine and mixed with 45 g. (0.22 mole) of powdered phosphorus pentachloride. The mixture was heated cautiously at first until the initial vigorous reaction had subsided and then at about 110° for 30 min. (the liberated bromine was swept away from time to time in a stream of nitrogen). After being cooled, the semisolid reaction mixture was triturated well with a mixture of ice and water. The solid was collected, washed with water and air-dried: yield, 20 g. (85%); m.p., 63°.[15] The crude disulfonyl chloride was stored in a freezer until used. Treating an ethyl ether solution of a sample of crude disulfonyl chloride with calcium chloride and Norit and then adding petroleum ether gave a 67% recovery of tiny white needles, m.p. 66°[15] (lit.[14] m.p. 66°).

N,N'-Dimethyl-1,5-pentanedisulfonamide (Ic). Anhydrous methylamine was intermittently bubbled through a filtered solution of 6.9 g. (0.026 mole) of crude 1,5-pentanedisulfonyl chloride in 140 ml. of benzene, cooled initially to 6° in an ice-water bath, until the exothermic reaction was complete (the flow of amine was stopped each time the temperature of the mixture reached 15°). The benzene and excess amine were then removed under reduced pressure. The solid residue was triturated with cold water, and the insoluble bissulfonamide[16] was collected and dried *in vacuo;* yield, 5.1 g. (77%); m.p., 145°. Recrystallization from water gave an 80% recovery of fine colorless needles, m.p. 148° (analysis given in Table I).

N,N'-Tetramethylenebis[methanesulfonamide] (IIb). A solution of 6.50 g. (56.8 mmoles) of methanesulfonyl chloride in 15 ml. of benzene was added dropwise to a well stirred suspension of 7.85 g. (56.8 mmoles) of anhydrous potassium carbonate in a solution of 2.50 g. (28.4 mmoles) of 1,4-butanediamine[17] at such a rate that the temperature of the mixture did not rise above 45°. The mixture was heated under reflux for an hour and then allowed to cool. The solid that had separated was collected, washed with benzene, air-dried and then triturated with 50 ml. of water.[18] The undissolved bisulfonamide was collected, washed sparingly with water and air-dried: weight, 2.31 g.; m.p., 132°. Additional product of m.p. 130° was obtained by concentrating the combined filtrate and washings; total yield, 2.75 g. (40%). Recrystallization of the major crop from methyl alcohol gave the analytically pure product of Table I as small colorless needles, m.p. 134°.

N,N'-Dimethyl-N,N'-dinitroso-1,5-pentanedisulfonamide (IIIc). Crude *N,N'*-dimethyl-1,5-pentanedisulfonamide (1.6 g., 6.2 mmoles) was dissolved in 18 ml. of warm formic acid,[19] the solution clarified by filtration and the filtrate cooled to 4° with stirring. To the resulting suspension was added dropwise a solution of 1.1 g. (16 mmoles) of sodium nitrite in 3 ml. of water. Stirring was continued at 4° for an hour after the addition was complete, and the solid that had formed was collected and washed with water. Dilution of the formic acid filtrate with the aqueous washings precipitated more solid. The combined precipitates were then washed well with ice-cold 2% aqueous sodium hydroxide. The residual solid was collected, washed with water and dried *in vacuo* over phosphorus pentoxide: yield, 1.35 g. (69%); m.p., 89° dec. Recrystallization from tetrahydrofuran–petroleum ether gave 1.1 g. of shiny yellow crystals, m.p. 87° dec. Analyses are given in Table I.

N,N'-Trimethylenebis[N-nitrosomethanesulfonamide] (IVa). *N,N'*-Trimethylenebis[methanesulfonamide] (3.99 g., 17.3 mmoles) was dissolved in 15 ml. of warm formic acid, and the solution was cooled to 3°. A solution of 2.98 g. (43.1 mmoles) of sodium nitrite in 5 ml. of water was added dropwise to the well stirred sulfonamide solution at 4–7° over a period of 40 min. After three quarters of the nitrite solution had been added, a yellow solid precipitated; additional formic acid (5 ml.) was added to thin the suspension. Stirring of the cold mixture was continued for 1 hr. after the addition was complete. Water (28 ml.) was added to the suspension to complete the precipitation, and the yellow solid was col-

(11) J. N. Baxter, J. Cymerman-Craigs, and J. B. Willis, *J. Chem. Soc.*, 669 (1955).

(12) 1,3-Propanedisulfonyl chloride was prepared similarly: crude yield, 82%; fine white needles from an ethyl ether–petroleum ether pair (ethyl ether solution treated with calcium chloride and Norit), m.p. 46.5–47°;[15] (lit.[10,13,14] m.p. 48°, 45°). 1,4-Butanedisulfonyl chloride, m.p. 86°;[15] was prepared according to B. Helferich and H. Grünert, *Ber.*, **74B**, 1531 (1941).

(13) W. Autenrieth and E. Bölli, *Ber.*, **58B**, 2144 (1925).

(14) P. W. Clutterbuck and J. B. Cohen, *J. Chem. Soc.*, **121**, 120 (1922).

(15) Kofler Heizbank.

(16) In preparations of Ia and Ib concentration of the aqueous filtrate gave additional crops of products.

(17) Aldrich Chemical Co., Inc., Milwaukee, Wis.

(18) Compound IIa was isolated from the benzene-insoluble solid by dissolving the solid in hot water, treating with Norit, adjusting *p*H to 6, evaporating to dryness *in vacuo*, extracting the residue with hot acetonitrile, evaporating the acetonitrile solution to dryness and recrystallizing the residue from methyl alcohol; yield 32% in 2 crops of colorless crystals, m.p. 115°. Compound IIc was isolated by stirring the benzene-insoluble solid in water, acidifying to *p*H 3 with hydrochloric acid and collecting the crude product that precipitated. The dried crude product, after being washed with boiling petroleum ether, was recrystallized from water; yield 42% of colorless plates, m.p. 110°.

(19) The ratio of formic acid to sulfonamide used in these nitrosations varied with solubility; a 25% excess of nitrite (usually in *ca.* 30% aqueous solution) per sulfonamide function was usually found expedient. The following formic acid ratios (ml. formic acid/g. bissulfonamide) were used in the nitrosations not described in detail: IIIa, 2.5; IIIb, 44; IVb, 4.1; IVc, 11.

lected, triturated with cold 2% aqueous sodium hydroxide, washed well with cold water and dried *in vacuo* over phosphorus pentoxide: yield, 2.60 g. (52%); m.p., 77° dec. Analytically pure pale yellow needles, m.p. 77° dec., were obtained by recrystallization of a small sample from methyl alcohol (see Table I). The major portion of the product was recrystallized from tetrahydrofuran–petroleum ether to give dense yellow crystals, m.p. 76–77° dec., in 80% recovery.

Dimethyl 1,4-butanedisulfonate (Vb). A methanolic solution of sodium methoxide (0.92 g., 40 mmoles, of sodium in 50 ml. of methyl alcohol) was added to a stirred solution of 5.1 g. (20 mmoles) of crude 1,4-butanedisulfonyl chloride in 50 ml. of methyl alcohol, cooled to 5° in an ice water bath, at such a rate that the temperature of the mixture did not rise above 15°. After the addition, the reaction mixture was stirred at room temperature for 1 hr. The white powder that had precipitated was collected by filtration, triturated with 25 ml. of cold water, and dried *in vacuo* over phosphorus pentoxide: weight, 1.37 g.; m.p., 88°. The methyl alcohol filtrate yielded a second crop, 0.85 g. of colorless plates, m.p. 86°. An additional 0.44 g. of colorless plates, m.p. 90°, was obtained by evaporating the above filtrate to dryness *in vacuo*, triturating the residue with cold water and recrystallizing the insoluble material from methyl alcohol: total yield, 2.66 g. (54%).[20] Recrystallization of the first crop from 25 ml. of methyl alcohol gave the analytically pure sample of Table I as shiny colorless plates, m.p. 90°, in 80% recovery.

N-Benzylmethanesulfonamide (VIa).[21] A solution of 10.7 g. (0.093 mole) of methanesulfonyl chloride in 50 ml. of benzene was added dropwise to a well stirred solution of 30 g. (0.28 mole) of benzylamine at such a rate that the temperature did not rise above 37°, addition time *ca.* 2.5 hr. The mixture was stirred for an additional half hour, allowed to stand overnight, then heated under reflux for *ca.* 1 hr. and cooled. The precipitated benzylamine hydrochloride was removed by filtration, and the solvent evaporated from the filtrate under reduced pressure. The oily residue was treated with 175 ml. of water, and the resulting mixture acidified to *p*H 1 with hydrochloric acid. The solid that formed was collected, washed with water and dried: yield, 13.5 g.; m.p., 64°. Additional crops (2.0 g.) melting in the range 64 to 66° were obtained when the filtrates were refrigerated; total yield, 84%. Recrystallization of the combined crops from benzene–petroleum ether gave 11.7 g. of colorless platelets, m.p. 65° (analysis given in Table I.)

N,N-Di(p-chlorobenzyl)methanesulfonamide (VIc). α,*p*-Dichlorotoluene (7.00 g., 43.5 mmoles) was added to a well stirred mixture of 2.00 g. (21.0 mmoles) of methanesulfonamide,[22] 6.00 g. (43.5 mmoles) of anhydrous potassium carbonate and 20 ml. of dimethylformamide. The mixture was heated at 100° for 1 hr., then cooled and poured into 100 ml. of water. The suspension (*p*H 9) was chilled and the white solid that had formed was collected, washed with water, and dried *in vacuo* over phosphorus pentoxide: yield, 4.42 g. (61%); m.p., 122°. Recrystallization from 35 ml. of isopropyl alcohol gave 3.55 g. of colorless needles, m.p. 124°, analysis of which is recorded in Table I.

4-(Methylsulfonyl)thiamorpholine (VId). To a well stirred mixture of 1.80 g. (19.0 mmoles) of methanesulfonamide,[22] 5.25 g. (38.0 mmoles) of anhydrous potassium carbonate and 15 ml. of dimethylformamide was added all at once 2.5 ml. (19 mmoles) of bis(2-chloroethyl) sulfide.[23] The mixture was heated at 100–110° for 2 hr., then cooled and poured into 25 ml. of water. The viscous semisolid that separated hardened when chilled, and was collected and washed with ethyl ether. The tan residue, after trituration with 2% aqueous sodium hydroxide solution, weighed 0.44 g., m.p. 131°. Recrystallization from isopropyl alcohol (after treatment with Norit) gave 0.24 g. of white platelets, m.p. 136° (analysis given in Table I).

The aqueous dimethylformamide filtrate was extracted with ethyl ether and the ethereal layer was combined with the above ether washings. Evaporations of the solvent left an orange oil in which long needles formed. These were collected, triturated with 2% sodium hydroxide solution, and recrystallized from isopropyl alcohol (to which the filtrate from the first recrystallization had been added) with Norit treatment: 0.40 g. of white platelets, m.p. 134°. Additional product (0.24 g., m.p. 134°) was obtained from the original alkaline extract by adjusting the *p*H to 7, evaporating to dryness, redissolving the residue in 10 ml. of water, acidifying to *p*H 3, and extracting the precipitate that formed with hot isopropyl alcohol. Total yield was 0.86 g. (25%).

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BIRMINGHAM 5, ALA.

(20) Compound Va was recovered from the methyl alcohol filtrate by evaporating under reduced pressure to a small volume, then adding small volumes of water and ethyl ether with cooling. The crude crystals thus obtained were triturated sparingly with cold water and recrystallized. Compound Vc was similarly isolated by adding ethyl ether to the concentrated methyl alcohol suspension, triturating the crystals thus obtained with water and recrystallizing from methyl alcohol to give colorless platelets. In subsequent preparations of these sulfonates, the use of an excess of sodium up to 10% appeared to stabilize the esters during the work-up.

(21) *N*-(*p*-Chlorobenzyl)methanesulfonamide (VIc) was prepared similarly, except that appreciable product was recovered from the benzene filtrate by evaporation, treatment of the residue with water and acidification, extraction of the dried precipitate with hot acetonitrile, and finally extraction with warm sodium hydroxide solution, acidification, and recrystallization of the precipitate from isopropyl alcohol.

(22) Preparation was based on that of G. M. McGowan, *J. prakt. Chem.* [2], **30**, 281 (1884), except that the crude product was extracted with hot acetonitrile. Evaporation of the solvent gave methanesulfonamide, m.p. 92°, in 90% yield. Duguet, *Rec. trav. chim.*, **21**, 75 (1902), reported m.p. 90°.

(23) A. M. Reeves and S. Love, *Science*, **107**, 204 (1948).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE AMERICAN UNIVERSITY OF BEIRUT]

Unsaturated Bile Acid Derivatives. I. Some Transformation Products from Hyodesoxycholic Acid[1]

MAKHLUF J. HADDADIN AND COSTAS H. ISSIDORIDES[2]

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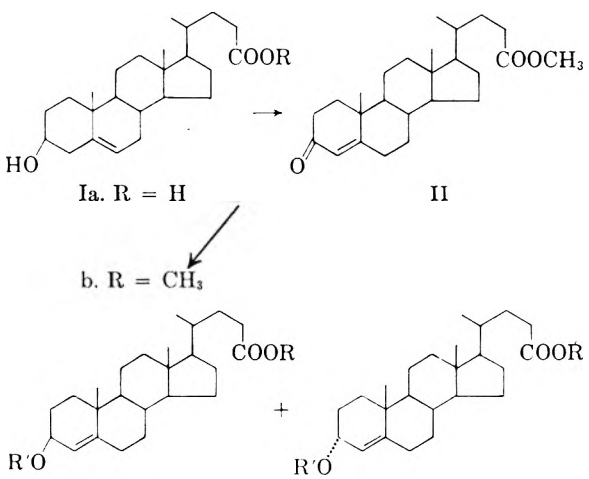
Methyl 3-keto-Δ^4-cholenate, readily obtainable from hyodesoxycholic acid, is reduced by sodium borohydride to a mixture of the 3-hydroxy epimers in which the 3β-epimer predominates. A preparation of methyl $\Delta^{3,5}$-choladienate from hyodesoxycholic acid is described.

$\Delta^{3,5}$-Cholestadiene and the two epimeric 3-hydroxy-Δ^4-cholestenes are well known compounds in the sterol series. However, relatively little work has been done on the corresponding compounds in the bile acid series. A recent method[3] for the preparation of these derivatives, by selenium dioxide oxidation of Δ^3-cholenic acid, gives a mixture of products and involves tedious separations. The present paper describes the preparation of $\Delta^{3,5}$-choladienic acid and the two epimeric 3-hydroxy-Δ^4-cholenic acids from the readily available hyodesoxycholic acid.

Our interest in hyodesoxycholic acid as a possible starting material was aroused by a recent article[4] describing an elegant method for the conversion of this compound to 3β-hydroxy-Δ^5-cholenic acid (Ia). Compound I was our key intermediate for the preparation of the two epimeric 3-hydroxy-Δ^4-cholenic acids (IIIa and IVa).

Oppenauer oxidation of Ib furnished methyl 3-keto-Δ^4-cholenate (II), which, upon reduction with sodium borohydride gave methyl 3β- and 3α-hydroxy-Δ^4-cholenate (IIIc and IVc) in the approximate ratio of 7:1. The predominance of the β-epimer in this reduction is not surprising in view of the high degree of stereospecificity in the reduction of Δ^4-3-ketones by metal hydrides.[5]



Ia. R = H
II
b. R = CH_3

IIIa. R = R′ = H
b. R = CH_3; R′ = Ac
c. R = CH_3; R′ = H

IVa. R = R′ = H
b. R = CH_3; R′ = Ac
c. R = CH_3; R′ = H

Separation of the β-epimer from the mixture *via* the digitonide left the α-epimer, which was isolated as the acetate (IVb) and purified by chromatography. The structure of IIIc as a Δ^4-3-ol was proved by its easy conversion to II by manganese dioxide at room temperature.[3,6] Further confirmation of the structures of the epimers is furnished by the molecular rotations, discussed later on.[7]

Sodium borohydride was chosen as the reducing agent in this investigation since it does not affect ester linkages. We later learned of the interesting finding of Sondheimer and Klibansky[5d] that sodium borohydride reduction of Δ^4-3-ketones may result partly in the saturation of the double bond. No such complication was experienced during the present investigation, although it is entirely possible that small amounts of the saturated product were formed but could not be isolated.

Dehydrotosylation of methyl hyodesoxycholate ditosylate offers a convenient but low-yield route to methyl $\Delta^{3,5}$-choladienate, easily recognizable by its ultraviolet spectrum and the strong levo rotation.[3] Work is being directed at present toward the preparation of this compound in better yield from other intermediates.

During this investigation we occasionally experienced difficulty in handling the free unsaturated hydroxy acids. The presence of the carboxyl group apparently enhances the tendency of the Δ^4-3-ol system to undergo dehydration or etherification in the presence of methanol. Similar difficulties were experienced previously by one of us[3] and have also

(1) Abstracted in part from the M.S. thesis of M. J. H., American University of Beirut, June 1959.

(2) To whom requests for reprints should be addressed.

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(7) For further discussion of the molecular rotation data see ref. (3).

been reported by others.[8] For this reason, chemical transformations were carried out, wherever possible, on the methyl esters.

The shift in molecular rotation in passing from II (M_D 348 chloroform) to IIIb (M_D 43 chloroform) is found to be −305, which is in close agreement with the values −301, −307 and −300 reported[5d,9] for the corresponding difference in molecular rotation between the Δ^4-3-ketone and the Δ^4-3β-OAc for the compounds Δ^4-cholesten-3-one, 17α-methyltestosterone and progesterone respectively. On the other hand, the shift in molecular rotation in passing from II to IVb (M_D 754 chloroform) is found to be +406, in agreement with the value +418 calculated[9] for the difference in passing from Δ^4-cholesten-3-one to 3α-acetoxy-Δ^5-cholestene.

EXPERIMENTAL[10]

Methyl hyodesoxycholate. Hyodesoxycholic acid (5 g., m.p. 194–197°) was refluxed with charcoal (0.5 g.) in methanol (20 ml.) for 5 min. The solution was filtered and the filtrate refluxed with another portion of charcoal, filtered, diluted with hot water to incipient cloudiness and allowed to crystallize. Yield 4.5 g., m.p. 198–199°. An ethereal suspension of the purified acid was esterified in the usual manner with diazomethane. The methyl ester, recrystallized from benzene *n*-hexane (1:1), melted at 120° with previous softening (lit.: m.p. 114°,[11] 86°,[12] 110–112°[13]).

3β-Hydroxy-Δ⁵-cholenic acid (Ia) was obtained from methyl hyodesoxycholate by the method of Bharucha and coworkers.[4] Esterification with diazomethane gave Ib, needles from ether–petroleum ether (2:1), melting at 143–144° (lit.[14] m.p. 144°).

Methyl 3-keto-Δ⁴-cholenate (II). To a solution of Ib (15 g.) in dry acetone (200 ml.) and dry benzene (200 ml.) at 75–80°, was added aluminum *t*-butoxide[15] (20 g.) in hot benzene (100 ml.). The mixture was kept at 80° for 11 hr., cooled, poured into 10% sulfuric acid (200 ml.) and extracted with benzene. The benzene extracts were dried and evaporated to dryness. Two recrystallizations from aqueous methanol gave prisms of II (11.5 g., 77%), melting at 125–126°; $[\alpha]_D$ +90° (*c* 1.22); $\lambda_{max}^{CH_3OH}$ 241 mμ (log ε 4.22) [Lit.: m.p. 126–127°,[3] 124–125°;[13,14,16] $[\alpha]_D$ +87° (c 1.3),[3] +66.13° (*c* 1CH$_3$OH);[17] log ϵ_{241} 4.22[3,13]].

Reduction of II with sodium borohydride and isolation of products. To a solution of II (4.1 g.) in methanol (300 ml.) was added sodium borohydride (1.2 g.) and the mixture kept at room temperature (15–20°) for 24 hr., poured into water (300 ml.) and extracted with ether. The ether extracts were dried and evaporated to dryness. The residue was dissolved in 90% hot ethanol and poured into a hot solution of digitonin (14 g.) in 90% ethanol (1100 ml.). The mixture was kept at room temperature for 24 hr. and worked-up as previously described.[3]

Methyl 3-β-hydroxy-Δ⁴-cholenate (IIIc) was obtained from the digitonide. Yield 3.2 g. (80%), m.p. 129–131°. The analytical sample, recrystallized from *n*-hexane, melted at 131–133°, $[\alpha]_D$ +48° (*c* 1.88).

Anal. Calcd. for $C_{25}H_{40}O_3$: C, 77.27; H, 10.38. Found: C, 76.99; H, 10.34.

On oxidation with manganese dioxide in chloroform (28°, 2 hr.), IIIc gave II, m.p. 125–126°.

Treatment of IIIc with acetic anhydride in pyridine gave the acetate (IIIb), long needles from methanol, m.p. 147–148°, $[\alpha]_D$ +10° (*c* 1.45).

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.04; H, 9.76.

Hydrolysis of IIIc (2.5 *N* methanolic potassium hydroxide at reflux for 1.5 hr.) gave 3β-hydroxy-Δ⁴-cholenic acid. The product was recrystallized from ethyl acetate, m.p. 180–182° (lit.[3] 180–182°).

Anal. Calcd. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 76.79; H, 10.24.

The mother liquor and ether washings from the digitonin precipitation were evaporated to dryness under reduced pressure and the residue extracted with ether. Evaporation of the ether extract gave a crude product (0.5 g.) which was acetylated (pyridine–acetic anhydride), and chromatographed on alumina. Elution with petroleum ether–benzene (7:3, 6:4) followed by several recrystallizations from methanol gave IVb, m.p. 145–147°; $[\alpha]_D$ +175° (c 0.99). (lit.[3] m.p. 147–149°); $[\alpha]_D$ +178° (*c* 1.1).

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 74.96; H, 9.77.

Methyl Δ³,⁵-choladienate. Methyl hyodesoxycholate ditosylate[4] (6 g.) was refluxed with 2,6-lutidine (30 ml.) for 1 hr. and the mixture was concentrated on a water bath under reduced pressure. The residue was treated with ice and extracted with ether. The combined ether extracts were dried and evaporated to dryness, and the residue chromatographed on alumina. Elution with petroleum ether and petroleum ether–benzene (9:1, 4:1, 7:3) gave an oil which solidified when rubbed with methanol. Repeated recrystallizations from methanol gave methyl Δ³,⁵-choladienate[3] (0.82 g., 26%), m.p. 96–98°, $[\alpha]_D$ −128° (*c* 1.09), $\lambda_{max}^{CH_3OH}$ 227.5, 235, 243 mμ, (log ε 4.28, 4.32, 4.12).

Anal. Calcd. for $C_{25}H_{38}O_2$: C, 81.03; H, 10.34. Found: C, 81.08; H, 10.38.

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BEIRUT, LEBANON

(8) See ref. (5d) and references therein.

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(10) Melting points are uncorrected. Rotations (rounded off to the nearest integer) were measured in chloroform solution, unless specified otherwise. Alumina used for chromatography was neutral, grade I "Woelm" to which 3% water was added. Ultraviolet spectra were determined in a Beckman model DU quartz spectrophotometer. Hyodesocycholic acid was obtained from Canada Packers Ltd., Toronto, Canada. Microanalyses by Pascher Mikroanalytisches Laboratorium, Bonn, Germany.

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[CONTRIBUTION NO. 22 FROM THE OLYMPIC RESEARCH DIVISION, RAYONIER INC.]

Infrared Spectra of Lignin and Related Compounds. II. Conifer Lignin and Model Compounds[1,2]

HERBERT L. HERGERT

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The infrared spectra of conifer lignin model compounds and degradation products were determined, and characteristic frequencies of carbonyl groups, ethylenic double bonds, aromatic rings, and hydroxyl groups are presented. These results are applied to lignins isolated from five different coniferous genera. The functional groups occurring in the lignin molecule are discussed and related to the mode of isolation.

Absorption spectrophotometry has been used increasingly as a supplement to purely chemical methods in order to elucidate the structure of gymnosperm and angiosperm lignin. While ultraviolet studies of the lignin molecule have been valuable,[3,4] the information provided is limited to aromatic ring substituents and conjugated groups. On the other hand, infrared spectra, which are potentially capable of yielding information concerning the lignin side chain, as well as aromatic and conjugated substituents, have been mainly used for characterization purposes.[5] In the present investigation, the infrared spectra of a large number of lignin products have been measured in order to determine whether differences exist between native (solvent-soluble) lignin[6] and mildly prepared whole wood lignin, whether lignin structure varies with genera, and to measure the changes introduced into the basic structure of the lignin molecule by commercially important isolation procedures such as the sulfite and kraft processes. In general, the procedure followed was to determine the effect, on the characteristic group frequencies of model compounds and low molecular weight lignin degradation products, of acetylation, methylation, treatment with alcoholic hydrogen chloride, *i.e.*, "ethanolysis," conversion to a sodium salt or phenolate, and reduction with sodium borohydride or lithium aluminum hydride. After assignments of frequencies to certain functional groups were made, comparisons of lignins isolated and treated by the same methods were then carried out.

EXPERIMENTAL

Spectra. The infrared instrument used in this work was a Model 21 Perkin-Elmer spectrophotometer equipped with sodium chloride optics and linear in wave number. Spectra were obtained as paraffin (Nujol) mulls, potassium bromide wafers, or films deposited from chloroform or dioxane. Liquid samples were run between salt plates separated by a lead spacer.

Compounds. Vanillin, vanillic acid, and related compounds were prepared in this laboratory by alkaline hydrolysis or copper oxide oxidation[7] of lignosulfonates derived from western hemlock wood. Acetylvanilloyl [1-(4-hydroxy-3-methoxyphenyl)-1,2-propanedione], α-hydroxy propiovanillone [2-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone], α-ethoxy propioveratrone [2-ethoxy-1-(3,4-dimethoxyphenyl)-1-propanone], guaiacyl acetone [1-(4-hydroxy-3-methoxyphenyl)-2-propanone], β-hydroxy coniferyl alcohol[8] [3-hydroxy-1(3,4-dimethoxyphenyl)-2-propanone], and 1-ethoxy-1-(4-acetoxy-3-methoxyphenyl)propanone-2 were obtained from Dr. J. A. F. Gardner. The latter compound was subsequently deacetylated by the procedure of Kulka and Hibbert.[9] Dehydrodiconiferyl alcohol and pinoresinol were obtained from Prof. H. Erdtman. Coniferin was isolated from western hemlock cambium.[10] Vanilloylformic acid[11] was obtained from Dr. D. W. Glennie. Apocynol [1-hydroxy-1-(4-hydroxy-3-methoxyphenyl)ethane] and methylated derivatives were obtained from Dr. M. Cronyn.[12] The hydroxyl, carbonyl, and aromatic stretching frequencies of this series of compounds are presented in Table I.

Lignin products. Native lignins were prepared according to Brauns' procedure[6] from the wood of Douglas fir (*Pseudotsuga menziesii*), Pacific silver fir (*Abies amabilis*), longleaf pine (*Pinus palustris*), western red cedar (*Thuja plicata*), and western hemlock (*Tsuga heterophylla*). Further purification was effected by repeated precipitation of dioxane solutions of native lignins into chloroform or by adsorption chromatography.[13] Extractive-free longleaf pine and hemlock wood were ground in a vibratory ball mill, constructed according to plans furnished by National Bureau of Standards,[14] to give milled wood lignin[15] in yields of 12 and 16%, respectively.

(1) Presented in part at the Wood Chemistry Symposium, Northwest Regional Meeting of the American Chemical Society, Seattle, Wash., June 12, 1956.

(2) Part I of this series: H. L. Hergert and E. F. Kurth, *J. Am. Chem. Soc.*, **75**, 1622 (1953).

(3) O. Goldschmid, *J. Am. Chem. Soc.*, **75**, 3780 (1953); *Anal. Chem.*, **26**, 1421 (1954).

(4) G. Aulin-Erdtman and L. Hegborn, *Svensk Papperstidn.*, **60**, 671 (1957); K. Freudenberg and G. Schuhmacher, *Sitzber. heidelberg. Akad. Wiss.*, 127 (1956).

(5) (a) E. Jones, *Tappi*, **32**, 167 (1949); (b) S. Kudzin, R. Debaun, and F. Nord, *J. Am. Chem. Soc.*, **74**, 4615 (1953); (c) G. DeStevens and F. Nord, *J. Am. Chem. Soc.*, **73**, 4622 (1953).

(6) (a) F. Brauns, The Chemistry of Lignin, Academic Press, New York, 1952, p. 51; (b) *J. Am. Chem. Soc.*, **61**, 2120 (1939).

(7) I. A. Pearl, *J. Am. Chem. Soc.*, **72**, 2309 (1950); I. A. Pearl and E. Dickey, *J. Am. Chem. Soc.*, **74**, 614 (1952); I. A. Pearl and D. L. Beyer, *J. Am. Chem. Soc.*, **76**, 2224 (1954); *Tappi*, **39**, 171 (1956).

(8) J. A. F. Gardner, *Can. J. Chem.*, **32**, 532 (1954).

(9) M. Kulka and H. Hibbert, *J. Am. Chem. Soc.*, **65**, 1185 (1943).

(10) O. Goldschmid and H. L. Hergert, unpublished work.

(11) D. W. Glennie, H. Techlenberg, E. T. Keaville, and J. L. McCarthy, *J. Am. Chem. Soc.*, **77**, 2409 (1955).

(12) M. Cronyn, Paper presented at the Northwest Regional Meeting of the American Chemical Society (June 1957).

(13) P. Enslin *J. Sci. Food Agr.*, **4**, 328 (1953).

TABLE I

HYDROXYL, CARBONYL, AND AROMATIC RING STRETCHING FREQUENCIES OF LIGNIN MODEL COMPOUNDS AND DEGRADATION PRODUCTS

Compound	Frequency (cm.$^{-1}$)		
	OH	C=O	Aromatic Ring
"Ethanolysis" Products			
Acetylvanilloyl[a]	3330	1700, 1649	1596,[d] 1587, 1502
α-Hydroxy propiovanillone[a]	3430, 3395,[e] 3140	1664	1596, 1587, 1512
α-Ethoxy propioveratrone[a]	—	1671	1590, 1582, 1509
α-Ethoxy propioveratrone[b]	3450[e]	1677	1596, 1589, 1517
Guaiacyl acetone[c]	3410	1705	1598, 1511
1-Ethoxy-1-guaiacyl propanone-2[a]	3429	1710	1600, 1512
1-Ethoxy-1-guaiacyl propanone-2 acetate[b]	—	1768, 1715	1602, 1512
Aldehydes			
Vanillin[a]	3145	1663	1595,[d] 1588, 1509
Vanillin acetate[a]	—	1752, 1699, 1688, 1675	1598, 1508
Vanillin-sodium salt[a]	3450,[d] 3230	1685,[e] 1655, 1638[e]	1582, 1548,[e] 1502
Veratraldehyde[a]	—	1696, 1684, 1672	1597, 1587, 1512
5-Formyl vanillin[a]	—	1683, 1650	1591, 1474
5-Carboxyl vanillin[a]	—	1678, 1655[d]	1578, 1483
Dehydrodivanillin[a]	3250	1673	1603, 1585, 1502
3,4-Dihydroxybenzaldehyde[a]	3320, 3230	1654, 1646	1596, 1537
4-Hydroxy benzaldehyde[a]	3140	1662	1594, 1515
Syringaldehyde[a]	3250	1668	1604, 1585, 1512
Benzaldehyde[c]	—	1702	1599, 1587
Coniferyl aldehyde[a]	3135	1652	1594, 1578, 1514
3,4-Dimethoxy cinnamaldehyde[18]	—	1661	1588, 1575
Cinnamaldehyde[c]	—	1672	1600, 1570, 1490
Ketones			
Acetovanillone[a]	3290	1653	1600, 1572, 1513
Acetovanillone acetate[a]	—	1768, 1680	1595, 1584, 1510
Acetovanillone-sodium salt[a]	3240	1639	1576, 1538, 1509
Acetoveratrone[c]	—	1672	1596,[d] 1590, 1513
p-Hydroxy acetophenone[a]	3160	1645	1600, 1585, 1514
p-Hydroxy acetophenone[b]	3200	1655	1605, 1575, 1515
p-Hydroxy propiophenone[a]	3180	1648	1600, 1568, 1510
Acetophenone[c]	—	1685	1599, 1482
β-Hydroxy coniferyl alcohol[a]	3435, 3355	1709	1599, 1505
β-Hydroxy coniferyl alcohol[b]	3450, 3370	1714	1605, 1513
Acids and Esters			
Vanillic acid[a]	3480	1677	1599, 1583, 1525
Vanillic acid acetate[a]	—	1760, 1686	1602, 1594,[d] 1509
Sodium vanillate[a]	3330	1550	1600, 1518
Methyl vanillate[a]	3540	1699	1600, 1515
5-Formyl vanillic acid[a]	3490	1672, 1651	1579, 1485
5-Carboxyl vanillic acid[a]	3410, 3210	1682,[d] 1655	1600, 1581, 1488
Vanilloyl formic acid[a]	3490	1735, 1625	1580, 1517
3,4-Dimethoxy benzoic acid[a]	—	1672	1590, 1518
Conidendrin[b]	3420	1754	1610, 1600, 1507, 1580

[a] Paraffin mull. [b] Kbr, pellet. [c] l, Liquid film. [d] Shoulder. [e] Weak.

Dioxane lignin was prepared from extractive-free wood samples previously used to prepare native lignins as follows: Twenty-gram samples of pulverized wood were placed in alundum thimbles and extracted for 2 hr. in a glass Soxhlet extractor with 250 cc. of dioxane and 2.5 cc. of concentrated hydrochloric acid. The extract was concentrated to 15 cc. *in vacuo* and poured into 500 cc. water. The water-insoluble lignin was dissolved in dioxane and precipitated into ether. Yield, 60–72% of the Klason lignin content of the wood. Methoxyl content varied from 14.7–15.2%.

Kraft lignin was prepared by bubbling carbon dioxide into the filtrate from a conventional kraft cook of western hemlock wood. The precipitate was filtered off, washed, and dried. Analyses indicated 2.3% sodium, 0.9% sulfur, 13.3% methoxyl, and an average diffusion coefficient of 23.1 mm.^{2}/day, *i.e.*, an apparent molecular weight[16] of 1870. The product was subsequently converted to the free acid by suspension in dilute sulfuric acid. After filtration, washing, and drying, the product was further purified by dissolving it in dry dioxane, filtering, and then precipitating it into dry ether. The product contained 0.05% sodium and 13.4% methoxyl. Similar products were prepared from pine and Douglas fir.

Calcium lignosulfonate was prepared from the filtrate of a conventional calcium-base sulfite cook of western hemlock according to the procedure of Gray and Crosby.[17] It con-

(14) F. Forziati, W. Stone, J. Rowen, and W. Appel, *J. Research Natl. Bur. Standards*, **45**, 109 (1950).

(15) A. Bjorkman, *Svensk Papperstidn.*, **59**, 477 (1956).

(16) V. Felicetta, A. Markham, Q. Peniston, and J. McCarthy, *J. Am. Chem. Soc.*, **71**, 2879 (1949).

(17) K. Gray and H. Crosby, U. S. Patent 2,801,994 (August 6, 1957).

tained 8.6% methoxyl, 4.69% calcium, and 5.2% sulfur. The free lignosulfonic acid was prepared by treating a 5% aqueous solution of the calcium lignosulfonate with a large excess of Amberlite IRC 120 resin. The solution was evaporated to 25% solids *in vacuo* and poured into dioxane to give a tan-colored precipitate which was washed with acetone, ether, and hexane. After drying in a vacuum desiccator over phosphorus pentoxide for 8 hr., the infrared spectrum was immediately determined. A desulfonated product was prepared by suspending 10 g. calcium lignosulfonate in 100 cc. 10% sodium hydroxide solution for 1 hr. at 175°. After cooling, the mixture was acidified with sulfuric acid and the precipitate purified similarly to kraft lignin. The product contained less than 0.2% sulfur.

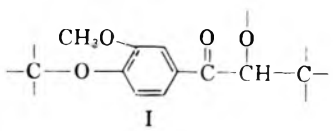
Acetate derivatives were prepared by treatment with acetic anhydride and pyridine. Phenolic hydroxyl groups were methylated in lignin products by refluxing 1 g. lignin in a mixture of 100 cc. dry acetone, 10 g. anhydrous potassium carbonate, and 3 g. dimethyl sulfate for 3 hr. Reduced lignins were prepared by lithium aluminum hydride reduction in dry tetrahydrofuran (3 hr.) or sodium borohydride in 50% methanol (4 hr.). Native lignin (1 g.) was alkylated[6,8] by refluxing for 3 hr. in 100 cc. absolute ethanol and 0.4 g. hydrogen chloride. The product was recovered by precipitation into ether. Ethanol–hydrochloric acid lignin was prepared by refluxing extractive-free wood with 0.5% ethanolic hydrogen chloride for 8 to 24 hr. The product was worked up in the same way as dioxane–hydrochloric acid lignin.

RESULTS

Native lignins. The infrared spectra of native lignins from five different coniferous genera were compared and found to be similar but not identical. It was concluded that the lignins differed in structure and/or in their content of extraneous matter. The most readily apparent difference is in the 1650–1775 cm.$^{-1}$ region. Silver fir, western red cedar, and hemlock native lignins have an absorption band with varying intensity at 1749, 1760, and 1751 cm.$^{-1}$, respectively, which is absent in the spectra of pine and Douglas fir native lignins. This band is not removed upon reduction with sodium borohydride, but disappears upon lithium aluminum hydride reduction, so it was attributed to the presence of a five-membered ring lactone carbonyl group. Examination of these native lignins by two dimensional paper chromatography indicated the presence of several extraneous compounds, one of which was identified as α-hydroxy matairesinol.[18,19] These compounds are relatively insoluble in ether and tend to be occluded with lignin during the precipitation into ether. Since they are somewhat more soluble in chloroform, repeated precipitations of a dioxane solution of hemlock native lignin into chloroform markedly decreased the 1751 cm.$^{-1}$ absorption band, and the presence of extraneous compounds on chromatograms.

The Douglas fir and hemlock native lignins further differed from the other native lignins and mildly prepared whole wood lignins in the relatively greater height of the 1600 cm.$^{-1}$ aromatic ring stretching band as compared with the 1510 cm.$^{-1}$ band. In phenolic extractives such as tannins, flavanones, etc., which contain a phloroglucinol and catechol nucleus, the 1600 cm.$^{-1}$ band is more intense than the 1500 cm.$^{-1}$ band, so this suggested that similar materials might be present in these native lignins as impurities and would be reflected in a higher phenolic hydroxyl content. This has been substantiated by an appreciably higher phenolic hydroxyl content of hemlock native lignin (3.8%) compared with longleaf pine or spruce native lignin (2.5–3.3%) as determined by ultraviolet alkaline difference spectra.[3] Furthermore, a leucoanthocyanin test[20] was positive. In the case of Douglas fir native lignin, a peak in the alkaline ultraviolet spectrum at 3300 Å and an infrared band at 1640 cm.$^{-1}$ indicated that the product was contaminated with traces of taxifolin glucoside[21] and/or taxifolin degradation products.

All of the native lignins show a moderately strong absorption at 1660 cm.$^{-1}$ and a very weak band at 1712 cm.$^{-1}$, both of which disappear upon reduction with sodium borohydride and must, therefore, be due to aldehyde or ketone groups. Methylation does not shift the frequency of either band. Acetylation shifts the frequency of the original 1660 cm.$^{-1}$ band to 1670 cm.$^{-1}$, but does not affect the frequency of the 1712 cm.$^{-1}$ band. The 1660 cm.$^{-1}$ band is unaffected by formation of a sodium salt of the native lignin, but the 1712 cm.$^{-1}$ band disappears and is replaced by a new band at 1575 cm.$^{-1}$ Since the 1710 cm.$^{-1}$ band reappears upon acidification, but is not now removable by sodium borohydride reduction, an aliphatic carboxyl group has evidently been formed. Examination of carbonyl frequencies of model compounds (Table I) leads to the conclusion that the 1660 cm.$^{-1}$ band originates from a ketone carbonyl alpha to an aromatic ring, with the *para-* position etherified and with an oxygen atom (as a hydroxyl group or etherified) in the two-position (I). The model for



I

this is α-ethoxy propioveratrone (Figure 1A). The slight shift obtained upon acetylation is attributed to the removal of intermolecular hydrogen bonds (which tend to lower carbonyl frequencies in the solid state) by acetylation of hydroxyl groups present in adjacent molecules. Alternatively, the slight shift may be due to acetylation of an adjacent hydroxyl group.[22] The aldehyde carbonyl frequency

(18) K. Freudenberg and L. Knof, *Chem. Ber.*, 90, 2857 (1957).

(19) H. Hergert, unpublished work.

(20) W. Pigman, E. Anderson, R. Fischer, M. Buchanon, and B. L. Browning, *Tappi*, **36**, 4 (1953); W. E. Hillis, *J. Soc. Leather Trades Chem.*, **38**, 91 (1954).

(21) H. L. Hergert and O. Goldschmid, *J. Org. Chem.*, **23**, 700 (1958).

(22) As an example of this, acetylation of phenacyl alcohol shifts the frequency from 1690 cm.$^{-1}$ to 1698 cm.$^{-1}$

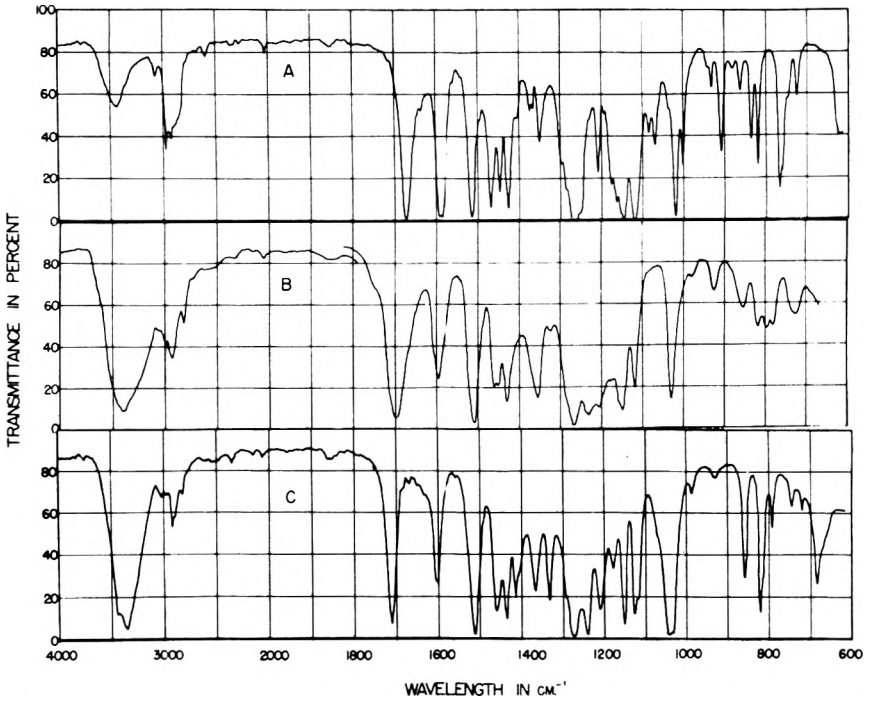


Fig. 1. Infrared spectra of: A. α-Ethoxy propioveratrone (wafer). B. Guaiacyl acetone (liquid). C. β-Hydroxy coniferyl alcohol (wafer)

of an etherified coniferylaldehyde also occurs in the 1660–1670 cm.$^{-1}$ region. Colorimetric studies[23] indicate that no more than one in twenty-five to thirty-five lignin monomeric units is a coniferylaldehyde group. Consequently, intensity considerations alone suggest that the 1660 cm.$^{-1}$ band in native lignin could originate only in a very small part from coniferylaldehyde groups. The 1712 cm.$^{-1}$ band must originate from a nonconjugated ketone carbonyl group. The model for this is guaiacyl acetone (Figure 1B) or the keto form of β-hydroxy coniferyl alcohol (Figure 1C). Treatment of these two compounds with alkali, as in the alkaline treatment of lignin, results in the destruction of the 1712 cm.$^{-1}$ ketone carbonyl and the formation of a carboxyl group, probably through oxidative cleavage. Comparison of the relative heights of the carbonyl stretching bands in the model compounds with those of lignin indicates the presence of about one conjugated α-carbonyl group per five monomers, *i.e.*, 0.2 CO per OCH_3, and about one nonconjugated carbonyl group per twenty-five monomeric units.

The spectra of the various native lignins contained only two distinct aromatic stretching bands, 1510–1515 and 1595–1603 cm.$^{-1}$, typical of an unconjugated guaiacyl nucleus. A very weak "shoulder" is also discernible at 1580–1585 cm.$^{-1}$ Since this band usually appears only in conjugated aromatic compounds, this band can be attributed to a vibration of the rings which are conjugated with an α-carbonyl group (structure I). A relatively strong band at 1150 cm.$^{-1}$, believed to originate from a 1:2:4 substituted aromatic ring,[24] occurs in all the guaiacyl compounds in Table I and also occurs in the native lignins. Moderately strong bands at 858 and 817 cm.$^{-1}$ due to monohydrogen and two adjacent ring hydrogens out-of-plane deformations, respectively, were observed in the native lignin and almost all of the guaiacyl model compound spectra.

An α,β- double bond conjugated with an aromatic ring is the only type of ethylenic double bond likely to be encountered in the lignin molecule. Measurement of model compounds containing aromatic conjugated *trans* double bonds (Table II)

TABLE II

ABSORPTION BANDS ASSOCIATED WITH *Trans*- DOUBLE BONDS CONJUGATED WITH AN AROMATIC RING

Compound	C=C Stretching	=CH Deformation
Cinnamic acid	1626	980
3-Methoxy-4-hydroxy cinnamic acid	1620	972
3-Methoxy-4-acetoxy cinnamic acid	1626	985
3,4-Dimethoxy cinnamic acid	1625	980
3,4-Dihydroxy cinnamic acid	1620	975
3,4-Diacetoxy cinnamic acid	1626	988
Cinnamaldehyde	1618	968
3-Methoxy-4-hydroxy cinnamaldehyde	1612	962
Isoeugenol	1618	962
Coniferyl alcohol	~1612	965
Coniferin	~1610	960
Dehydrodiconiferyl alcohol	~1610	965
Guaiacyl glycerol β-coniferyl ether	~1608	965

(23) E. Adler, K. J. Bjorkvist, and S. Haggroth, *Acta Chem. Scand.*, 2, 93 (1948); E. Adler, *Ind. Eng. Chem.*, 49, 1377 (1957).

(24) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen and Co., London, 323 pp. (1954).

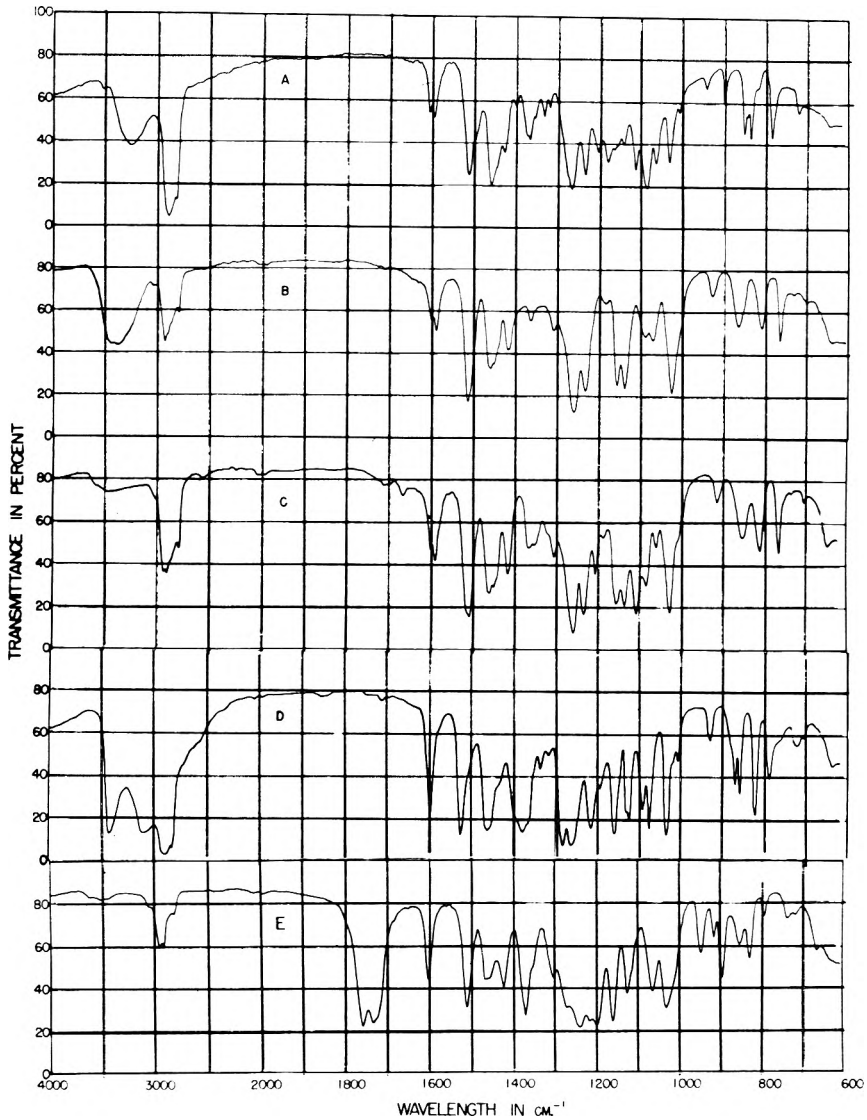


Fig. 2. Infrared spectra of: A. 1-Ethoxy-1-(4-hydroxy-3-methoxyphenyl)ethane (mull). B. 1-Hydroxy-1-(3,4-dimethoxyphenyl)ethane (liquid). C. 1-Methoxy - 1 - (3,4 - dimethoxyphenyl)ethane. D. 1-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-ethane (apocynol) (mull). E. Apocynol diacetate (film)

indicated that the C = C stretching vibration occurs in the range of 1608-1626 cm.$^{-1}$, while the C—H out-of-plane deformation absorbs at 960-988 cm.$^{-1}$ The absence of an absorption band at 1610-1625 cm.$^{-1}$ and the extremely weak band at 970 cm.$^{-1}$ suggests that very few double bonds (probably less than one for each twenty monomers) are present in the native lignin molecule.

Bands at 3400 (shoulder at 3190), 1220, 1087, and 1043 cm.$^{-1}$ are interpreted as arising from hydroxyl group vibrations. The O—H stretching band at 3400 cm.$^{-1}$ is broad, indicating hydrogen bonding. Phenolic hydroxyl groups give rise to a 1200-1225 cm.$^{-1}$ absorption in guaiacyl compounds which is attributed to the aryl C—O stretching mode and is thus assigned in lignin. The intensity of this band is lowered upon methylation of the lignin phenolic groups as is the 1200 cm.$^{-1}$ band in vanillyl alcohol and α-hydroxy propiovanillone upon methylation. Similar methylation of apocynol causes the band to disappear entirely.

The O—H deformation or C—O stretching band was found to occur at about 1000 cm.$^{-1}$ for benzyl alcohols, 1040 cm.$^{-1}$ for primary alcohol groups, and 1075-1090 cm.$^{-1}$ for secondary hydroxyl groups in the model compounds studied. Since aliphatic ethers also absorb at 1085-1120 cm.$^{-1}$ and the C—O deformation of the methoxyl groups occurs at 1030 cm.$^{-1}$,[25] assignment of the absorption bands with certainty in this area of the lignin spectrum is difficult. Comparison of the spectral effect of acetylation and methylation of lignin with model compounds led to the conclusion that the both aliphatic ether linkages and secondary hydroxyl groups are present in the native lignin molecule and are responsible for the 1082-1087 cm.$^{-1}$ absorption band. The presence of both phenolic and aliphatic hydroxyl groups was further confirmed by the presence of strong 1760 and 1740 cm.$^{-1}$ ester carbonyl stretching bands in the acetate spectra. Methoxyl group and aromatic-aliphatic ether ab-

(25) L. H. Briggs, L. D. Colebrook, H. M. Fales, and W. C. Wildman, *Anal. Chem.*, 29, 904 (1957).

TABLE III

INFRARED FREQUENCY ASSIGNMENTS (TENTATIVE) OF NATIVE LIGNIN AND SEVERAL GUAIACYL MODEL COMPOUNDS

Assignment	Frequency (Cm.$^{-1}$) 1-Hydroxy 1-guaiacyl ethane (Apocynol)	β-Guaiacyl-glycerol coniferyl ether[a]	β-Hydroxy coniferyl alcohol	Southern pine native lignin	Western hemlock native lignin
O—H stretching (H-bonded)	3420	3390	3440	3400	3420
	3100		3360	3150[c]	3160[c]
C—H stretching (methoxyl groups and side-chain CH)	[b]	2920	2920	2920	2920
	[b]	~2850	2820	2850	2875, 2820[c]
C=O stretching					
Aliphatic ketone			1712	1712	1712
p-Substituted aryl ketone				1660	1655
C=C stretching		1653[d]			
C=C skeletal vibrations (aromatic ring)	1597	1608, 1587	1602, 1597	1606	1607
	1525	1515	1512	1512	1512
C—H deformation (asymmetric)	[b]	1462	1461	1462	1462
Unassigned (present in all guaiacyl compounds examined)	[b]	1414	1435, 1415	1423	1432
C—H deformation (symmetric)	1365	1364	1362	1365	1365
C—O stretching, aromatic (methoxyl)	1263, 1282	1270	1270	1270	1268
C—O stretching, aromatic (phenol)	1216	1222	1235, 1212	1220	1232, 1215
Unassigned (methoxyl group)	1192	~1185	1178	~1190	~1185
Unassigned (1:2:4 substitution)	1160	1159	1152	1153	1155[c]
Unassigned	1132	1131	1127	1135	1145
Unassigned (aromatic ether)	1124	~1120[c]	1118	~1125[c]	1120
C—O deformation (aliphatic ether or secondary hydroxyl)	1092, 1076	1085		1087	1082
C—O deformation (primary hydroxyl)		1040[c] (?)	1042[c]	1043	1043[c]
C—O deformation (methoxyl group)	1035	1031	1034	1031	1031
Unassigned	1010[d]		987[d]		990[d]
=CH out-of-plane deformation (*trans*)		965		970[d]	968[d]
Unassigned (possibly OH out-of-plane deformation)	931		~930		~930
C—H out-of-plane deformation					
(One H, aromatic ring)	860, 872	857	858	858	857
(Two H, aromatic ring)	825	814	825, 816[c]	817	815

[a] K. Freudenberg and W. Eisenhut, *Chem. Ber.*, **88**, 626 (1955). [b] Band obscured by Nujol. [c] Shoulder. [d] Very weak.

sorptions occurred at 2920, 2850, 1462, 1365, 1270, 1190, 1125, and 1031 cm.$^{-1}$, identical with guaiacyl model compounds. The band assignments of longleaf pine and purified western hemlock native lignin, which appeared to be relatively free of extraneous constituents, and several lignin model compounds, which contain functional groups believed to be present in lignin, are summarized in Table III.

Milled wood lignin. Bjorkman's recently discovered procedure[15] for lignin isolation from extractive-free wood appears to give a product structurally less altered than any other procedure devised to date. The infrared spectra of pine- and hemlock-milled wood lignins were compared with each other and with corresponding native lignins. Although no major differences in wave lengths of the absorption bands were observed, differences in the relative intensities of the bands were apparent, especially in the 1000–1250 cm.$^{-1}$ region. Since all of these lignin samples were isolated by the same procedure, the spectral differences must be interpreted as indicating structural differences in the lignin molecule which are dependent upon genera. The spectral region in which these differences are most conspicuous involves ether linkages and hydroxyl groups, so it may be concluded that lignins from different genera differ in molecular structure. If Freudenberg's hypothesis is correct, *viz.*, that lignin polymerization proceeds through a number of different dimeric products[26] which vary mainly in ether linkages and hydroxyl groups, then the structural differences in lignins from different sources would involve different proportions of the dimers in the polymer.

The milled wood lignins shows a relatively strong band at 1660 cm.$^{-1}$ and a weaker band at 1710–1715 cm.$^{-1}$ Both of these bands are stronger than those in the corresponding native lignins. They appear to be due to the same type of carbonyl groups, *i.e.*, an unconjugated ketone alpha to an aromatic ring with the *para-* position etherified, since the characteristic shifts upon acetylation, reduction, and treatment with base are identical in both cases. Differences in ring substitution were suggested by the relative heights of the 815 and 850–860 cm.$^{-1}$ C—H out-of-plane deformation bands. The 860 cm.$^{-1}$ band, which indicates one free ring hydrogen atom, is stronger than the 815 cm.$^{-1}$ band (two adjacent ring hydrogens) in the milled wood lignins while the reverse was observed with native lignins. This may indicate a much

(26) K. Freudenberg, *Angew. Chem.*, **68**, 81 (1956).

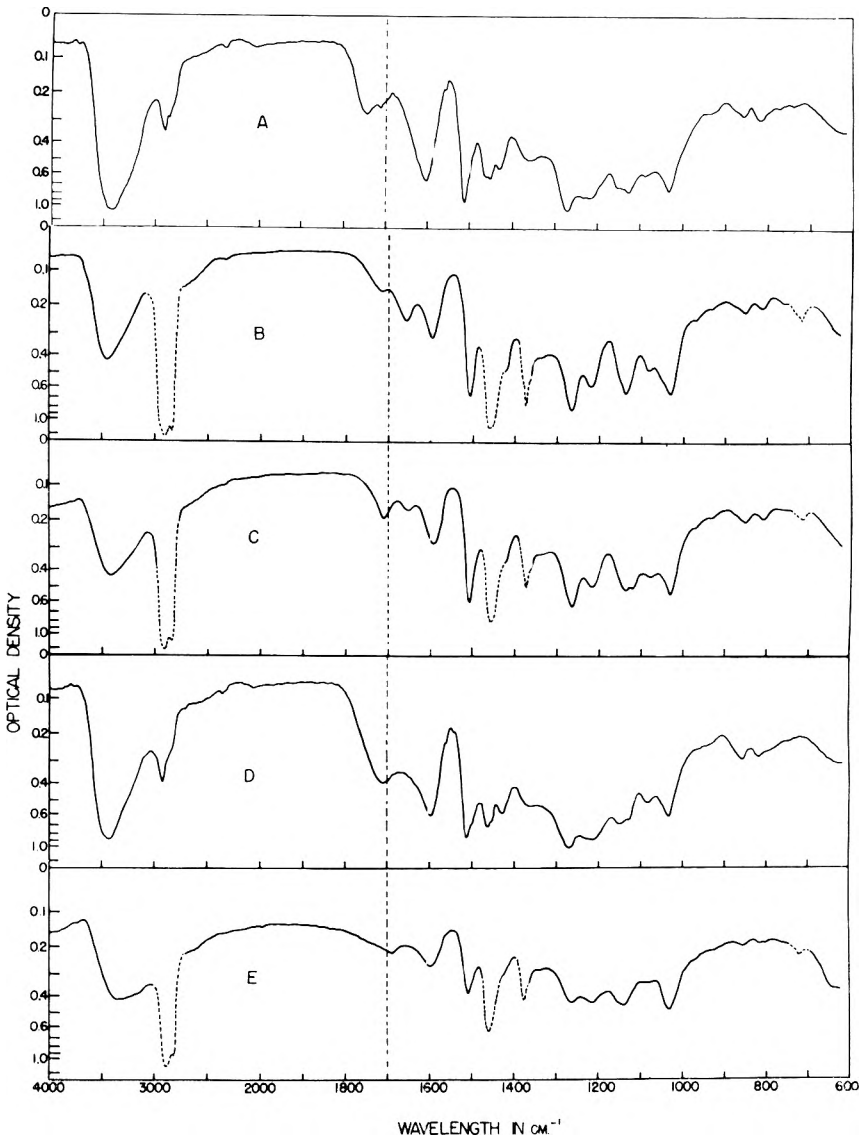


Fig. 3. Infrared spectra of western hemlock lignin: A. Native lignin (wafer). B. Milled wood lignin (mull). C. Dioxane lignin (mull). D. Kraft lignin (wafer). E. Lignosulfonic acid (mull). Dotted lines indicate bands due to paraffin in mulls

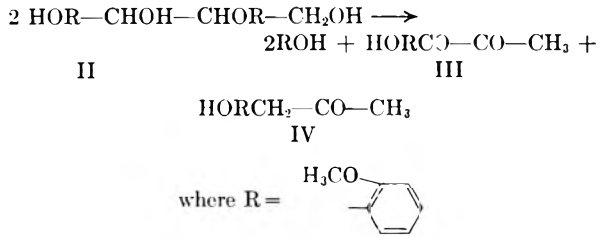
higher degree of substitution in the 5-position of wood lignin as compared with native lignins.

Further differences between milled wood and native lignins are apparent from a comparison of the spectra of the acetate derivatives (determined as potassium bromide wafers of equal concentration). The total hydroxyl content, as evidenced by the intensity of the acetate ester carbonyl stretching bands, was markedly higher in native lignin than milled wood lignin. The ratio of aliphatic to phenolic hydroxyl groups (as indicated by the aliphatic ester band, 1735–1740 cm.$^{-1}$, and phenolic ester band, 1760 cm.$^{-1}$) was higher in the milled wood lignin than the native lignin. The 1085 cm.$^{-1}$ band, which appears to indicate the presence of aliphatic ether linkages in the acetate derivative, is markedly higher in the milled wood lignins than in the native lignins. This suggests that some of the oxygen atoms, appearing as hydroxyl groups in native lignin, are bound in aliphatic ether linkages in whole wood lignin.

Dioxane lignin. One of the disadvantages of the use of milled wood lignin for structural studies is that preparation is exceedingly slow and results in very small amounts of material. Both of these difficulties may be circumvented by the use of dioxane–hydrochloric acid as an extraction medium.[27] The spectra of dioxane lignins from five coniferous genera were similar but not identical. Although this provided further evidence for the variation of lignin structure with genera, there was indication of structural rearrangement which had taken place during isolation. The 1710 cm.$^{-1}$ band was appreciably stronger than the corresponding band in native or milled wood lignin. It is due to an unconjugated ketone carbonyl group which is apparently formed during the isolation process. Treatment of native or milled wood lignin with dioxane–hydro-

(27) (a) O. Engel and E. Wedekind, *Ber.*, **69B**, 2434 (1936); (b) H. Kiefer and E. Kurth, *Tappi*, **36**, 14 (1953); (c) E. Adler, J. M. Pepper, and E. Eriksoo, *Ind. Eng. Chem.*, **49**, 1391 (1957).

chloric acid similarly results in an intensified 1710 cm.$^{-1}$ band, while dioxane–hydrochloric acid treatment of native lignin reduced with lithium aluminum hydride results in the formation of both unconjugated and conjugated carbonyl groups. Further differences in dioxane lignin and milled wood lignin are indicated by the higher phenolic hydroxyl content of dioxane lignin, as evidenced by a more intense 1760 cm.$^{-1}$ phenolic acetate carbonyl stretching band in the acetate derivative, and differences in the 1125–1150 cm.$^{-1}$ bands, which are related to aromatic aliphatic ether linkages. All of these changes are paralleled in the treatment[27c] of the guaiacyl ether of guaiacyl glycerol (II) with dioxane–hydrochloric acid in which guaiacol is liberated and vanilloyl acetyl (III) and guaiacyl acetone are formed by dehydration and rearrangement.



This strongly points to the presence of similarly substituted guaiacyl glycerol units in lignin. If dioxane–hydrochloric acid treatment of wood is extended from 2 to 12 or 24 hr., additional changes are found in the 1000–1250 cm.$^{-1}$ area of the spectrum. This suggests that further extensive rearrangements have taken place, and strongly indicates that short extraction periods, *i.e.*, 2 hr., should be used in the dioxane–hydrochloric acid procedure if relatively unchanged lignin is desired.

Alcoholysis of lignin. When lignin is isolated from wood with methanol or ethanol and hydrochloric acid, or when native lignin is treated with these same reagents, the alkoxyl content is appreciably increased. Brauns concluded that the methoxyl or ethoxyl groups introduced in the lignin molecule were attached to a carbonyl group, probably in an acetal linkage. As proof of this, he cited[28] the infrared study of Jones,[5a] in which it was stated that the absorption band in the spectrum of native lignin at 1663 cm.$^{-1}$, which was attributed to an aldehyde or ketone group, was absent in the spectrum of native lignin methylated with methanol–hydrochloric acid. In direct opposition to this, Adler and Gierer,[29] who believe that alkylation with methanol–hydrochloric acid involves a reaction with benzyl alcohol groups, observed that the carbonyl band in the infrared spectrum of native lignin did not disappear upon methylation with methanol–hydrochloric acid. During the present study, the spectra of native lignin treated with ethanol–hydrochloric acid and of ethanol–hydrochloric acid wood lignin were determined. Both products showed absorption bands at about 1650 cm.$^{-1}$ and 1710–1715 cm.$^{-1}$, in agreement with the work of Adler and Gierer. The unconjugated carbonyl band (1710 cm.$^{-1}$) is appreciably stronger than in the original lignin, while the 1650 cm.$^{-1}$ band is slightly less intense. Treatment of reduced native lignin with methanol–hydrochloric acid results in a product which also shows bands at these same frequencies. Other differences in the spectra, *i.e.*, in the 1000–1200 cm.$^{-1}$ and 750–900 cm.$^{-1}$ regions indicate that considerable structural rearrangements have taken place. These are interpreted as hydrolysis to liberate phenolic hydroxyl groups and dehydration to form carbonyl groups, as in dioxane lignin, and methylation of secondary (benzyl) alcohol groups. In view of this, it appears unwarranted to draw conclusions concerning the structure of wood lignin which are based exclusively on the study of alcoholysis lignin.

Kraft lignin. The spectra of kraft lignins differed depending upon whether they were precipitated with carbon dioxide or mineral acid from the alkaline pulping liquor. Chemical analyses of the product precipitated with carbon dioxide showed it to contain 2.3% sodium, and the spectrum had an absorption band at 1580–1590 cm.$^{-1}$ typical of carboxylate ion.[30] Absorption at 1660–1720 cm.$^{-1}$ was absent. Upon subsequent acidification with sulfuric acid, the sodium content was reduced to a negligible value, and the spectrum (Figure 3D) now showed a moderately strong band at about 1713 cm.$^{-1}$, which was assigned to the stretching frequency of a nonconjugated carboxyl group. Kraft lignins also contain a conjugated ketone carbonyl group which shows an absorption at about 1650 cm.$^{-1}$; however, this functional group appears to be conjugated through the aromatic ring to a *para*-phenolic hydroxyl rather than to a *para*-ether linkage as in the original wood lignin. This is evidenced through a shift of the band to about 1635 cm.$^{-1}$ upon conversion of the lignin to a sodium salt.

The remainder of the spectrum of acidified kraft lignin closely resembled the dioxane lignin spectrum. Comparison of spectra (potassium bromide pellets of equal concentration) indicated the kraft lignin to have slightly higher intensities of the 1600 cm.$^{-1}$ and 1220 cm.$^{-1}$ bands and weaker intensities for the 1515, 1125, 1085, and 1030–1035 cm.$^{-1}$ bands. These differences are interpreted as indicating that the kraft process causes an increase in phenolic hydroxyl content through ether cleavage and loss of methoxyl group and, possibly, some loss of aliphatic hydroxyl groups either through dehy-

(28) Ref. 6a, pp. 230–231.

(29) E. Adler and J. Gierer, *Acta Chem. Scand.*, 9, 84 (1955).

(30) Infrared evidence of carboxyl groups in kraft lignin has also been suggested by J. J. Lindberg, *Finska Kemistsamfundets Medd.*, 64, 23 (1955).

dration or mercaptan or sulfide formation. Unfortunately, the carbon-sulfur vibrations are relatively weak and occur at 600–700 cm.$^{-1}$ region, which was not readily accessible with the equipment available in this laboratory.

Lignosulfonates. The spectral shift observed upon conversion of sodium and calcium lignosulfonates to free lignosulfonic acids by ion exchange indicated the presence of carboxyl groups in lignosulfonates, although the amount appears to be less than that present in kraft lignins. Unconjugated carbonyl groups are absent and conjugated carbonyl groups are present in relatively small amount, except in lignosulfonates which have been treated with alkali. In the latter case, an appreciable content of ketone carbonyl groups conjugated with a free *para*-hydroxyl group is indicated.

The absorption bands in the lignosulfonic acid spectrum, as compared to dioxane–hydrochloric acid lignin, are rounded or less well defined. The 815 and 860 cm.$^{-1}$ bands are very weak. This strongly suggests higher molecular weights (increases in molecular weight usually produce a more diffuse spectrum), structural rearrangement and/or condensation. Colthup[31] suggests the following series of absorption bands for sulfonic acids and salts: 1260–1150 cm.$^{-1}$ (strong), 1080–1010 cm.$^{-1}$ (medium) and 600–700 cm.$^{-1}$ (medium). A strong but broad band at 1200–1210 cm.$^{-1}$, a band at 1040 cm.$^{-1}$ (evidenced by markedly increased absorption at this wave length as compared with dioxane–hydrochloric acid lignin), and a medium intensity band at 650 cm.$^{-1}$ were observed in the lignosulfonic acid. The band at 1200–1210 cm.$^{-1}$ is somewhat more pronounced in the lignosulfonate salt. Both the 1210 and 1040 cm.$^{-1}$ bands occur at the same frequency as absorption bands already present in the unsulfonated lignin molecule, so they are not particularly valuable for diagnostic studies. The 650 cm.$^{-1}$ band does not occur in unsulfonated lignin. Desulfonation of a sodium lignosulfonate by treatment with sodium hydroxide at elevated temperatures results in a loss of the 650 cm.$^{-1}$ band and a marked decrease in the 1040 and 1210 cm.$^{-1}$ absorptions. The spectrum of the desulfonated lignosulfonate, though containing bands of approximately the same wave lengths, is readily distinguishable from the dioxane lignin spectrum. Considerable structural alteration has apparently occurred in the desulfonation process, including increase in phenolic hydroxyl content and loss of methoxyl groups.

Although considerable information about the structure of conifer lignin has been gained by a study of their infrared spectra, the work reported here also indicates that elucidation of lignin structure may be even more difficult than hitherto suspected. Thus, not only are native lignins not identical with whole wood lignin, but lignin structure appears to vary with genera. Further difficulties are involved in the fact that many previous investigators have attempted to apply their results on lignins isolated by processes such as alcoholysis, sulfonation, etc., to lignin as it exists in wood. Infrared spectra show, however, that many of these lignins are rearranged during isolation; consequently structural studies based on them are of limited value for this purpose. Since generic differences in lignins are apparent from the spectra, it is proposed that future work should be devoted to functional group analyses of lignins isolated by the same process from various genera, and that the enzyme systems and cambial constituents (lignin intermediates) of various genera and species be compared. In this way many past discrepancies in the lignin literature are likely to be clarified.

(31) N. Colthup, *J. Opt. Soc. America*, 40, 397 (1950).

SHELTON, WASHINGTON

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Reaction of Saccharin with Amines. *N*-Substituted-3-Amino-1,2-benzisothiazole-1,1-dioxides

CALVERT W. WHITEHEAD AND JOHN J. TRAVERSO

Received December 17, 1959

Saccharin reacts with excess amines to produce *N*-substituted 3-amino-1,2-benzisothiazole-1,1-dioxides. Under the same conditions *N*-methylsaccharin produces *N*-substituted *o*-methylsulfamylbenzamides. Saccharin with one equivalent of amine produces *N*-substituted *o*-sulfamylbenzamides. The reaction products of hydrazine hydrate with saccharin and *N*-methylsaccharin have been assigned structures based on the similarity of their infrared spectra to that of benzoic acid hydrazide.

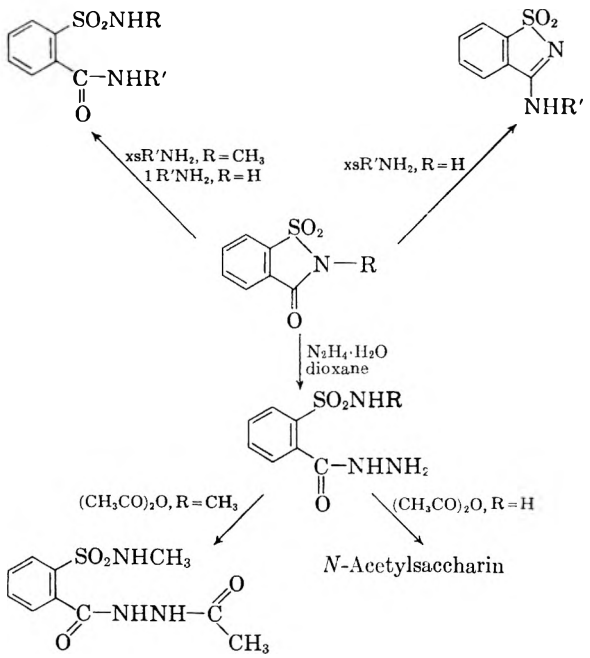
A number of 3-amino-1,2-benzisothiazole-1,1-dioxides were prepared for pharmacological evaluation as diuretic or hypoglycemic agents. As in the case of arylamines,[1] refluxing saccharin with alkyl- and aralkylamines boiling at least at 130° for eight hours gave crystalline 3-amino-1,2-benzisothiazole-1,1-dioxides. Derivatives of lower boiling amines

(1) A. Mannessier-Mameli, *Gazz. chim. ital.*, **65**, 51 (1935); *Chem. Abstr.*, 29, 3996 (1935).

were made by the amination of pseudosaccharin chloride. These compounds are all weak acids with pK'_a values of about 12.5 in 66% dimethylformamide. All the 3-amino-1,2-benzisothiazole-1,1-dioxides have a bitter taste.

Under the conditions which produced the 3-amino-1,2-benzisothiazole-1,1-dioxides, *N*-methylsaccharin yielded benzamide derivatives. *N*-substituted *o*-methylsulfamylbenzamides were obtained when *N*-methylsaccharin was refluxed with excess amines boiling at least at 130°. The *N*-substituted *o*-sulfamylbenzamides were prepared by refluxing saccharin with one equivalent of amine in chlorobenzene solvent. The *o*-sulfamylbenzamides are weakly acidic with pK'_a values of 12.4 while the *o*-methylsulfamylbenzamides have pK'_a values of 13.3 in 66% dimethylformamide.

A similar situation occurred when hydrazine hydrate was used as a reactant under milder conditions. In aqueous solution saccharin and hydrazine hydrate merely formed the salt. In dioxane, saccharin and hydrazine hydrate produced a compound with the empirical formula $C_7H_9N_3O_3S$ after initial salt formation. *N*-Methylsaccharin also reacted with hydrazine hydrate in dioxane to give a product of $C_8H_{11}N_3O_3S$.



The infrared spectra of the two compounds are very similar and suggest like structures. In acetonitrile solution $C_8H_{11}N_3O_3S$ shows amide carbonyl absorption (1658 cm.$^{-1}$), NH_2 deformation (*ca.* 1635 cm.$^{-1}$), amide II (1520 cm.$^{-1}$) and SO_2 stretching absorption (1337, 1175 cm.$^{-1}$). $C_7H_9N_3O_3S$ exhibits amide carbonyl absorption (1660 cm.$^{-1}$), NH_2 deformation (1637 cm.$^{-1}$), amide II (1527 cm.$^{-1}$) and SO_2 stretching absorption (1353, 1173 cm.$^{-1}$). The hydrazine hydrate reaction product of *N*-methylsaccharin ($C_8H_{11}N_3O_3S$) was assigned the structure *o*-methylsulfamylbenzoylhydrazine because of the similarity of the infrared spectrum to that of benzoic acid hydrazide. The solution spectrum (chloroform) of $C_8H_{11}N_3O_3S$ contains NH stretching absorption (3440, 3342, ca. 3285 cm.$^{-1}$), amide carbonyl (1667 cm.$^{-1}$), amide II (1467 cm.$^{-1}$), NH_2 deformation (1625 cm.$^{-1}$) and SO_2 absorption (1337 and 1170 cm.$^{-1}$). In chloroform solution benzoic acid hydrazide exhibits NH absorption (3460, 3340 cm.$^{-1}$), amide carbonyl (1670 cm.$^{-1}$), amide II (1478 cm.$^{-1}$) and NH_2 deformation absorption (1627 cm.$^{-1}$). The shapes and relative intensities of these bands are comparable. Removal of the amide NH and NH_2 deformation bands in the spectra of the deuterated compounds (prepared by exchange with deuterium oxide) establishes the correctness of these assignments. Thus the hydrazine hydrate reaction product of saccharin ($C_7H_9N_3O_3S$) is *o*-sulfamylbenzoylhydrazine.

o-Sulfamylbenzoylhydrazine has an acidic pK'_a 12.0 in 66% dimethyl formamide whereas *o*-methylsulfamylbenzoyl-hydrazine has pK'_a 12.7. Alkyl substitution on the sulfamyl group decreases the acid strength as exemplified by *N*-cyclohexyl-*o*-sulfamylbenzamide (pK'_a 66% dimethylformamide 12.4) and *N*-cyclohexyl-*o*-methylsulfamylbenzamide (pK'_a 66% dimethylformamide 13.3). Although both benzoic acid hydrazide and benzenesulfonamide are weakly acidic (pK'_a 66% dimethylformamide *ca.* 14.0, 13.1), the group titrated in the *o*-sulfamylbenzoyl hydrazines must represent the acidic dissociation of the sulfamyl group. Alkyl substitution on the sulfamyl group would not be expected to lower the acidity of the acid hydrazide.

Both *o*-sulfamylbenzoylhydrazines were treated with acetic anhydride under mild conditions. *o*-Methylsulfamylbenzoylhydrazine produced a normal derivative, 1-acetyl-2-(*o*-methylsulfamylbenzoyl) hydrazine (pK'_a 66% dimethylformamide 10.0). Acetylation of benzoic acid hydrazide greatly increases the acidity (1-acetyl-2-benzoylhydrazine, pK'_a 66% dimethylformamide 11.3). *o*-Sulfamylbenzoylhydrazine, however, produced a cleavage product identified as *N*-acetylsaccharin.

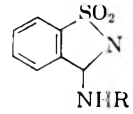
EXPERIMENTAL

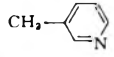
N-Substituted-3-amino-1,2-benzisothiazole-1,1-dioxides (Table I). *Method A.* One-tenth mole of saccharin was added to excess alkyl- or aralkylamine boiling at least at 130°. After initial salt formation the saccharin went into solution and refluxing was continued for 8 hr. The excess amine was then removed under reduced pressure and ether was added to the residue. The crystalline product was collected and again washed with ether. When it was difficult to remove high boiling amines, ether was added directly to the cooled reaction mixture and the crystalline product was filtered off. The 3-amino-1,2-benzisothiazole-1,1-dioxides were purified by crystallization from ethanol or aqueous ethanol.

Method B. Pseudosaccharin chloride[2] (0.05–0.10 mole)

(2) J. R. Meadow and E. E. Reid, *J. Am. Chem. Soc.*, 65, 457 (1943).

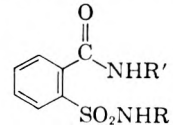
TABLE I. *N*-SUBSTITUTED 3-AMINO-1,2-BENZISOTHIAZOLE-1,1-DIOXIDES

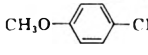
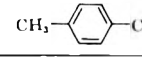


R	Formula	M.P.	Yield, %[a]	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
CH_3	$C_8H_8N_2O_2S$	292 dec.	25 B	48.96	49.09	4.11	4.29	14.28	14.33
CH_2CH_2OH	$C_9H_{10}N_2O_3S$	238	31 A	47.77	47.55	4.45	4.42	12.38	12.58
n-C_3H_7	$C_{10}H_{12}N_2O_2S$	215	61 B	53.55	53.32	5.39	5.36	12.49	12.49
iso-C_5H_{11}	$C_{12}H_{16}N_2O_2S$	166	20 B	57.11	57.31	6.39	6.35	11.10	11.24
$(CH_2)_3N(CH_3)_2$	$C_{12}H_{17}N_3O_2S$	150[b]	41 A	53.91	53.90	6.41	6.54	15.72	15.57
	$C_{13}H_{11}N_3O_2S$	224	55 A	57.13	57.10	4.06	3.97	15.38	15.09
cyclohexyl	$C_{13}H_{16}N_2O_2S$	248	40 A	59.06	59.08	6.10	6.09	10.60	10.68
$CH_2C_6H_5$	$C_{14}H_{12}N_2O_2S$	209	55 A	61.74	62.31	4.44	4.46	10.29	10.30
$CH_2CH_2C_6H_5$	$C_{15}H_{14}N_2O_2S$	244	52 A	62.91	62.92	4.93	4.94	9.78	10.04
p-$CH_3C_6H_4CH_2$	$C_{15}H_{14}N_2O_2S$	222	56 A	62.91	62.44	4.93	5.30	9.78	9.79
m-$CH_3C_6H_4CH_2$	$C_{15}H_{14}N_2O_2S$	214	55 A	62.91	62.87	4.93	4.98	9.78	9.81
p-$CH_3OC_6H_4CH_2$	$C_{15}H_{14}N_2O_3S$	209	46 A	59.58	59.40	4.66	4.48	9.27	9.10

[a] A, Prepared by Method A; B, prepared by Method B. [b] Crystallized from benzene.

TABLE II. *N*-SUBSTITUTED-*o*-SULFAMYLBENZAMIDES



R	R′	Formula	M.P.	Yield, %	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
H	cyclohexyl	$C_{13}H_{18}N_2O_3S$	196	21	55.29	55.52	6.42	6.62	9.92	9.63
H	$C_6H_5CH_2$	$C_{14}H_{14}N_2O_3S$	103	31	57.93	57.74	4.86	4.63	9.65	9.67
CH_3	cyclohexyl	$C_{14}H_{20}N_2O_3S$	130	53	56.73	56.97	6.80	6.71	9.45	9.18
CH_3	$C_6H_5CH_2$	$C_{15}H_{16}N_2O_3S$	105	33	59.19	59.39	5.30	5.63	9.20	9.14
H	$C_6H_5CH_2CH_2$	$C_{15}H_{16}N_2O_3S$	108	20	59.19	59.41	5.30	5.06	9.20	8.82
H		$C_{15}H_{16}N_2O_4S$	115	15	56.23	56.44	5.03	5.14	8.74	8.75
CH_3		$C_{16}H_{18}N_2O_3S$	104	49	60.35	60.39	5.70	6.02	8.80	8.53

was added portionwise to two equivalents of the appropriate amine in dioxane. The mixture was then heated on the steam bath for 1 hr. The dioxane was removed under reduced pressure and dilute ethanol was added to the residue. The solution was treated with carbon if necessary and then filtered. The products were crystallized by concentrating the solution and cooling. The 3-amino-1,2-benzisothiazole-1,1-dioxides were purified by crystallization from ethanol or aqueous ethanol.

N-Substituted-o-sulfamylbenzamides (Table II). Saccharin (0.10–0.20 mole) was added to chlorobenzene to which one equivalent of the appropriate amine had been added. The mixture was refluxed for 8 hr. and then the solvent was removed under reduced pressure. The residue was acidified by the addition of dilute hydrochloric acid and cooled. The material which crystallized was collected and recrystallized from dilute ethanol. The *o*-sulfamylbenzamides were purified by crystallization from aqueous ethanol.

N-Substituted-o-methylsulfamylbenzamides (Table II). *N*-Methylsaccharin[3] (0.05–0.10 mole) was added to excess alkyl- or aralkylamine boiling at least at 130°. The mixture was refluxed for 8 hr. and then as much of the excess amine as possible was removed under reduced pressure. Dilute hydrochloric acid was added to the residue and the acidic solution was cooled to induce crystallization. The material which crystallized was collected and recrystallized from dilute ethanol. The *o*-methylsulfamylbenzamides were purified by crystallization from aqueous ethanol.

o-Sulfamylbenzoylhydrazine. Eighteen grams (0.10 mole) of saccharin was heated on the steam bath for 5 hr. with 5 g. (0.10 mole) of 100% hydrazine hydrate in 250 ml. of dioxane. After the mixture had become homogeneous most of the dioxane was removed under reduced pressure and the crystalline residue was collected. The product was crystallized from ethanol to yield 16.5 g. (77%) of material. The *o*-sulfamylbenzoylhydrazine was purified by crystallization from ethanol, m.p. 180° dec.

Anal. Calcd. for $C_7H_9N_3O_3S$: C, 39.06; H, 4.21; N, 19.53. Found: C, 39.06; H, 4.10; N, 19.81.

o-Methylsulfamylbenzoylhydrazine. Twenty grams (0.10 mole) of *N*-methylsaccharin was added to 150 ml. dioxane. Five grams (0.10 mole) of 100% hydrazine hydrate was added to the solution and the mixture was heated on the steam bath for 4 hr. The dioxane was removed under reduced pressure and the residue was dissolved in ethanol and filtered. The product was crystallized by concentrating the ethanol solution and cooling. The *o*-methylsulfamylbenzoylhydrazine was purified by crystallization from ethanol to yield 17 g. (74%) of material, m.p. 140°.

Anal. Calcd. for $C_8H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33. Found: C, 42.04; H, 4.92; N, 18.18.

N-Acetylsaccharin. Five grams of *o*-sulfamylbenzoylhydrazine was warmed on the steam bath with 40 ml. acetic anhydride to dissolve the solid. The mixture was allowed to stand overnight at room temperature. The excess acetic anhydride was removed under reduced pressure and the residue was dissolved in ethanol. The ethanol solution was concentrated and cooled to yield 3 g. of material with m.p. 191° (lit.[4] m.p. 193°) after recrystallization from ethanol. The infrared spectrum of this material was identical with that of an authentic sample of *N*-acetylsaccharin.

Anal. Calcd. for $C_9H_7NO_4S$: C, 48.00; H, 3.12; N, 6.23. Found: C, 47.84; H, 2.82; N, 6.07.

1-Acetyl-2-(o-sulfamylbenzoyl)hydrazine. Five grams of *o*-methylsulfamylbenzoylhydrazine was warmed on the steam bath with 35 ml. acetic anhydride and then allowed to stand overnight at room temperature. The excess acetic anhydride was removed under reduced pressure and the residue was dissolved in ethanol. Concentration of the solution and cooling yielded 3.5 g. of material. The 1-acetyl-2-(*o*-sulfamylbenzoyl)hydrazine was recrystallized from ethanol m.p. 164°.

Anal. Calcd. for $C_{10}H_{13}N_3O_4S$: C, 44.27; H, 4.83; N, 15.49. Found: C, 44.17; H, 4.97; N, 15.78.

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[CONTRIBUTION NO. 1587 FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Electron Exchange Polymers. XIII. The Preparation of β-Vinylanthraquinone[1]

MIGUEL FERNANDEZ-REFOJO, YUE-LIANG PAN, KENNETH A. KUN, AND HAROLD G. CASSIDY

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The synthesis of β-vinylanthraquinone (2-ethenylanthraquinone) from 2-methylanthraquinone is described. 2-Methylanthraquinone is oxidized to the 2-aldehyde which is converted to anthraquinone-2-acrylic acid. This yields β-vinylanthraquinone upon decarboxylation. The vinyl compound is characterized by physical and chemical methods. It appears possible to polymerize the vinyl compound and to prepare copolymers with styrene, with α-methylstyrene, and with maleic anhydride using free-radical initiators. The yields are low, and the products have not been characterized.

Anthraquinone has been shown not to interrupt the polymerization of styrene, as the presence of anthraquinone during polymerization has no effect on the molecular weight of the polystyrene produced.[2] Anthraquinone is also reported not to react with free radicals from azodiisobutyronitrile.[3] Moreover, three vinylanthracenes have been pre-

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pared: the 1-, 2- and 9-compounds;[4] it is observed that they polymerize. These findings show that under the conditions of the experiments neither the reducibility of anthraquinone nor the size of the parent anthracene molecule prevent vinyl polymerization. It thus seemed feasible to prepare a vinylanthraquinone, and from it to prepare a polyvinylanthraquinone which would contribute an additional type of ring system to our class of oxidation reduction, or electron exchange polymers.[5] The preparation and properties of β-vinyl anthraquinone (2-ethenylanthraquinone) are reported here, as well as some attempts at polymerization.

EXPERIMENTAL

Anthraquinone-2-aldehyde diacetate.[6] Twenty-five grams of 2-methylanthraquinone was dissolved in a hot mixture of 625 ml. glacial acetic acid and 925 ml. acetic anhydride. The mixture was held at 5–10° while 25 ml. of concentrated sulfuric acid, followed by a solution of 30 g. chromic oxide in 30 ml. acetic acid, were added. The addition of the chromic solution should be done with vigorous stirring and should be completed in 2 hr. The mixture was stirred for about 4 more hr. at 5–10° then allowed to warm to room temperature. The greenish solution was poured into ice water, and the resulting precipitate filtered, washed five times with distilled water, and dried. Extraction with chloroform removed the desired product and left as a residue the byproduct, anthraquinone-2-carboxylic acid. Removal of the chloroform yielded a solid which was recrystallized twice from 95% ethyl alcohol. Pure anthraquinone-2-aldehyde diacetate so produced formed yellow, crystalline leaflets, m.p. 145–146° (corr.); yield 22.5 g., (59%).

Anthraquinone-2-aldehyde.[6] Twenty-eight grams of anthraquinone-2-aldehyde diacetate was dissolved in 650 ml. warm acetic acid, and 280 ml. conc. hydrochloric acid was added. The mixture was refluxed 10–15 min. and allowed to cool to room temperature. As the long, light yellow needles which formed are sensitive to light, becoming gray on exposure, the material was kept in the dark and handled in dim light. The crystalline product, dried *in vacuo* over sodium hydroxide pellets, melts at 187–188°, yield: 17.5 g. (89.6%). The filtrate, poured into ice water, yielded about 2 g. of nearly pure aldehyde, m.p. 185–188°, as a light yellow solid, apparently not sensitive to light.

Anthraquinone-2-acrylic acid. When this substance was prepared by the method of Eckert,[7] using a Perkin reaction, the yield was only fair, and the crude product was difficult to purify. The procedure of Hershberg and Fieser[8] gave excellent results. In a 250 ml. round bottom flask, 9.6 g. anthraquinone-2-aldehyde (0.040 mole), 15 g. malonic acid (0.144 mole), and 50 ml. pyridine were refluxed gently (oil bath). At first, the solids dissolved, then in 2 or 3 min. with increased gas evolution and foaming, the mixture set suddenly to a pasty mass. The mixture was heated for 1 hr. with occasional shaking, then 7.5 g. (0.072 mole) of malonic acid and 15 ml. pyridine were added and the mixture heated 1 hr. longer. The mixture was allowed to cool, and was filtered and the yellow solid washed thoroughly with pyridine five times and then with ethyl alcohol. Soluble impurities were thus removed, leaving a yellow solid which, vacuum dried, melted at 333–335°, and weighed 10.5 g. Yield 92.8%.

2-Vinylanthraquinone. Catalytic decarboxylation methods were used to prepare vinylanthraquinone from anthraquinone-2-acrylic acid.[8,9] Ten parts of the acid were heated with 1 part of catalyst in 7 to 8 parts of quinoline at its boiling point (230–240°). After 20 to 30 min., when the evolution of gas had stopped (longer heating decreases the yield), the brown solution containing some solid particles was cooled and extracted with ether. The extract was washed with 4*N* hydrochloric acid (care) four or five times, and with water. Upon drying the ether solution over anhydrous sodium sulfate and removing the ether, a crude 2-vinylanthraquinone was obtained, which could be purified by vacuum sublimation. Alternatively, the brown solution may be poured into excess 2*N* hydrochloric acid to form the soluble quinoline salt. The product was washed free of acid and dried. The charcoal-gray solid remaining was extracted with hot 95% ethyl alcohol. Removal of the alcohol from the extract, by distillation, left crude 2-vinylanthraquinone. Both methods gave nearly the same yields.

The catalysts used were: copper powder, yield 21.4%; basic cupric carbonate, yield 22.8%. When the latter catalyst was added to the boiling solution of anthraquinone-2-acrylic acid in quinoline a slightly improved yield of 25.7% of theory was obtained.

Vacuum-sublimed 2-vinylanthraquinone still smelled of quinoline. Two recrystallizations from ethyl acetate gave a product almost free from quinoline. This formed clusters of yellow crystals, m.p. 175–177°. The substance is slightly soluble in carbon tetrachloride, ether, and glacial acetic acid. It is soluble in toluene, in ethylene dichloride and in warm alcohol, and very soluble in chloroform. The substance shows the —C=C— stretching vibration at 6.11 μ in the infrared region.

Anal. Calcd. for $C_{16}H_{10}O_2$: C, 82.05; H, 4.30. Found: C, 82.25; H, 4.32.

Bromination with pyridine sulfate dibromide[10] calculated for 1.00 double bond; found: 0.88. Hydrogenation in ethyl acetate, using platinum oxide to yield the ethylanthrahydroquinone gave the following results: 0.0523 g. should consume 10.01 ml. hydrogen (S.T.P.). Found: 11.8 ml. A control with 0.1691 g. ethylanthraquinone calcd. 16.03 ml. Found: 18.2. Evidently the hydrogenation easily goes further—possibly to anthranol. The hydrogenation product from vinylanthraquinone is oxidized by air[11] to 2-ethylanthraquinone, with disappearance of fluorescence. The product was shown to be identical with an authentic sample of 2-ethylanthraquinone: m.p. 104.4–107.3°; authentic sample, 107.4–108.3°; mixed m.p. 106.4–108.3°. Infrared spectra were superimposable.

Ozonization of 2-vinylanthraquinone under the conditions used by Hawkins[4a] yielded as the final product anthraquinone-2-carboxylic acid, m.p. 288–290°; authentic sample 290–291°; mixture 290–291°. Infrared spectra were superimposable.

N.M.R. examination. An examination of the nuclear magnetic resonance spectra of vinyl- and ethylanthraquinone produced the expected results. Measurements were made with Varian V-4300 high-resolution N.M.R. spectrometer operating at a frequency of 60 Mc./sec. and a field strength of approximately 14,000 gauss. The anthraquinones were

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dissolved in deuterochloroform using tetramethylsilane as an internal reference for a scale of shielding values.[12] Vinylanthraquinone showed the twelve strong lines of the ABC (approximately ABX) system,[13] $-CH_X=CH_AH_B$, which comprise three symmetrically split quartets centered at values of τ[12]: (X) 3.16, (A) 4.00, and (B) 4.50 with splittings: (X) 10.2 and 17.4 cps., (A) 1.2 and 17.4 cps., and (B) 1.2 and 10.2 cps. Coupling between geminal protons A and B within trigonally hybridized methylene is expected to be small as in styrene and *p*-methylstyrene.[14]

Ethylanthraquinone showed the typical spectrum for an ethyl group with the methylene quadruplet centered at 7.28 τ and the methyl triplet centered at 8.70 τ. Both compounds showed a pair of complex peaks for the aromatic hydrogens which centered at 1.77 and 2.25 τ.

Attempted polymerization of vinylanthraquinone. The following experiments were carried out in a flask with adapter carrying a two-way stopcock so that when monomer, solvent, and catalyst had been introduced the flask could be repeatedly evacuated and filled with nitrogen.

a. *With azobisisobutyronitrile.* 2-Vinylanthraquinone (referred to as monomer) 0.1019 g., 0.001 g. azodiisobutyronitrile, and 10 ml. reagent toluene were heated under nitrogen at 80° for 18 hr. There was neither turbidity nor apparent viscosity change. A further portion of 0.0034 g. catalyst (total 4.32% based on monomer) was added and after 23 hr. the mixture was seen to be turbid. Methanol precipitated 0.0073 g. solid, softening point 190–210°. The infrared spectrum showed the main peaks of anthraquinone but lacked the vinyl absorption at 6.12 μ. Residue from the mother liquors also lacked this peak.

b. *With benzoyl peroxide.* Benzoyl peroxide, 0.004 g., monomer 0.1037 g. in 10 ml. toluene, heated under nitrogen at 80° produced a turbidity after 4 hr., and a precipitate at 24 hr. The solid, removed and washed, weighed 0.0171 g. and softened at 320–330°. To the mother liquors 0.003 g. of catalyst was added and after 32 hr. 0.0164 g. of solid had precipitated. Its characteristics were the same as those of the first product. Again 0.003 g. catalyst was added to the filtrate and after 23 hr. at 80° under nitrogen, a turbid solution was present. Methanol in excess precipitated 0.013 g. solid, with a softening point of 210–220°. Infrared spectra indicated the same anthraquinone structure as the previous fractions. Total product 0.0465 g. (44.8%).

c. *With titanium tetrachloride.* To a solution of 0.1029 g. monomer in 10 ml. ethylene dichloride at −30° was added 0.05 to 0.07 ml. 99.5% titanium tetrachloride. An orange precipitate formed at once. After 2 hr. at low temperature the mixture was brought to room temperature and 95% ethanol added. The orange colored material gave way to a clear yellowish solution. Removal of solvents and working up the products yielded 0.0893 g. (86.78%) of monomer, identified by m.p. and IR.

d. *With sodium.* To a blue solution of 0.0106 g. sodium in *ca.* 20 ml. ammonia at its boiling point, 0.1024 g. monomer in 10 ml. toluene was added. The blue color remained unchanged. After several hours a reddish precipitate had formed on the wall of the flask. Finally, 0.5 g. ammonium chloride was added, the blue color being discharged at once. The ammonia was allowed to evaporate and the product worked up to yield 0.089 g. (86.9%) of monomer, identified by m.p. and infrared.

e. *Copolymerization with styrene* was attempted using 0.1 g. monomer, 0.5 g. freshly distilled styrene, (molar ratio 1:11), 0.006 g. benzoyl peroxide, in 10 ml. toluene. After 24 hr. at 80° under nitrogen there was no apparent increase in viscosity. Methanol in excess precipitated 0.051 g. yellow-white powder, softening at 138–148°, and exhibiting in the infrared peaks characteristic of anthraquinone, and the aromatic absorption of benzene at 6.69 and 6.89 μ.

f. *Copolymerization with α-methylstyrene* was attempted using 0.1 g. monomer, 0.5 g. α-methylstyrene (molar ratio 1:11) and 0.006 g. benzoyl peroxide in 10 ml. toluene. After 19 hr. at 80° under nitrogen, the mixture was cooled and excess methanol added to precipitate 0.0101 g. (1.8% of both monomers) of a solid softening at 165–195°, showing bands in the infrared at 3.47, 6.69, 6.82, 6.93 μ and a small band at 5.80 μ.

g. *Copolymerization with maleic anhydride* was attempted using 0.234 g. monomer, 0.099 g. maleic anhydride (molar ratio 1:11) and 1% benzoyl peroxide in 20 ml. toluene. After 23 hr. at 80° under nitrogen a precipitate was present. Methanol in excess was added, to precipitate 0.046 g. solid (13.8% on both monomers). Using a similar mixture but heating at 100° for 17 hr. produced 0.043 g. (12.9%) of similar product. Using a preparation containing a monomer-maleic anhydride ratio of 1:10, and 2% benzoyl peroxide based on monomer, for 41 hr. at 80°, under nitrogen, 0.0383 g. (11.5% if monomers react 1:1) of product was obtained, softening point 245–257°. The infrared of these products exhibits the characteristic carbonyl groups of both monomers: 5.94 μ for anthraquinone, 5.40 and 5.60 μ for the anhydride.

RESULTS

2-Vinylanthraquinone has been prepared starting with 2-methylanthraquinone. It appears to be homopolymerized in poor yield by radical techniques, and may be copolymerized, also in poor yield, with styrene, α-methylstyrene, and maleic anhydride. The polymerization of styrene seems to be inhibited by the anthraquinone derivative. That the reaction with maleic anhydride is not of the Diels-Alder type may be assumed from the observation that no reaction occurs in the absence of catalyst and that the Diels-Alder reaction is unaffected by initiators or inhibitors.[15]

That no polymerization occurred with the cationic initiator (which functions best when electrons can be released at the double bond) is consistent with the electron-withdrawing effect of the carbonyl group, which is expected readily to remove electrons from the vinyl group. Further, anthraquinone can combine with one or two molecules of aluminum trichloride. The latter complex is insoluble in ethylene dichloride, and is orange in color.[16] The behavior of monomer with titanium tetrachloride presents an analogy. The Lewis acid, attached to the oxygen(s) of the vinylanthraquinone would be expected further to deactivate the vinyl group toward a cationic initiator.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, CASE INSTITUTE OF TECHNOLOGY]

Mannich Reaction Mechanisms

THOMAS F. CUMMINGS[1] AND J. REID SHELTON

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A modified method for following the course of the Mannich reaction is described which makes it possible to analyze for formaldehyde in the presence of aldehydes or ketones. Kinetic data on the reaction between cyclohexanone, dimethylamine, and formaldehyde are presented, and mechanisms consistent with the data are proposed. Different mechanisms are indicated for acidic and basic media. Complex combinations of mechanisms appear to take place at intermediate *p*H values.

The base-catalyzed reaction appears to involve the reaction of a carbanion (derived from the active hydrogen compound) with the aminomethylol by an S_N2 mechanism. The rate increases at higher *p*H values.

The reaction in acid media appears to involve the reaction of a carbonium ion (derived from the aminomethylol) with the active hydrogen compound. The rate is slower than for the reaction in basic media and is independent of *p*H at low *p*H values.

The Mannich reaction[2] involves the combination of an aldehyde, usually formaldehyde, with ammonia or a primary or secondary amine, and with a compound containing an activated hydrogen. The reaction may be illustrated by the following equation:

$$R_2NH + HCHO + R'H \longrightarrow R_2N{-}CH_2{-}R' + H_2O$$

The active hydrogen compound, R'H, is most frequently a ketone, an acid, or an ester, although recently work has been done with nitroalkanes.[3-7]

The mechanism of this reaction has been the subject of considerable discussion. Bodendorf and Koralewski[8] concluded from their experiments that neither the condensation of the formaldehyde with the amine nor with the active hydrogen compound to yield the corresponding methylols showed the true course of the reaction. Lieberman and Wagner[9] presented an attractive mechanism involving the formation of a carbonium ion, $R_2NCH_2^+$ from the amine and formaldehyde and also the formation of a carbanion, $R':^-$, by the removal of a proton from the active hydrogen compound. The final, essentially irreversible step was the combination of the carbonium ion and carbanion to yield the Mannich base.

Alexander and Underhill[10] carried out a kinetic study on the Mannich reaction involving dimethylamine, formaldehyde, and ethylmalonic acid in acid solution. Their experiments showed third-order kinetics with no primary salt effect. This contradicts the mechanism of Lieberman and Wagner, which postulated the final and rate-controlling step as the reaction between the two ions which should show a primary salt effect. The mechanism presented in their paper was only postulated for acidic media. The most significant objection to their conclusion is that they ignore the fact that the amine is largely present in the salt form and this alters the prediction of specific hydronium ion dependence, as will be shown later.

RESULTS AND DISCUSSION

In view of the conflicting evidence in the prior literature, it was decided that an investigation should be made into the mechanism of the Mannich reaction, particularly in basic medium. A kinetic study was carried out after the development of an improved method for following the variation in the concentration of formaldehyde in the presence of compounds such as aldehydes and ketones which interfere with the usual analytical procedures. Using equivalent quantities of dimethylamine and formaldehyde and the active hydrogen compound, cyclohexanone, the progress of the reaction was followed by the variation in the concentration of the formaldehyde that was not combined to form the Mannich base. The procedure involved analysis for the formaldehyde which might be combined in the form of methylols of the amine or the active hydrogen compound, as well as the unreacted formaldehyde.

No primary salt effect could be demonstrated. As seen in Table I, there is no appreciable change in the rate constant when the ionic strength was varied from zero to 0.09. Above this concentration there is a slight increase with increasing ionic strength. This is to be expected when the solvation of potassium chloride is taken into account. This is in agreement with the findings of Alexander and Underhill[10] and would eliminate the mechanism of Lieberman and Wagner as such; but if their mechanism were modified to take into account the probable effect of changing the *p*H of the solution,

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TABLE I

EFFECT OF VARIATION OF IONIC STRENGTH UPON THE THIRD-ORDER RATE CONSTANT

Run	*p*H	*M* HCHO	T.	g. KCl	k, M^{-2} min.$^{-1}$	Ionic Strength
74	10.6	0.096	26	0.0000	0.329	0.00
82	10.6	0.093	25	0.1865	0.329	0.01
85	10.6	0.093	25	0.1867	0.278	0.01
83	10.6	0.093	25	0.7452	0.329	0.04
86	10.6	0.093	25	0.7458	0.316	0.04
84	10.6	0.093	25	1.6781	0.329	0.09
87	10.6	0.093	25	1.6762	0.316	0.09
79	10.6	0.096	25	2.9851	0.500	0.16
80	10.6	0.096	25	4.6595	0.500	0.25
81	10.6	0.096	25	9.1349	0.615	0.49

a reasonable mechanism fitting the data can be postulated.

Increasing the concentration of the hydronium ion would certainly reduce the concentration of the carbanion formed by the removal of a proton from the active hydrogen compound. If this concentration were reduced to negligible proportions, the course of the reaction would have to be through some other intermediate. On the other hand, as the *p*H of the solution was increased, the concentration of the carbanion would be increased and the concentration of the carbonium ion (formed by the removal of the hydroxyl group from the aminomethylol) would be reduced. If the carbonium ion concentration were reduced to a negligible value, the reaction would have to proceed through some other intermediate.

TABLE II

EFFECT OF VARIATION IN *p*H AND TEMPERATURE UPON THE THIRD-ORDER RATE CONSTANT

Run	*p*H	*M* HCHO	T.°	k, M^{-2} min.$^{-1}$
103	10.6	0.1046	6.5	0.0223
100	1.15	0.1046	25	0.0005
94	3.23	0.1046	25	0.0005
96	5.05	0.1046	25	0.0005
97	5.92	0.1046	25	0.0005
98	6.90	0.1046	25	0.0027
102	8.21	0.1046	25	complex
90	9.75	0.1046	25	0.240
91	10.06	0.1046	25	0.260
89	10.23	0.1046	25	0.290
93	11.00	0.1046	25	0.290
108	1.02	0.1046	50	0.0033
110	2.13	0.1046	50	0.0033
112	3.20	0.1046	50	0.0033
114	4.19	0.1046	50	0.0030
116	5.02	0.1046	50	0.0050
117	6.07	0.1046	50	complex
118	7.05	0.1046	50	complex
122	8.00	0.1046	50	complex
124	8.90	0.1046	50	0.735
104	10.60	0.1046	50	3.19
109	1.10	0.1046	70	0.0050
111	2.09	0.1046	70	0.0050
113	3.18	0.1046	70	0.0180
94	3.23	0.1046	70	0.0193
95	4.15	0.1046	70	complex
96	5.05	0.1046	70	complex
97	5.92	0.1046	70	complex
119	8.00	0.1046	70	complex
120	8.55	0.1046	70	8.03
107	10.60	0.1046	70	17.95

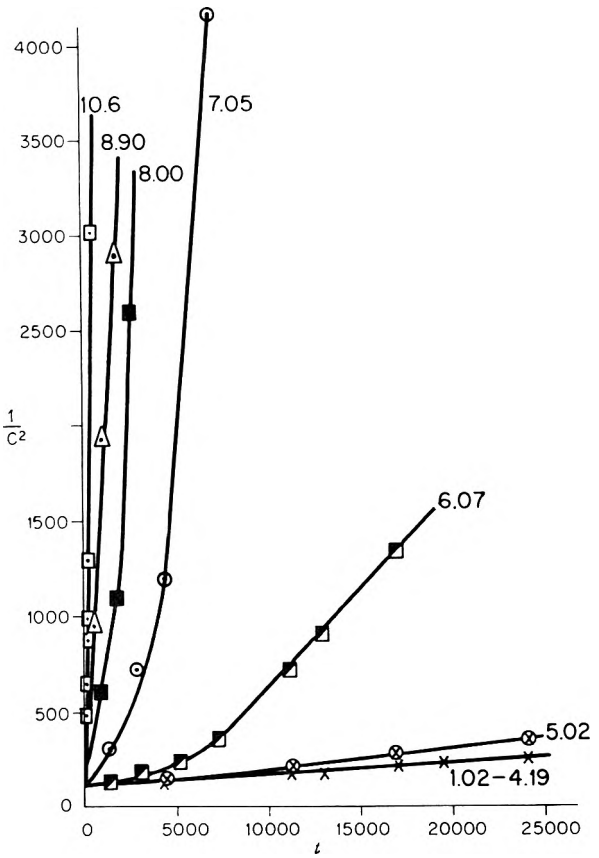


Fig. 1. Third-order plot of the utilization of formaldehyde in the Mannich Reaction

$\frac{1}{C^2}$ *vs.* t at various *p*H levels
C = mole/l.
t = min.

Runs were made at various *p*H values from 1 to 11 and at temperatures from 6.5° to 70°. If the reaction were to follow third-order kinetics, a plot of $1/C^2$ *vs.* time should give a straight line, where C is the concentration of each of the three reactants remaining at any time t. Fig. 1 is a plot of the reciprocal of the square of the concentration (the reactants were added in equivalent quantities to the solution) *vs.* time in minutes for various *p*H values at 50°. Similar curves for data obtained at 25° and 70° can be plotted. From these plots the overall rate constants for the reaction were determined, when the data gave straight lines. If the plot were not a straight line, the rate constant was recorded as complex. In this manner the rate constants in Tables I and II were determined. Other duplicating runs were made which are not included, but check these data.

In Fig. 1 it can be seen that the plots for *p*H values in the range 1 to 5 are reasonably straight lines and that the rate constant is approximately

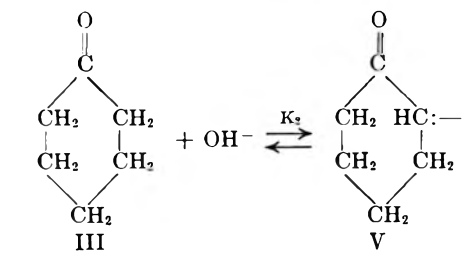
the same in each case. The plot for *p*H 6 no longer is a straight line and the rate is much faster. Each succeeding increase in *p*H increases the rate. With the *p*H approximately 9, the plot once more becomes a straight line. The rate increases with increasing *p*H until *p*H 10.6 is reached. Apparently there is a change of mechanism as the *p*H changes from acid to base.

From Table II it can be seen that the rate constant is quite temperature dependent. The rate constant at *p*H values from 1 to 6 at 25° was indistinguishable from one *p*H value to the next. Above this the rate increases, becomes complex—in that the plot of $1/C^2$ *vs.* time is no longer a straight line—and then follows third-order kinetics with gradually increasing rate constants at higher *p*H values approaching a constant value above a *p*H of 10. At 50° the reaction becomes complex at a lower *p*H than at 25° and at even a lower *p*H at 70°.

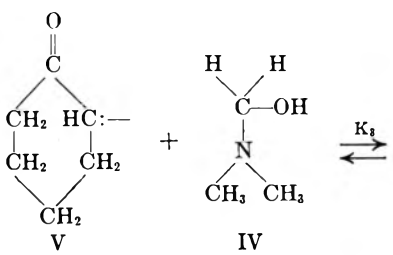
A mechanism which is consistent with the data for the basic medium follows:

$$(CH_3)_2NH + HCHO \underset{}{\overset{K_1}{\rightleftharpoons}} (CH_3)_2NCH_2OH \qquad (1)$$

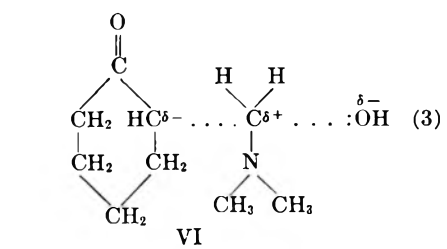
I II IV



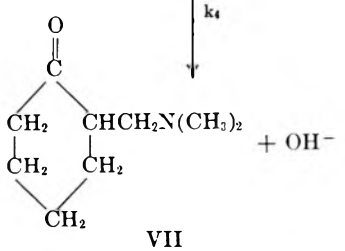
III V



V IV



VI



VII

Dimethylamine (I) combines with formaldehyde (II) to set up an equilibrium with the dimethylaminomethylol (IV). Cyclohexanone (III) reacts with hydroxide ion to set up an equilibrium with the carbanion (V) and water. Intermediates (IV) and (V) react by an S_N2 mechanism to form an equilibrium concentration of the activated complex, or transition state (VI), which decomposes by a relatively irreversible rate-controlling step to yield the Mannich base (VII).

The rate equation is:

$$\text{Rate} = \frac{dx}{dt} = k_r(\text{VI}) \qquad (4)$$

$$= k_rK_3(\text{IV})\,(\text{V}) \qquad (5)$$

$$= k_rK_3K_2K_1(\text{I})\,(\text{II})\,(\text{III})\,(OH^-) \qquad (6)$$

$$= k\,[(CH_3)_2NH]\,[HCHO]\,[C_6H_{10}O]\,[OH^-] \qquad (7)$$

which predicts that at any given *p*H at which this mechanism predominates, the reaction should exhibit third-order kinetics and that with increasing *p*H the rate should increase. This is borne out by the increase in the rate, Fig. 1, with increasing *p*H, and above *p*H 9 third-order kinetics are observed at 50°.

The deviation from third-order kinetics for the reaction in the region between *p*H 5 and *p*H 9, while third-order kinetics are followed above and below these values, suggests that the mechanisms are different in acidic and basic media and that both mechanisms are involved in varying degrees at the intermediate *p*H values.

A mechanism for acid solution follows which fits our data and that of Alexander and Underhill. It is a modification of the mechanism which they considered and rejected on the basis that it predicted specific hydronium ion catalysis. The proposed mechanism differs in that the amine is recognized as being present in equilibrium with the salt form in acid media.

$$(CH_3)_2NH_2^+ + A^- \underset{}{\overset{K_6}{\rightleftharpoons}} (CH_3)_2NH + HA \qquad (8)$$

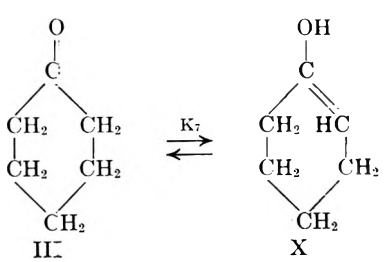
VIII I

$$(CH_3)_2NH + HCHO \underset{}{\overset{K_1}{\rightleftharpoons}} (CH_3)_2NCH_2OH \qquad (9)$$

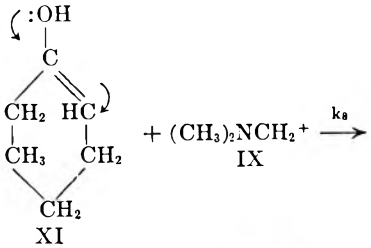
I II IV

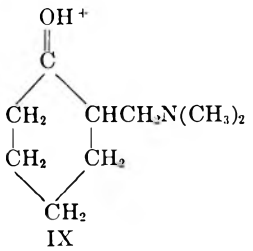
$$(CH_3)_2NCH_2OH + HA \underset{}{\overset{K_6}{\rightleftharpoons}} (CH_3)_2NCH_2^+ + H_2O + A^- \qquad (10)$$

IV IX

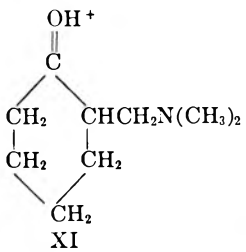


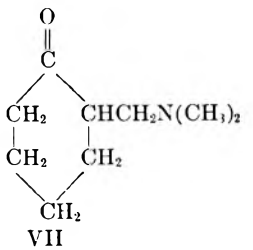
II X





(12)





(13)

From the above equations, with equation (12) essentially irreversible and rate-determining:

$$\text{Rate} = \frac{dx}{dt} = k_8K_7K_6K_1K_5\,[(CH_3)_2NH_2^+]\,[HCHO] \times [C_6H_{10}O] \quad (14)$$

$$= k\,[(CH_3)_2NH_2^+]\,[HCHO]\,[C_6H_{10}O] \quad (15)$$

An S_E2 mechanisn at the α-carbon atom of cyclohexanone analogous to the S_N^2 mechanism shown for the reaction in basic medium can be formulated as an alternative to equations (11), (12) and (13).

The rate equation for this modification is identical with equation (15). Thus, either route predicts that in acid medium the rate is independent of the acid concentration which is what was observed at sufficiently low *p*H values. In the case of Alexander and Underhill where an acid was employed as the active hydrogen compound, if the reactive form is the acid, as shown in their equations, then another term would have to be introduced into the rate equation to account for the equilibrium between the acid form and the ionic form—at *p*H 4 the compound exists about 90% as the monoanion—and this would make the rate equation once again dependent upon the concentration of the hydronium ion.

Lieberman and Wagner[9] reported that in general the methylenebisamines could be substituted for the amine plus formaldehyde in the Mannich reaction. In their mechanism, as mentioned earlier, the carbonium ion, $R_2NCH_2^+$, was used. They postulated that it was formed either by the removal of the hydroxyl group from the aminomethylol, or through the formation of the methylenebisamine and the subsequent decomposition to the carbonium ion. As both routes involve equilibrium reactions, it is not possible to distinguish between them for both yield third-order kinetics. The formation of the methylol is used in our mechanism because it is the shorter, simpler route.

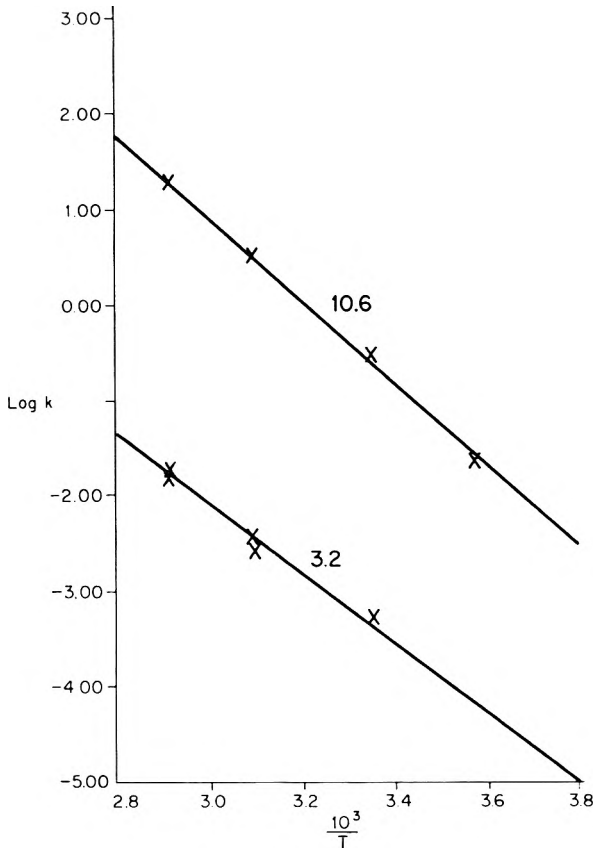


Fig. 2. Plot of the Arrhenius Equation

$\log k$ *vs.* $\frac{1}{T}$

at *p*H = 10.6 and *p*H = 3.2

$k = \frac{\text{liter}^2}{\text{mol.}^2\cdot\text{min.}}$

T = °K

A plot of log K *vs.* 1/T, at two *p*H values, was prepared, Fig. 2, based on the Arrhenius equation:[11]

$$\frac{d\ln k}{dT} = \frac{\Delta E^*}{RT^2}$$

$$\log k = \frac{-\Delta E^*}{2.303RT} + C$$

(11) C. F. Prutton and S. H. Maron, *Fundamental Principles of Physical Chemistry*, Revised Edition, Macmillan, New York, 1951, 634–635.

where k is the rate constant, ΔE^* is the energy of activation, T is the absolute temperature and C is the constant of integration. From the slope of the plot of log k vs 1/T, ΔE^*, a composite energy of activation, can be determined from the following equation:

$$\text{slope} = \frac{-\Delta E^*}{2.303R} = \frac{-\Delta E^*}{4.58}$$

As can be seen in Fig. 2, the points fall quite close to a straight line. The best straight line was determined by a modification of the method of least squares.

Although the plot gives an energy of activation which is a composite value for the several equilibria involved as well as the rate-determining step, and is therefore of little value in itself, the observation that the points do fall closely on a straight line is significant. Theory demands that such a composite energy of activation should produce a straight-line plot and the observation that they do is an indication that the data are valid.

EXPERIMENTAL

Equimolar quantities of dimethylamine and formaldehyde were used in all of the experiments. The quantity of the active hydrogen compound used was determined by the number of α-carbons which had hydrogens attached. In the case of cyclohexanone, with two equally reactive α-carbons, 0.5 mole of the ketone was used to each mole of formaldehyde.

Reaction of cyclohexanone, formaldehyde, and dimethylamine. All solutions were approximately 0.1*M* in dimethylamine and formaldehyde. A weighed sample of cyclohexanone was transferred to a 250 ml. volumetric flask followed by addition of buffer and amine with dilution to approximately 180 ml., and finally the formaldehyde was added. The solution was then made up to 250 ml., shaken and placed in the constant-temperature bath. In the case of the low temperature run, 6.5°, the solutions were cooled to reaction temperature before the final addition of the formaldehyde and dilution to 250 ml. The same procedure was used in the runs at 50° and 70° for basic solutions. The rate of reaction in acid solution was so slow that the error introduced by mixing first and then placing in the baths was negligible.

The cyclohexanone was weighed on an analytical balance (to ±0.0001 g.) in a beaker and rinsed into the volumetric flask. The approximately 1.2*N* dimethylamine, 0.5*M* formaldehyde and the buffer solutions were pipetted in. The buffer solutions used were made from hydrochloric acid, potassium chloride, potassium dihydrogen orthophosphate, boric acid, and sodium hydroxide as recommended by Diehl and Smith[12] with the modification that an equivalent quantity of hydrochloric acid was added to each solution below *p*H 9 to equal the dimethylamine added, in addition to the buffer recommended. The *p*H of the solution was taken with a *p*H meter, at room temperature, both at the start of the run and toward the end. There was little or no variation in *p*H during the runs.

Determination of Formaldehyde. Duplicate samples were taken from the volumetric flask at given time intervals. These samples were pipetted immediately into 50 ml. Nessler's Reagent as prepared by Alexander and Underhill.[10] These solutions were shaken intermittently for a minimum of 5 min., following which a solution containing 35 ml. 2*N* acetic acid and 50 ml. acetone was added. This solution was shaken for a minimum of 15 min.—a greater length of time made the filtration easier—then filtered. The mercury precipitate was rinsed with water to eliminate acetone from the filter paper. When the run had gone to or beyond 70% conversion, it was necessary to rinse with acetone first to remove any Mannich base in the precipitate and then with water. The precipitate and filter paper were returned to the flask into which the 5 ml. samples had originally been pipetted, 25 ml. 0.1*N* iodine solution was pipetted in, followed by approximately 25 ml. water. The mixture was shaken intermittently for 30 to 60 min., and the excess iodine was titrated with 0.1*N* sodium thiosulfate. This procedure permitted analysis for the formaldehyde that was combined with the ketomethylol or the aminomethylol as well as that which was present as free formaldehyde.[10] The modification of the procedure of Alexander and Underhill was made necessary by the interference of cyclohexanone and other carbonyl compounds with the determination. The essential feature of the modification is the filtration which separates the mercury from the carbonyl compounds prior to the reaction with iodine. This procedure has been tested with other ketones and some aldehydes, and appears to be a satisfactory method of analysis for formaldehyde, although in the case of aldehydes the presence of other aldehyde groups must be taken into account in the calculations.

Runs were made at various ionic strengths, at various *p*H values, and various temperatures in order to determine the effects of these variants on the rate of the reaction. Typical results are recorded in Tables I and II. Many additional check runs were made which confirm the results as reported here.

PEORIA, ILLINOIS

(12) H. Diehl and G. F. Smith, *Quantitative Analysis*, Wiley, New York, 1952, 455.

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, FLORIDA STATE UNIVERSITY]

The Decomposition of Bis(o-iodophenylacetyl) Peroxide

J. E. LEFFLER AND A. F. WILSON

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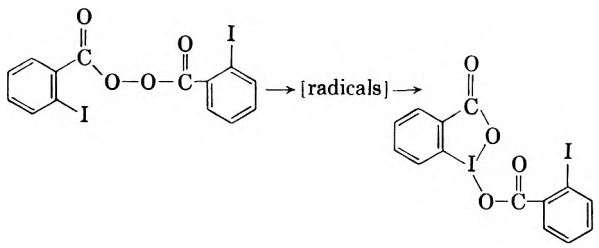
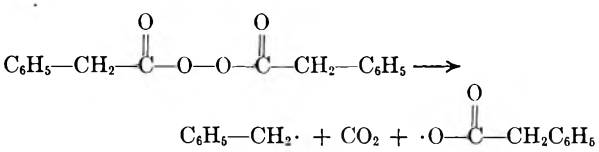
Unlike bis(*o*-iodobenzoyl) peroxide, bis(*o*-iodophenylacetyl) peroxide decomposes without any apparent participation by the iodo substituents. Its decomposition produces radicals capable of initiating vinyl polymerization. The decomposition can also take a polar, acid-catalyzed path; the acid catalysis constants are extremely sensitive to changes in solvent. The rates and products of the decomposition reactions resemble those for the decomposition of bisphenylacetyl peroxide. The behavior of various other iodo-substituted compounds is reported briefly.

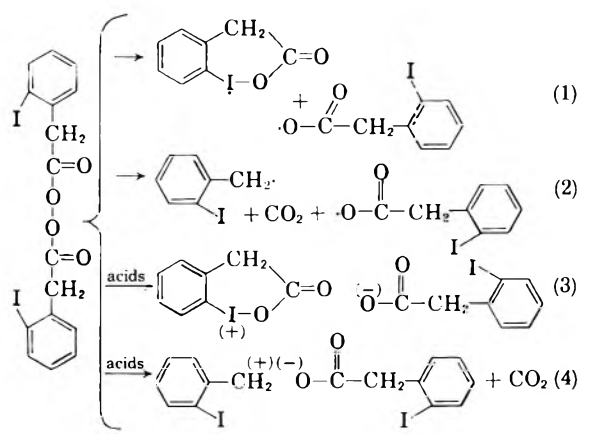
The iodo substituents in bis(*o*-iodobenzoyl) peroxide[1] and in *t*-butyl *o*-iodoperbenzoate[2] markedly accelerate the decomposition of those compounds, apparently by a free radical analog of the neighboring group effect.



Bis(phenylacetyl) peroxide is also exceptionally unstable, apparently because of its ability to form a molecule of carbon dioxide and a resonance-stabilized benzyl radical in a concerted process,[3] and is sensitive to acid catalysts.



Bis(*o*-iodophenylacetyl) peroxide is also very unstable. By analogy with the peroxides previously studied several paths appear plausible for the rate determining step:



Each of these processes involves a lowering of the energy of activation due to resonance or to the incipient formation of new bonds; in each case the lowering of the activation energy would be to some extent counteracted or even outweighed entirely by the corresponding resonance entropy.[4] As far as can be seen from an examination of molecular models, processes involving an even larger number of simultaneous changes in the bonding of the iodo and carboxy groups might also be possible. However, the prediction of the activation entropy for such multiply concerted processes is complicated by the fact that the entropy associated with the rotation about any given bond axis depends on the radius of gyration; it therefore depends on the configuration of the rest of the molecule and hence on the extent to which rotation about any of the other bonds is restricted by the process of activation. We therefore can not predict which of the several processes would have the lowest activation free energy and the greatest rate even though it is clear that the most highly concerted process would have the lowest activation energy.

The kinetics and products of the reaction. Table I shows the principal products of the reaction in various solvents in the absence of added acids. These are consistent with Equation 2 for a concerted formation of carbon dioxide, an iodobenzyl radical, and an iodophenylacetoxy radical. The decomposition of the peroxide initiates the polymerization of vinyl monomers. No cyclic trivalent iodine compound analogous to that formed in the decomposition of bis(*o*-iodobenzoyl) peroxide was observed. The first order rate constants (Table II) are close enough to those for the decomposition of the unsubstituted bis(phenylacetyl) peroxide to make participation by the iodo substituent in the rate-determining step highly unlikely.

The decomposition of the peroxide in the presence of acids is somewhat less accelerated than in the case of bis(phenylacetyl) peroxide. The products of decomposition in the presence of a strong acid

(1) J. E. Leffler, R. D. Faulkner, and C. C. Petropoulos, *J. Am. Chem. Soc.*, **80**, 5435 (1958).

(2) J. C. Martin and W. G. Bentrude, *Chem. and Ind.*, 192 (1959).

(3) P. D. Bartlett and J. E. Leffler, *J. Am. Chem. Soc.*, **72**, 3030 (1950).

(4) "Resonance entropy" is a convenient term for the entropy loss associated with the special, relatively static configurations required for resonance or for orbital overlap.

TABLE I

Solvent and Conditions	Product	Mole %, Product / Peroxide	Recovery, % Benzyl Groups	Recovery, % Carbonyl Groups
Acetone, 0° air present[a]	2,2′-Diiododibenzyl	21 to 22; (26)[a]	21 (26)[a]	
	o-Iodobenzyl alcohol[b]	68 to 78 (52)[a]	37 (26)[a]	
	o-Iodobenzyl *o*-iodophenylacetate[b]	0; (15)[a]	0 (15)[a]	
	o-Iodophenylacetic acid	68; (46)[a]	34 (23)[a]	
		Total	82[b] (90)[a,b]	
Toluene, 0°, N_2 atmosphere	2,2′-Diiododibenzyl	42	42	
	o-Iodobenzyl alcohol[b]	17 to 20	9	
	o-Iodobenzyl *o*-iodophenylacetate[b]	27	27	13.5
	o-Iodophenylacetic acid	2 to 3	1	1
	Carbon dioxide	139 to 143	—	70
		Total	79[b]	84
Chloroform, 0°, N_2 atmosphere	2,2′-Diiododibenzyl	28	28	
	o-Iodobenzyl alcohol[b]	41	20.5	
	o-Iodobenzyl *o*-iodophenylacetate[b]	18	18	
	o-Iodophenylacetic acid	9	4.5	
		Total	71[b]	
Thionyl chloride, 0°, air present	2,2′-Diiododibenzyl	0	0	
	o-Iodobenzyl chloride	84	42	
	o-Iodobenzyl alcohol	3.8	2	
	o-Iodobenzyl *o*-iodophenylacetate	5.1	5	
	o-Iodophenylacetic acid	3.4	2	
		Total	51	
Toluene, 0.2*M* trichloroacetic acid, N_2 atmosphere	Carbon dioxide	93	—	47

[a] Yields from a run in which air was carefully excluded. [b] Some of the *o*-iodobenzyl alcohol is formed during the isolation of the ester, which partially hydrolyzes during chromatography on alumina. The acid moiety of the ester remains on the alumina and is not recovered.

appear to be largely carbon dioxide and *o*-iodobenzyl *o*-iodophenylacetate rather than *o*-iodobenzyl esters of the catalyzing acid. Some *o*-iodophenylacetic acid and some iodobenzyl alcohol were isolated, the latter probably because of partial hydrolysis of the ester on the alumina column. In dichloroacetic acid as a solvent and catalyst the *o*-iodobenzyl *o*-iodophenylacetate formed is readily isolated in pure form; in benzene or toluene in the presence of trichloroacetic acid the quantitative isolation of the pure ester is much more difficult. However, the oils accompanying the ester in the experiment in toluene appear to be largely *o*-iodobenzyl *o*-iodophenylacetate both on the basis of their hydrolysis products and on the basis of their infrared spectrum. The yield of carbon dioxide in the acid-catalyzed reaction in toluene is close to one mole per mole of peroxide. The amount of polystyrene produced by the decomposition of the peroxide in styrene in the presence of 0.05 molar trichloroacetic acid is only about one quarter of that produced in styrene without added acid, indicating that the acid-catalyzed decomposition probably goes by way of a non-radical mechanism.

Table II gives the first order rate constants for the decomposition of the peroxide in various media at 0°. The reaction is first order within a given run. However, increases in the initial peroxide concentration, at least in chloroform, slightly increase the rate constant. As in the case of bis(phenylacetyl) peroxide, there is some induced decomposition. Fig. 1 shows a first order plot of the data for a typical run in chloroform.

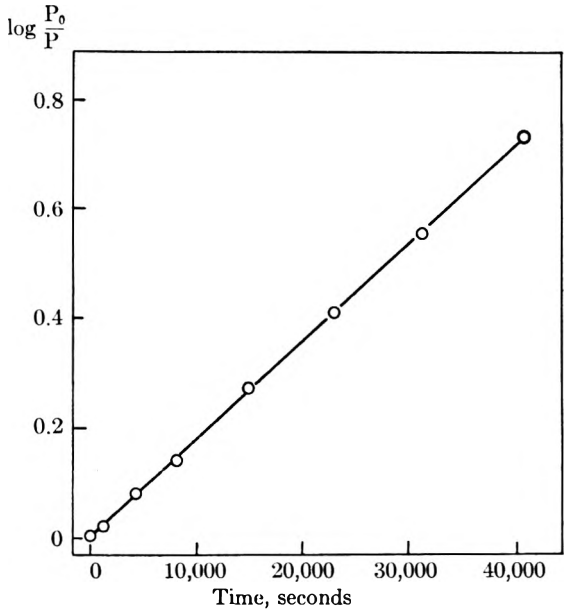


Fig. 1

The decomposition of bis(*o*-iodophenylacetyl) peroxide is also subject to acid catalysis. In toluene at 0° the catalysis constants for trichloroacetic acid are such that the acid-catalyzed part of the decomposition should amount to about 40% in the

TABLE II

Medium	Initial Peroxide Concentration, M	k (sec^{-1} at 0°) $\times 10^5$
Chloroform	0.0204	3.98
	.035	4.19
	.105	4.14
	.152	4.67
	.212	4.49
Chloroform with 0.232M benzoic acid	0.21	4.19
0.216M trichloroacetic acid	.16	7.8
Toluene	0.1	1.30
Toluene with 0.089M trichloroacetic acid	0.1	8.66
0.165M trichloroacetic acid		15.2
0.185M trichloroacetic acid		19.1
Acetone	0.1	2.60
Acetone with 0.296M trichloroacetic acid	0.098	2.60

presence of 0.01M trichloracetic acid. The data available for bis(phenylacetyl) peroxide in the same solvent (but at 18°) correspond to 80% decomposition by the acid-catalyzed process in the presence of 0.01M trichloroacetic acid.[3]

The acid-catalysis of the decomposition of bis(*o*-iodophenylacetyl) peroxide is strikingly dependent on the solvent. Thus in chloroform the rate is increased by less than a factor of two by 0.216M trichloroacetic acid while in acetone not even 0.296M trichloroacetic acid has a detectable effect. The proportions of acid-catalyzed decomposition in the presence of 0.01M trichloroacetic acid in the three solvents would be: toluene, 40%; chloroform 3%; acetone, zero or <0.2%. The reaction in toluene in the absence of added acid shows no auto-catalysis in spite of the greater efficiency of the acid-catalyzed reaction in that solvent; however, the amount of acid produced in toluene is exceptionally low (Table I). The suppression of polymerization by trichloroacetic acid in styrene is consistent with a fast acid-catalyzed decomposition of the peroxide in that solvent. The lack of such an effect by trichloroacetic acid in acrylonitrile suggests that acid catalysis is very slight in acrylonitrile, just as it is in acetone.

The effect of iodo substituents in other reactions. In connection with our experiments on bis(*o*-iodophenylacetyl) peroxide we had occasion to examine briefly the reactions of various other iodo compounds.

Gentle heating of 4-*t*-butyl-2,6-diiodophenol with benzoyl peroxide in benzene produces a transient blue color, probably because of the aryloxy free radical.[5] The blue color fades and is replaced by red, but no quinonoid product is readily isolable from the reaction mixture.

Diazomethyl *o*-iodophenyl ketone is readily converted into *o*-iodophenylacetic acid or its ethyl ester by means of the Wolff reaction with no observable diversion to products attributable to participation by the iodo substituent.

The rearrangement of *o*-iodobenzoyl azide and the Hofmann reaction of *o*-iodobenzoyl amide also proceed in the normal way.

Attempted preparation of *t*-butyl *o*-iodophenylperoxycarbamate from the isocyanate[6] gave a yellow oil which always decomposed violently during chromatography just as the bands began to separate and while they were still near the top of the alumina column. The reaction of the isocyanate with perbenzoic acid gave a complex mixture from which was isolated *o,o'*-diiodoazobenzene.

EXPERIMENTAL

Diazomethyl o-iodophenyl ketone. The procedure of Newman and Beal[7] for the preparation of diazoketones was used. The diazomethyl *o*-iodophenyl ketone crystallized during removal of the ether; it was often accompanied by a viscous oil, m.p. 60–61° after two recrystallizations from carbon tetrachloride. Additional product could be obtained by chromatography of the mother liquor, yield 60%.

o-Iodophenylacetic acid and methyl ester. To 32.2 g. of the diazo ketone in about 250–300 cc. of absolute methanol at room temperature was added with stirring a solution of 3 g. of silver benzoate in 31 g. of triethyl amine over a period of 1 to 2 hr. After filtration and removal of the methanol, the liquid residue was dissolved in ether, washed with water, dried over magnesium sulfate, and distilled. Yield of methyl ester, 29.0 g., b.p. 114° at 1.5 mm. The ester was hydrolyzed by warming with 5N alkali containing a little alcohol and the acid purified by precipitation from sodium bicarbonate solution after extraction from ether. The acid melted at 117° after recrystallization from aqueous methanol.[8] Equivalent weight: Calcd., 262.1; found 262.4.

o-Iodophenylacetyl Chloride. The acid was heated for 1 hr. at 40° or below with a 25% excess of pure thionyl chloride. After removal of the thionyl chloride at the water pump the acid chloride was distilled, b.p. 145° at 15 mm. The thionyl chloride was first distilled from about 1/5 its volume of quinoline, then from about 2/5 of its volume of linseed oil.

Bis(o-iodophenylacetyl) Peroxide.[9] The acid chloride, 1.12 g., 30% hydrogen peroxide, 0.92 g., and a solution of 0.8 g. sodium hydroxide in 2 cc. of water were cooled in an ice bath. First the cold hydrogen peroxide and then the cold sodium hydroxide solution were added to the cold acid chloride. The mixture was then stirred in an ice bath until no trace of the liquid acid chloride remained and the white, crystalline peroxide had precipitated. The product was

(5) *Cf.* C. C. Cook and B. E. Norcross, *J. Am. Chem. Soc.*, **78**, 3797 (1956); I. E. Mueller, K. Ley, and W. Keidaisch, *Ber.*, **88**, 1819 (1955); G. M. Coppinger, *J. Am. Chem. Soc.*, **79**, 501 (1957).

(6) For the general behavior of peroxycarbamates see E. L. O'Brien, F. M. Beringer, and R. B. Mesrobian, *J. Am. Chem. Soc.*, **79**, 6238 (1957).

(7) M. S. Newman and P. Beal, III, *J. Am. Chem. Soc.*, **71**, 1506 (1949).

(8) W. S. Rapson and R. G. Shuttleworth, *J. Chem. Soc.*, 487 (1941) report 114°.

(9) Preparation of the peroxide on a larger scale is not recommended.

shaken with chloroform precooled to below 0° for a few seconds until the peroxide dissolved. The solution was then transferred to a larger flask and cooled in Dry Ice–acetone to freeze out the water. The ice and other solids were washed with more cold chloroform and the combined chloroform extract quickly washed with cold sodium bicarbonate in a separatory funnel. The remaining traces of the aqueous layer were again removed by cooling in a Dry Ice-acetone bath, the solution filtered, and concentrated in vacuum below 0° to a volume of 15–20 cc. Cold methanol was then added. If the peroxide did not precipitate at this point removal of solvent in vacuum was continued until precipitation occurred. The solid peroxide (kept at or below 0°) was recrystallized from chloroform by adding methanol, both solvents being at 0°.

The peroxide may be dried *in vacuo* at 0°, but it decomposes explosively at room temperature. The yield was about 40%. The filtered and dried material usually assayed about 80% regardless of the number of recrystallizations. This may be due either to an unavoidable but reproducible amount of decomposition during the crystallization or, less probably, to a tendency for a certain proportion of the peroxide to decompose during the analysis. Peroxide determinations were carried out by adding the solid peroxide (or a 1 ml. aliquot from a kinetic run) to an excess of sodium iodide in acetone, diluting with water, and titrating the iodine to a starch end-point with sodium thiosulfate solution.

The decomposition of bis(o-iodophenylacetyl) peroxide. Unless otherwise specified in the tables, the peroxide was decomposed in 20–25 cc. of degassed solvent. A stream of prepurified nitrogen was passed through the solvent to protect the reaction mixture from contamination with air during the addition of the peroxide or the removal of samples. Temperature control was by means of a bath of crushed ice and water. The peroxide was dried *in vacuo* at a low temperature before addition to the reaction mixture. Aliquots for analysis were removed by means of a precooled pipet.

Polymerization initiation by bis(o-iodophenylacetyl) peroxide. A solution of 0.255 g. of bis(*o*-iodophenylacetyl) peroxide in 13.3 g. of freshly distilled and degassed styrene contained 1.5 g. of polystyrene after decomposition at 0°. A solution of 0.217 g. of the peroxide in 13.0 g. of styrene and 0.12 g. of trichloroacetic acid yielded 0.36 g. of polymer under the same conditions. The polystyrene was isolated by precipitation from ether on addition of methanol. A solution of 0.425 g. of the peroxide in 11.6 g. of acrylonitrile at 0° became turbid in a few minutes and solid in about 1 hr. Similar results were obtained in the presence of the peroxide plus 0.1 g. trichloroacetic acid in acrylonitrile.

Decomposition products from bis(o-iodophenylacetyl) peroxide. Carbon dioxide was swept from the solution of the decomposing peroxide at 0° by a stream of nitrogen. Water and solvent vapor were removed by means of a Dry Ice trap and a magnesium perchlorate tube and the carbon dioxide trapped and weighed in a tube containing ascarite. For the isolation and estimation of the nonvolatile products the reaction mixtures after removal of the solvent were extracted with sodium bicarbonate; the *o*-iodophenylacetic acid recovered was identified by its melting point. The neutral residue was then further separated by elution chromatography on alumina, in most cases giving three main fractions: *o,o'*-diiododibenzyl, *o*-iodobenzyl *o*-iodophenylacetate, and *o*-iodobenzyl alcohol.

o,o'-Diiododibenzyl. This substance was the first product to be eluted from the alumina column, coming off with 20% benzene–80% hexane. M.p. after recrystallization from methanol, 101.5–102°.

Anal. Calcd. for $C_{14}H_{12}I_2$: C, 38.73; H, 2.79; I, 58.48, mol. wt. 434. Found: C, 38.98; H, 2.81; I, 58.24; mol. wt. 514 (camphor).

The melting point was not depressed on mixing with a sample synthesized by treating *o*-iodobenzyl bromide with magnesium in benzene.

o-Iodobenzyl o-iodophenylacetate. This substance was the second to be eluted from the alumina column and came off with 40% benzene–60% hexane. After recrystallization from hexane it melted at 85.5–86°.

Anal. Calcd. for $C_{15}H_{12}O_2I_2$: C, 37.68; H, 2.53; I, 53.09. Found: C, 38.25; H, 2.65; I, 52.77.

Saponification gave the acid and alcohol, identified by their melting points and mixed melting points. The ester was partly hydrolyzed during chromatography on alumina: 0.048 g. put on the column gave on elution 0.034 g. of the recovered ester plus 0.0032 g. of the alcohol.

o-Iodobenzyl alcohol. This substance was eluted from the column with 10% ether–90% benzene. After recrystallization from hexane and from methanol-water it melted at 90.7–91.1°.

Anal. Calcd. for C_7H_7IO: C, 35.9; H, 2.88; I, 54.1, mol. wt. 234. Found: C, 35.88; H, 3.01; I, 54.04; mol. wt. 246 (camphor). The melting point was not depressed by a sample synthesized by hydrolyzing *o*-iodobenzyl bromide.

N,N'-Bis(2-iodobenzoyl)hydrazine. This substance was formed during the attempted preparation of 2-iodobenzoylhydrazine from the acid chloride and hydrazine hydrate. After recrystallization from ethanol, it melted at 267°.

Anal. Calcd. for $C_{14}H_{10}O_2I_2N_2$: C, 34.17; H, 2.05; N, 5.69; I, 51.58. Found: C, 33.73; H, 1.70; N, 6.19; I, 50.50.

o-Iodobenzoyl azide. The azide was prepared from *o*-iodobenzoyl chloride and sodium azide in aqueous acetone following the general procedure of Smith.[10] The azide was an oil which slowly evolved nitrogen and solidified at room temperature and which on one occasion inflamed spontaneously.

N,N'-Bis(o-iodobenzoyl)urea. This substance was formed from the wet *o*-iodobenzoyl azide on standing. After recrystallization from acetone it melted at 232.5° dec.

Anal. Calcd. for $C_{15}H_{10}I_2N_2O$: C, 33.65; H, 2.17; N, 6.04; I, 54.70. Found: C, 33.49; H, 2.22; N, 6.17; I, 54.29.

Ethyl N-o-iodophenylcarbamate. This substance was formed by treating the crude *o*-iodobenzoylazide reaction mixture with a large excess of ethanol. Sodium chloride was removed by filtration, most of the ethanol was distilled and the urethane precipitated by adding water. After two crystallizations from 50% aqueous ethanol, it melted at 50.5°.

Anal. Calcd. for $C_9H_{10}INO_2$: C, 37.14; H, 3.46; N, 4.81; I, 43.6. Found: C, 37.43; H, 3.66; N, 4.71; I, 43.26.

t-Butyl N-o-iodophenylperoxycarbamate. The general method of O'Brien, Beringer, and Mesrobian was used.[6] Freshly prepared *o*-iodobenzoylazide (0.01 mole) was separated from the aqueous acetone by addition of water and decantation. It was then treated with 0.01 mole or less of *t*-butyl hydroperoxide in benzene. Nitrogen was slowly evolved during about 1 hr. and the solution turned yellow. Concentration of the solution *in vacuo* gave a precipitate of *N,N'*-bis(*o*-iodophenyl)urea and a yellow oil. Chromatography of the oil on neutral alumina in petroleum ether caused a violent reaction with ejection of the alumina just as the bands were beginning to separate. Elution of the alumina with petroleum ether after the decomposition gave a red-brown tar. A variation of the experiment in which the azide was permitted to rearrange to isocyanate before the *t*-butyl hydroperoxide was added gave similar results, as does the use of basic alumina. Chromatography on magnesium sulfate did not separate the mixture.

o,o'-Diiodoazobenzene. A similar experiment using perbenzoic acid in chloroform instead of *t*-butyl hydroperoxide in benzene gave a rapid reaction on adding a few drops of pyridine. The solution turned red, then black, and became hot. The product was a complex mixture which gave a large number of bands on chromatography on neutral alumina. The first fraction (eluted with benzene) gave red needles, m.p. 151.5–152.5° from methanol. Recrystallization from ethanol lowered the melting point; recrystallization from ether gave a product melting at 149.8–150.5°.

(10) P. A. S. Smith, *Org. Reactions*, Vol. III, p. 387.

Anal. Calcd. for $C_{12}H_8N_2I_2$: C, 33.21; H, 1.86; N, 6.46. Found: C, 32.96; H, 1.57; N, 6.64.

Hofmann reaction of o-iodobenzamide. To a solution of 0.06 cc. of bromine in 0.24 g. of sodium hydroxide and 2 cc. of water, prepared at 0°, was added 0.24 g. of powdered *o*-iodobenzamide. The mixture was stirred for 20 min. at 0°; most of the benzamide dissolved. Stirring was continued in the ice bath for another 1.5 hr., then the mixture was allowed to stand at room temperature for 1 hr. After decanting from a very small undissolved residue the mixture was heated at 80° for 2 hr. On cooling, the *o*-iodoaniline crystallized, m.p. 54–56°, yield 0.20 g.; acetyl derivative, m.p. 109.5–110.5°.

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TALLAHASSEE, FLA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, CASE INSTITUTE OF TECHNOLOGY]

Addition of Halogens and Halogen Compounds to Allylic Chlorides. III. Relative Rates of Halogen Addition to Allylic Chlorides

J. REID SHELTON AND LIENG-HUANG LEE[1]

Received September 1, 1959

The magnitude of the deactivation of an ethylenic double bond by electron-attracting groups varies with the type, number, and position of the substituents. Thus, the relative reactivity toward addition of halogen decreases in the order: propene > allyl chloride > 3,3-dichloropropene > 3,3,3-trichloropropene. Isomers of the di- and trichloropropenes containing vinylic halogen were found to be less reactive. Allylic halides were found to add halogen approximately one thousand times faster than the corresponding vinylic halides.

Parts I and II of this series[2] described the additions of halogen compounds to allylic chlorides. This paper is concerned with a study of halogen addition to allylic chlorides. The influence of substituents on the rate of the addition of bromine to ethylenic compounds was investigated by Ingold and Ingold[3] and by Anantakrishnan and Ingold.[4,5] A competitive bromine addition method was used in the presence of methylene chloride at −35° and −78°. The reduced velocity for each ethylenic compound was obtained by comparing the rate of bromine addition of the compound with that of ethylene as unity,[5] *e.g.*, ethylene, 1.0; propene, 2.0; isobutylene, 5.5; trimethylethylene, 10.4; tetramethylethylene, 14.0.

Swedlund and Robertson[6] examined the rate of halogen addition to halogen derivatives of ethylenes. Chlorine was used instead of bromine for the determination of the relative rates which were obtained by comparing the k_2 values calculated at X = 50% (X = halogen absorption). The k_2 values were calculated from the curves by plotting the percentage of halogen absorption against time. The original values were revised in one of their later papers,[7] based on a new value for allyl bromide of 1.3×10^{-2} instead of 3×10^{-1}. (The revised values are included in Table II.)

This study was undertaken to investigate the influence of the number and position of electron-attracting substituents upon the reactivity of the double bond. The methods of preparation for the allylic chlorides used are given in Part I of this series. The kinetic method of Swedlund and Robertson[6] was employed for the rate studies. Vinyl bromide was used as the reference compound to correlate the data of this study with the values on relative rate given in their papers. Except for allyl chloride, chlorine was used instead of bromine to measure the rates of addition. In this type of study, iodine and its compounds are used for the determination of rates for the more reactive olefins; bromine is used for the moderately reactive olefins; and chlorine is commonly used for the less reactive olefinic compounds. The relative rates are obtained from comparisons of rates within one set of data and between one set and another irrespective of the halogen used, provided that there is a compound common to both sets. It has been found[8] that the rate ratio for chlorine and bromine addition, under a given set of conditions is about 250 to 1 and is not critically affected by the structure and reactivity of the olefin. The relative rates for a given pair of compounds are about the same regardless of whether they are determined by chlorine or bromine addition.

The results of the study of relative rates of halo-

(1) This is an abstract of a part of the doctoral thesis submitted by Lieng-Huang Lee, Present address: Dow Chemical Company, Midland, Mich.

(2) Part I, *J. Org. Chem.*, **23**, 1876 (1958); Part II, *J. Org. Chem.*, **24**, 1271 (1959).

(3) C. K. Ingold and E. H. Ingold, *J. Chem. Soc.*, 2354 (1931).

(4) S. V. Anantakrishnan and C. K. Ingold, *J. Chem. Soc.*, 984 (1935).

(5) S. V. Anantakrishnan and C. K. Ingold, *J. Chem. Soc.*, 1396 (1935).

(6) B. E. Swedlund and P. W. Robertson, *J. Chem. Soc.*, 630 (1947).

(7) P. W. Robertson, J. K. Heyes, and B. E. Swedlund, *J. Chem. Soc.*, 1014 (1952).

(8) P. B. D. De la Mare and P. W. Robertson, *J. Chem. Soc.*, 2838 (1950).

TABLE I

RATES AND RELATIVE RATES OF ADDITION OF CHLORINE TO ALLYLIC CHLORIDES

Compounds	Solvents	t (50%), min.	Rates (k_2) l. mole^{-1} min.$^{-1}$	Relative Rates (CH_2=CH_2 = 1.0)
Vinyl bromide[a]	HOAc	22.0	3.3×10^{-1}	1.3×10^{-5}
3,3-Dichloropropene	HOAc	11.0	6.7×10^{-1}	2.6×10^{-5}
cis-1,3-Dichloropropene	HOAc (10% H_2O)	7.3	1.0	2.5×10^{-6}
trans-1,3-Dichloropropene	HOAc (10% H_2O)	8.7	8.5×10^{-1}	2.1×10^{-6}
cis-Dichloroethylene[b]	HOAc (20% H_2O)	700.0	1.1×10^{-2}	4.4×10^{-9}
trans-1,3-Dichloropropene	HOAc (20% H_2O)	1.3	5.1	2.1×10^{-6}
3,3,3-Trichloropropene	HOAc (20% H_2O)	10.3	7.2×10^{-1}	2.9×10^{-7}
3,3,3-Trichloropropene	HOAc (40% H_2O)	1.5	4.9	2.9×10^{-7}
1,1,3-Trichloropropene	HOAc (40%) H_2O)	8.5	8.6×10^{-1},	5.1×10^{-6}

[a] Vinyl bromide was used as a standard and as a reference to standardize the method. [b] *cis*-Dichloroethylene value was used for comparison.[5]

gen addition to allylic chlorides are given in Table I. Table II is a summary of relative rates reported in the literature together with the values obtained in this study on the influence of electron-attracting substituents upon the rate of halogen addition.

TABLE II

INFLUENCES OF SUBSTITUENTS ON RELATIVE RATES OF ADDITION OF HALOGEN TO OLEFINIC COMPOUNDS

Compounds	Relative Rates	References
Propene	2.0	5
Ethylene	1.0	5, 6, 7
Allyl fluoride	3.4×10^{-2}	7
Allyl chloride	1.9×10^{-2}	7
Allyl bromide	1.3×10^{-2}	7
Allyl cyanide	2.7×10^{-3}	7
s-Dichloroisobutylene	2.4×10^{-4}	7
3,3-Dichloropropene-1	2.6×10^{-5}	
Vinyl bromide	1.3×10^{-5}	6
cis-1,3-Dichloropropene-1	2.5×10^{-6}	
trans-1,3-Dichloropropene-1	2.1×10^{-6}	
3,3,3-Trichloropropene-1	2.9×10^{-7}	
1,1,3-Trichloropropene-1	5.1×10^{-8}	
cis-Dichloroethylene	4.4×10^{-9}	6
trans-Dichloroethylene	2.2×10^{-9}	6
Trichloroethylene	1.3×10^{-11}	6

The effect of allylic halogen upon the reactivity of the double bond toward electrophilic addition of halogen is shown by the 100-fold decrease in rate for allyl chloride as compared to propylene. Introduction of a second allylic halogen, as in 3,3-dichloropene, gave a further 1000-fold decrease; and a third allylic halogen, as in 3,3,3-trichloropropene, gave another 100-fold decrease in the relative rate. One vinyl halogen is about as effective as two allylic halogens in decreasing the reactivity of the double bond toward halogen addition. The effect of vinylic and allylic halogen upon the relative reactivity of the double bond is compared in Table III. A 1000-fold difference in magnitude is shown in each case for a change of a single halogen from one type to the other in an otherwise identical structure. The theoretical implications of these relationships will be discussed in the concluding paper of this series.

TABLE III

COMPARISON OF THE EFFECT OF VINYL AND ALLYLIC HALOGEN UPON THE RELATIVE RATES OF HALOGEN ADDITION

Vinyl Halides	Allylic Halides	Difference in magnitude
CH_2=CHX, 10^{-5}	CH_2=CH—CH_2X, 10^{-2}	10^{-3}
XCH=CHX, 10^{-9}	XCH=CH—CH_2X, 10^{-6}	10^{-3}
X_2C=CH—X, 10^{-11}	X_2C=CH—CH_2X, 10^{-8}	10^{-3}

EXPERIMENTAL

A. *Addition of bromine. Reagents.* Dry bromine (Michigan Chemical Co.) was redistilled with potassium bromide. Acetic acid (Du Pont, ACS Standard) melted at 16.4–16.6°. The allylic chlorides: had the following b.p.'s allyl chloride (45°, 760 mm.), 3,3-dichloropropene (81–82.5°, 742.5 mm.) and 3,3,3-trichloropropene (45°, 103 mm.).

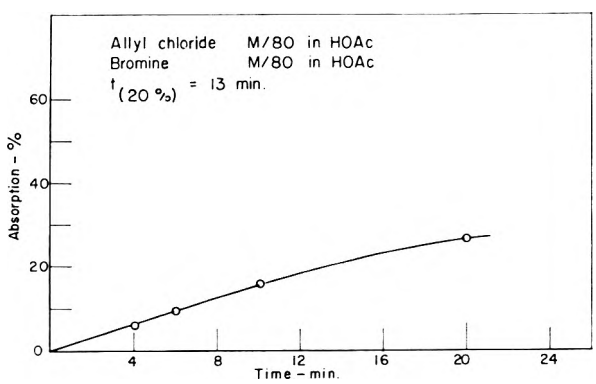

Fig. 1a. Bromine addition to allyl chloride

Procedure. The concentrations of the reactants are expressed as the concentration of the final solution. For example, for all bromine addition experiments, 5 ml. of the allylic chloride in glacial acetic acid (0.025M) and 5 ml. of bromine in glacial acetic acid (0.025M) were mixed in a 10-ml. colored volumetric flask to give a solution .0125M in each. For each time interval, 1 ml. of sample was taken out by a 1-ml. syringe (precision 0.001 ml.) and transferred into

an iodine flask containing 10 ml. potassium iodide solution (5%). The solution was titrated with 0.01*N* sodium thiosulfate solution.

The values of X (% absorption of bromine) were plotted against time. From the resultant curves, as illustrated in Figure 1a, values of k_2 were calculated in (l.) (g.-mole)$^{-1}$ (min.)$^{-1}$. The results for the homogeneous reactions are reproducible.

B. *Addition of chlorine. Reagent.* Chlorine gas was dissolved in glacial acetic acid to prepare the solutions of required concentrations. Besides glacial acetic acid, three other aqueous acetic acid solutions were used: 10% water, 20% water and 40% water in acetic acid. Allyl chloride, 3,3-dichloropropene, and 3,3,3-trichloropropene were the same materials used for the bromine addition; 1,1,3-trichloropropene (b.p. 132°, 760 mm.), *cis*-1,3-dichloropropene (b.p. 104°, 760 mm.), *trans*-1,3-dichloropropene (b.p. 112°, 760 mm.), and vinyl bromide (b.p. 16°, 760 mm.) also were used in this experiment.

Procedure. Most of the procedure is identical with that of bromine addition, except that a special correction had to be made for the slight evaporation of chlorine.

The following sets of experiments were performed with different concentrations of acetic acid solutions. They could not be done at one concentration because of the great variation of rate. This procedure is valid provided a known value for one compound is available for each set of experimental conditions. Thus in Table II the relative rates for vinyl bromide and *cis*-dichloroethylene were known. The relative values obtained for *trans*-1,3-dichloropropene and 3,3,3-trichloropropene in the aqueous acetic acid with 20% water were in turn used as known values for comparisons made in solutions with 10% and 40% water in the acetic acid. It was found that the more dilute the acetic acid solution, the faster the rate for the less reactive allylic chlorides.

(a) In glacial acetic acid: (1) 3,3-Dichloropropene (*M*/10), Chlorine (*M*/80). (2) Vinyl bromide (*M*/10), Chlorine (*M*/80).

(b) In aqueous acetic acid solution (10% water): (1) *cis*-1,3-Dichloropropene (*M*/10), Chlorine (*M*/80). (2) *trans*-1,3-Dichloropropene (*M*/10), Chlorine (*M*/80).

(c) In aqueous acetic acid solution (20% water): (1) *trans*-1,3-Dichloropropene (*M*/10), Chlorine (*M*/80). (2) 3,3,3-Trichloropropene (*M*/10), Chlorine (*M*/80).

(d) In aqueous acetic acid solution (40% water): (1) 3,3,3-Trichloropropene (*M*/10), Chlorine (*M*/80). (2) 1,1,3-Trichloropropene (*M*/10), Chlorine (*M*/80).

The values of X (% absorption of chlorine) were plotted against time as illustrated in Figure 1b and the rate k_2 evaluated from the slope (see Table I).

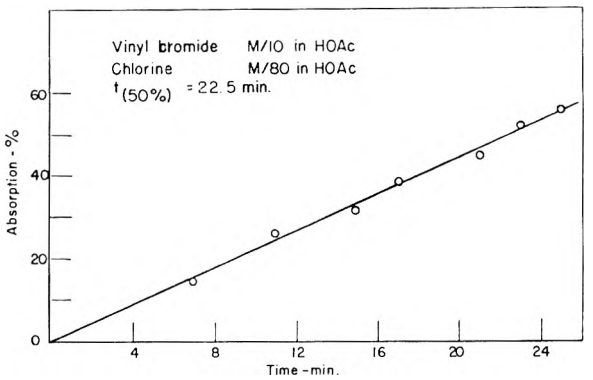

Fig. 1b. Chlorine addition to vinyl bromide

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CLEVELAND 6, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, THE HEBREW UNIVERSITY]

On the Nitration of D-Fructose. I.

AHARON H. SHAMGAR AND JESHAYAHU LEIBOWITZ

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Fructose was nitrated by nitronium sulfate. Six compounds were isolated, either as nitrate esters or—after denitration—as derivatives of fructose, four of which could be identified as dimeric condensation compounds of fructose anhydrides. Three of them are described: difructose-anhydride I, diheterolevulosan I, and diheterolevulosan II. A suggestion is put forward on the mechanism of their formation.

In their effort to identify possible decomposition products of cellulose nitrate[1] a large number of simple and compound sugars have been nitrated by Will and Lenze,[2] using nitronium sulfate as nitrating agent. Most of the sugars yielded the expected fully nitrated products, with the exception of xylose, glucose, fructose, and sucrose. From the monosaccharides crystalline nitrates of the anhydrides of the corresponding sugar could be obtained, besides some amorphous nitration products of ill-defined character. Complete nitration of xylose, glucose, and sucrose has been performed in more refined ways;[3-5] however, no success in full nitration of fructose has been reported.

This sugar differs from the others in its behavior towards strong mineral acids, the action of which causes dehydration and dimerization.[6] The properties of six difructose dianhydrides were summarized by Wolfrom *et al.*[7] The existence of monomeric

(1) W. Will, *Ber.*, **24**, 400 (1891).

(2) W. Will and F. Lenze, *Ber.*, **31**, 68 (1898).

(3) L. Brissaud, *Mem. services chim. état*, **30**, 120 (1943).

(4) G. Fleury and L. Brissaud, *Compt. rend.*, **222**, 1051 (1946).

(5) E. J. Hoffmann and V. P. Hawse, *J. Am. Chem. Soc.*, **41**, 235 (1919).

(6) A. Pictet and J. Chavan, *Helv. Chim. Acta*, **9**, 809 (1926).

(7) M. L. Wolfrom, W. W. Binkley, and H. W. Hilton, *J. Am. Chem. Soc.*, **74**, 2867 (1952).

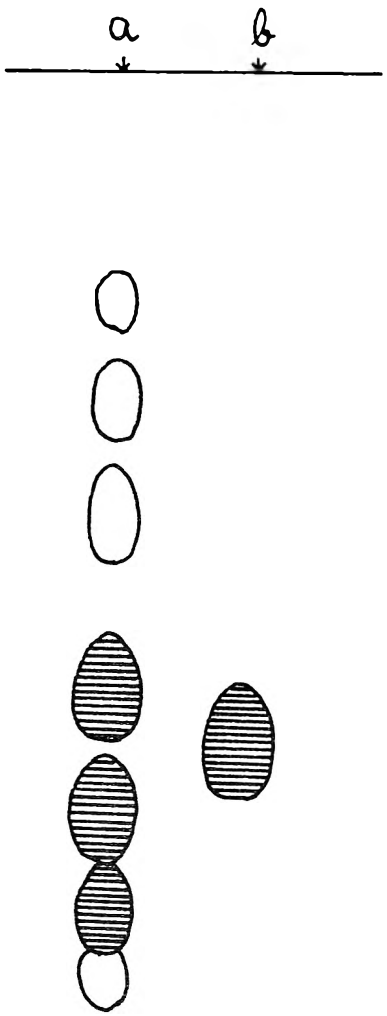

Fig. 1. a. Reduction products of the noncrystalline fraction (III) obtained by nitration of fructose. b. D-Fructose

fructose anhydrides has been reported several times[6,8] and a suggestion put forward that these compounds dimerize rapidly. The only well defined monomeric fructose anhydride was prepared by Sarel and Leibowitz[9] by nitration under non-acid conditions.

The purpose of the present work is to reinvestigate the nitration products of fructose as described by Will and Lenze.[2]

By the action of nitronium sulfate on fructose a dextrorotatory amorphous powder (I) was obtained which could be separated into an ethanol soluble fraction (II) and an insoluble sirup (III). From II and III two crystalline compounds separated (IV and V), both proving to be nonreducing hexanitrates of a difructose dianhydride. IV and V differed markedly in their x-ray diffraction pattern, but had similar positive rotatory power and the same analytical composition and infrared absorption spectra. On catalytic reduction they were both converted into the same substance (VIII), identified as "Difructose Anhydride I". Renitration of VIII yielded IV again. IV and V are therefore one substance, exhibiting dimorphism; they are apparently the "α-fructosan trinitrate" described by Will and Lenze,[2] but they constitute a small fraction only of I. No other homogeneous fructose derivative could be isolated from I by fractionation from different solvents or by chromatography which produced but a minute quantity of another crystalline substance (VI) which proved to be nitrogen-free and is presumably an oxidation product of fructose (*meso*-tartaric acid?).

Compound III was subjected to catalytic hydrogenolysis,[10] using low hydrogen pressure. The dextrorotatory crude reduction product (VII) reduced Fehling's solution rapidly and was developed by paper chromatography into 7 spots, none of which is identical with fructose (Fig. 1). Six crystalline compounds could be obtained by column chromatography, three of which were identified with well defined fructose derivatives, namely "Difructose Anhydride I" (VIII), "Diheterolevulosan I" (IX), and "Diheterolevulosan II" (X). A fourth substance (XI) falls into a new class of nonreducing compound carbohydrates, consisting of fructose and methylglyoxal; this substance will be described elsewhere. The remaining two crystalline compounds (XII, XIII) show exceptionally high values of optical rotatory power.

The nature of the products isolated so far reveals that the action of nitronium sulfate on fructose results in esterification, polymerization, dehydration, anhydride formation, oxidation, and cleavage of the C—C bonds.

The complete absence of fructose from VII (Fig. 1) seemed rather surprising, since this sugar is kept in the acidic nitration medium for not more than 20–30 minutes. Most of this period is necessary for sufficient separation of the products from the reaction mixture. By using a technique for extracting the crude nitration product which further minimizes the contact between the product and the reactants, a levorotatory product (XV) was obtained. Its reduction product (XVI) could be resolved by paper chromatography into four strong and seven faint spots, predominant among them a spot identical with fructose (Fig. 2).

Thus, the initial formation of a nitrate of monomeric fructose has been demonstrated. This result could be confirmed by chromatographic analyses of the denitration products derived from the crude nitrates which have been prepared from fructose in the absence of sulfuric acid, according to the methods of Brissaud[3] (XVII) and Oldham[11] (XIX). In both cases the fructose spot was prominent in the paper chromatogram (Fig. 2).

(8) L. Sattler and F. W. Zerban, *Sugar*, 39, No. 12, 28 (1944).

(9) M. Sarel and J. Leibowitz, *J. Org. Chem.*, 24, 141 (1959).

(10) L. P. Kuhn, *Anal. Chem.*, 20, 276 (1950).

(11) J. W. H. Oldham, *J. Chem. Soc.*, 127, 2840 (1925).

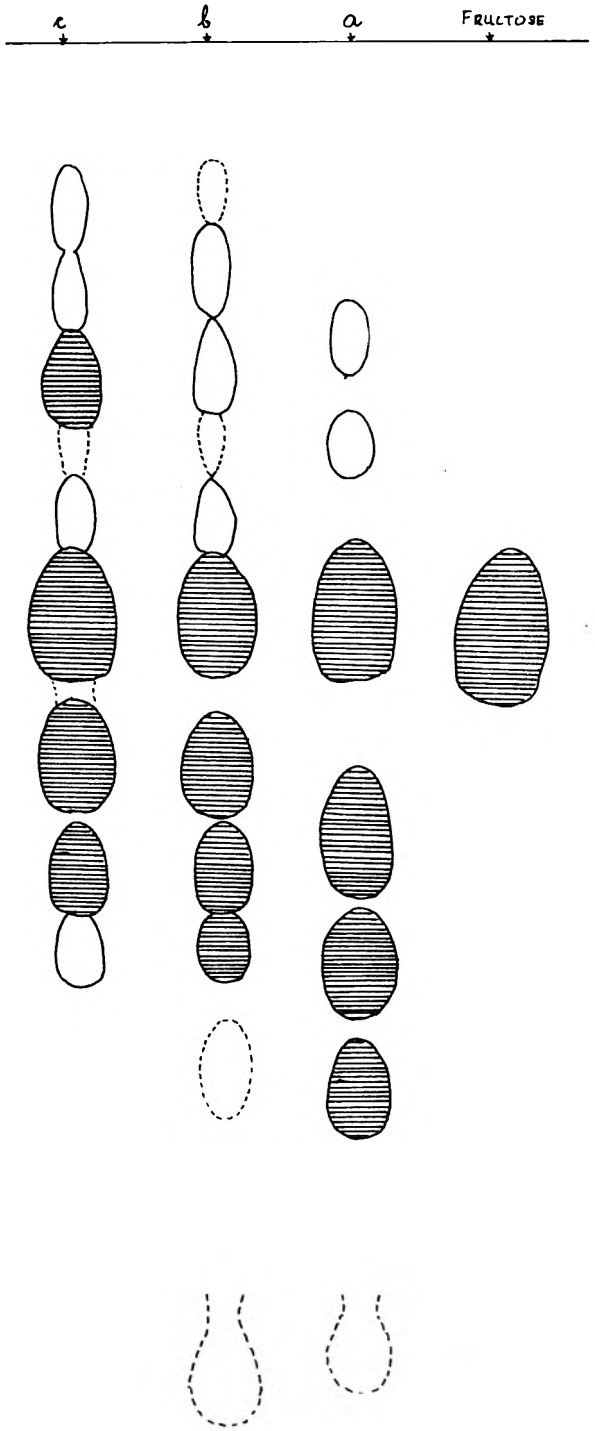

Fig. 2. a. D-Fructose nitrated by an HNO_3-P_2O_5 mixture and reduced. b. D-Fructose nitrated by HNO_3-H_2SO_4 (method B) and reduced. c. D-Fructose nitrated by an HNO_3-AcOH-Ac_2O mixture and reduced

The formation of difructose dianhydrides by dry[12] or concentrated aqueous hydrochloric acid[6] never exceeded 50%, although the time of reaction might last several days. After acid treatment of inulin Jackson and Goergen[13] were able to isolate difructose dianhydrides but could not obtain them from D-fructose treated in a similar manner.

Difructose anhydride I was formed by the action of concentrated nitric acid on inulin acetate.[14]

In our experiments it has been shown that nitrates of fructose are formed initially but that these subsequently undergo anhydridization and dimerization. It can be presumed that tetra- and penta-nitrates of fructose exceed free fructose in their reactivity. Nitrate groups on C-1, C-2, and C-3 would differ considerably in the mechanism of the fission of their C—O—NO_2 linkages. The removal of an —ONO_2 group from C-2 of fructose might produce anhydro derivatives with or without Walden inversion; both these possibilities have been realized in the case of the hydrolysis of β-acetonitro glucose.[15] The formation of a monomeric anhydride from (XVII), as β-2,3-*anhydro*-fructofuranose (XXI) of Sarel and Leibowitz, demands a free hydroxyl group on C-3 as it exists in D-fructose 1,2,4,6-tetranitrate. This incomplete nitration takes place only when the introduction of the nitrate group is performed by dinitrogen pentoxide or nitric acid in acetic anhydride, while the nitronium ion in a strong acid medium effects complete esterification. Fructose, nitrated by nitronium sulfate and reduced, yielded only traces of XXI, and no XXI was found after the action of nitric acid in presence of phosphorus pentoxide.

The spontaneous decomposition of penta- or 1,3,-4,6-tetra-nitrate of fructofuranose can be compared to the action of nitric acid on triacetyl inulin.[14] The free ketolic OH on C-2 might acquire acidic properties by the influence of the neighboring nitrate-oxygen atom on C-1 of a neighboring molecule. This mechanism implies the liberation of nitric acid (or nitrous gases) from the nitrate esters—a phenomenon which in fact could be observed.

However, the large variety of products obtained by the action of acids on fructose indicates the co-existence of several reaction mechanisms. In a strongly acidic medium C-2 undoubtedly serves as potential carbonium ion,[16] thus facilitating the formation of an unstable epoxy-ring after elimination of nitric acid (Fig. 3a) or alternatively, the formation of a more stable anhydric bond with some C—O—NO_2 group of a second molecule, also with the elimination of HNO_3. In case this reaction is performed with the C-1-ONO_2 group—which seems most probable—the conditions for the formation of a dioxan-like structure are realized, as the second molecule is able to react in a similar way with the first one (Fig. 3b). Less probable is the formation of an anhydride involving C—3—ONO_2 (Fig. 3c), although a compound of this type

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Probable mechanisms of anhydride formation in a strong acid medium

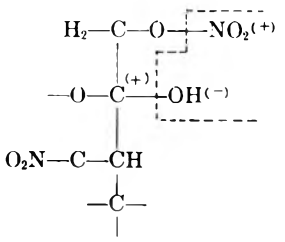

Fig. 3a

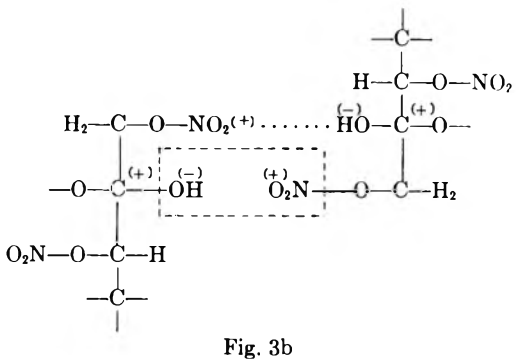

Fig. 3b

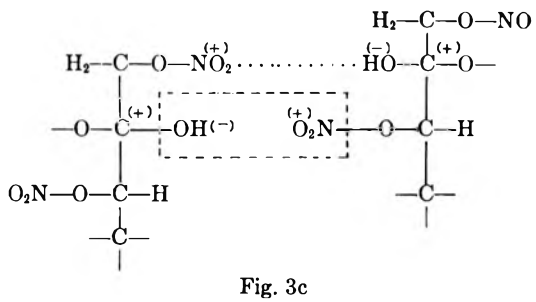

Fig. 3c

has been isolated.[17] Any other type of anhydric bond which did not result in a dioxan-like structure, would be unstable and probably undergo fission under the conditions of the reaction.

Moreover, the nitrated products undergo more easily a C—C fission which produces three-carbon-derivatives, as will be shown in a subsequent paper.

EXPERIMENTAL

Reagents. Absolute nitric acid (d_{15} 1.52) was prepared by vacuum distillation[18] of a mixture consisting of 1 part of nitric acid 70% and two parts of sulfuric acid 98% (v./v.) at temperatures not exceeding 20° (0.4 mm. Hg), and the distillate was collected in liquid air. D-*Fructose* (N.B.C.) was ground and sieved (mesh 100 and up) and dried over phosphorus pentoxide to constant weight. Dry *ethanol*, used for crystallizations, was prepared from commercial absolute ethanol by means of magnesium and iodine.[19] *Acetic acid and acetic anhydride* were freshly distilled before use. *Chloroform* was cleaned by means of aqueous sulfuric acid and washed with water until neutral, dried over calcium chloride, and distilled. *Nitrobenzene* was washed with water, dried over anhydrous soda and lyophillized at 2×10^{-2} mm. Hg.

Catalytic hydrogenolysis was carried out in a Parr apparatus at a hydrogen pressure of 60 lb./sq. inch (approx. 4 atm.), using twice as much palladium catalyst,[10] 10% on charcoal, as nitrates. After 20 min. the reactions with diphenylamine and Nessler's reagent were negative.

Quantitative chromatographic separations were carried out by means of a column containing a mixture of Florex-Celite (Hiflo)[20] 5:1, using 200 g. of the adsorbent for each gram of the carbohydrate mixture.[7]

Paper chromatographic separations (descending) were performed on Whatman No. 1 filter paper (for chromatography). If not stated otherwise, the developing mixture consisted of 9 parts butanol, 8 parts water, and 5 parts pyridine. Each separation was run in duplicate, using for spot detection resorcinol 0.25% in phosphoric acid (85%), diluted 1:10 by ethanol in one case, and anthrone reagent in the other case. The location of the spots was copied with a soft lead pencil as described by Sattler and Zerban.[21]

Analyses. Nitrogen determinations were carried out according to Kuck *et al.*,[22] using either a solution of the nitrate ester in 96% ethanol or dry material in a tiny aluminum cup, which dissolved completely within 1 min. X-ray powder diffraction diagrams were photographed with a Guinier-De Wolfe camera (dispersion constant 4 mm./degree) with Cuα K radiation.[23] Infrared absorption spectrography was carried out on a Baird IR Spectrophotometer Model B, using a sodium chloride prism. Carbon/hydrogen determinations were carried out by Drs. G. Weiler and F. B. Strauss, G. B. Oxford. Melting points were determined by a Fisher-Jones apparatus and are uncorrected.

Procedures. Nitration of D-*fructose by nitronium sulfate* (Method A).[2] Thirty grams of D-fructose was dissolved in 300 ml. abs. nitric acid at 10° by addition in small portions (2–3 min.) and 600 ml. of sulfuric acid (precooled to 5°) was added with constant stirring over a period of 15–20 min., keeping the temperature of the reaction mixture at 15–18°. Soon turbidity set in and a sirup was formed. After all the acid was added, the mixture was transferred to a separating funnel and the sirup allowed to separate (15–30 min.). The turbid acid mixture was removed and the sirup allowed to run into a large mortar containing crushed ice, whereupon it turned into a white solid. This was thoroughly ground, the water-ice layer decanted and fresh ice added. After 15–20 repetitions of this procedure the ice water was neutral towards litmus. The solid was then dried by suction and then kept overnight *in vacuo* over P_2O_5 at 5°. In this way 32–35 g. of the crude product (I) was obtained, $[\alpha]_D^{22}$ +11° (ethanol).

Anal. Found: N, 12.9.

Separation of the trinitrates: (a) I was partly dissolved by shaking mechanically for 4 hr. with 50 ml. of abs. ethanol, yielding a colorless solution (II) and a yellowish sirup (III). II was kept at room temperature for two weeks during which fine needles (IV) separated. By recrystallization from absolute ethanol large monoclinic rods were obtained, $[\alpha]_D^{28}$ +49.5° (abs. ethanol, *c* 1.9), $[\alpha]_D^{27}$ +49° (*c* 8.6 in absolute methanol), $[\alpha]_D^{25}$ +37.7° (*c* 6.1 in benzene).

(17) M. L. Wolfrom and M. G. Blair, *J. Am. Chem. Soc.*, 70, 2406 (1948).

(18) An airbalasted "Speedivac" rotatory pump, single stage model 1SC30, Edwards & Co. Ltd., London, was used.

(19) A. I. Vogel, *Practical Organic Chemistry*, Longmans, Green & Co. Ltd., London, 1951, p. 166.

(20) Florex XXX, a fuller's earth type produced by the Floridin Company, Warren, Pa. Celite (Hiflo) a silicious filter-aid produced by Johns Manville Company, New York, N. Y.

(21) L. Sattler and F. W. Zerban, *Ind. Eng. Chem.*, 41, 1401 (1949).

(22) J. A. Kuck, A. Kingsley, D. Kinsey, F. Sheeham, and G. F. Swigert, *Anal. Chem.*, 22, 604 (1950).

(23) The authors are indebted to Prof. A. Alexander and Dr. Z. Kalman of the Department of Physics of the Hebrew University, for carrying out these measurements.

Anal. Calcd. for $C_6H_7N_3O_{11}$: C, 24.24; H, 2.32; N, 14.14. Found: C, 24.5; H, 2.66; N, 14.1.

Melting point was 140° with a distinct transformation at 125°. At this latter temperature the transparent needles turn spontaneously opaque, but show no sign of melting until the temperature of 140° is reached. This transformation does not cause any change in weight or rotatory power: after recrystallization of the opaque substance from ethanol, IV is regained quantitatively.

(b) When the mother liquor of IV was concentrated by slow evaporation over a course of several weeks at room temperature, it turned slowly into a thin sirup from which small tetrahedric crystals (V) separated. The thin sirup was diluted with some cold ethanol and V was removed rapidly by decantation and filtration. Further small quantities of V were obtained after slurrying III with sufficient cold ethanol and could be separated by filtration. After treatment with cold abs. ethanol V remained in the form of small prismatic spheres, m.p. 138°, $[\alpha]_D^{25}$ +47.6° (*c* 1.47 in methanol).

Anal. Calcd. for $C_6H_7N_3O_{11}$: C, 24.24; H, 2.32; N, 14.14. Found: C, 24.15; H, 2.45.

V showed the same transformation at 124–125° as IV. When V was dissolved in warm methanol or ethanol and the solution cooled, a mixture of IV and V resulted; upon repetition of this, V was completely converted into IV. No complete reconversion of IV into V was successful; however some V was formed when a hot abs. ethanolic solution of IV was slowly concentrated by a stream of dry air.

IV and V rapidly decomposed when heated with camphor or benzophenone and were only slightly soluble in cold benzene. Molecular weight determinations were carried out in colorless nitrobenzene: 0.4602 g. (IV) in 18.10 g. (15 ml.) nitrobenzene—ΔT = 0.31°; mol. wt. = 575. 0.4602 g. (IV) in 24.19 g. (20 ml.) nitrobenzene—ΔT = 0.23°; mol. wt. = 580. 0.0427 g. (V) in 3.65 g. (3 ml.) nitrobenzene ΔT = 0.14°; mol. wt. = 586. 0.0427 g. (V) in 6.10 g. (5 ml.) nitrobenzene ΔT = 0.08°; mol. wt. = 608. $C_6H_7O_2(NO_3)_3$ theor. mol. wt. = 594.

Both IV and V showed identical infrared absorption bands at 1665 cm.$^{-1}$; 1306 cm.$^{-1}$; 1280 cm.$^{-1}$, characteristic for nitrate esters. X-ray powder diffraction data of IV: 5.05 (1 = strongest); 4.70 (4); 4.00 (2); 3.80 (5); 3.65 (3).

X-ray powder diffraction data of V: 8.40 (3); 5.55 (4); 5.05 (7); 4.65 (8); 4.30 (1); 3.80 (2); 3.55 (5); 2.85 (6). V might well contain some amount of IV.

From the sirupy concentrate of II minute amounts of cubic crystals (VI), m.p. 138°, separated after several weeks. VI was free of nitrogen, optically inactive, and did not reduce Fehling's solution. It dissolves in alkaline solution.

Anal. Found: C, 29.87; H, 3.02.

VI might well be impure mesotartaric acid (m.p. 140°, C, 32.0; H, 3.0), but its quantity was insufficient for recrystallization.

Catalytic reduction of IV *and* V. Compound IV (0.089 g.) was dissolved in 4 ml. of dioxan and diluted with 6 ml. of 95% ethanol. One-tenth gram of palladium catalyst, 10% on charcoal, was added and this mixture shaken under hydrogen pressure of 1360 lb./sq. inch for 10 min. The filtrate of the resulting mixture gave no reaction with diphenylamine, Nessler's reagent, or Fehling's reagent. A white sirup (0.053 g.) could be isolated (97.5%) and from its abs. ethanol solution small crystalline aggregates were formed (VIII); $[\alpha]_D^{22}$ +27.5° (*c* 3.8 in water), m.p. 164–165° (uncorr.).

Anal. Calcd. for $C_6H_{10}O_5$: C, 44.44; H, 6.22. Found: C, 44.26; H, 6.59.

Compound V (0.239 g.) was reduced as described above, forming 0.120 g. (88%) of a colorless sirup. After treatment with abs. ethanol, crystals identical with VIII appeared.

Acetylation of (VIII). Compound VIII (376 mg.) was dissolved in 2.0 g. of acetic anhydride and 0.4 g. sodium acetate added. The mixture was heated to 140° for 30 min. and then kept for 40 hr. at 70°. On cooling to room temperature and neutralization, a jelly-like precipitate was formed that was extracted by 3 × 20 ml. of chloroform. After evaporation of the solvent a sirup remained, containing some acetic acid that was removed by distillation with toluene. The sirup was taken up in some ether and crystallized by addition of benzene, yielding 470 mg. (70%) of the hexaacetate of difructose anhydride I. $[\alpha]_D^{18}$ +0.56° (*c* 8.89 in chloroform); m.p. 138°. This hexaacetate showed a transformation at 126–127°, similar to the transformation observed with IV and V, *i.e.*, its long transparent needle-like crystals turned spontaneously opaque with no signs of melting. This hexaacetate (55 mg.) was subjected to deacetylation by a methanolic solution of barium methoxide. After shaking the mixture for 4 hr. at room temperature, it was neutralized by *N* sulfuric acid in methanol over a period of 5 hr., the resulting suspension filtered with a filter aid and concentrated *in vacuo*. Recrystallization from abs. ethanol yielded 34.5 mg. (77% theor.) of (VIII).

Nitration of VIII. Compound VIII (30.8 mg.) was dissolved in 2 ml. of a mixture containing abs. nitric acid, acetic acid, and acetic anhydride at a ratio of 2:1:1 (w./w.), all freshly distilled.[3] A white precipitate was formed that was introduced into 30 ml. ice water. By centrifugation a yellowish jelly-like aggregate separated; this was washed with ice water until neutral, filtered, and air-dried. One-tenth gram of decolorizing carbon (Norit A) was added to its alcoholic solution, filtered off, and the clear solution concentrated until a jelly-like precipitate appeared. This was redissolved by gentle heating and inoculated with IV. Overnight a nearly quantitative yield of crystalline IV was obtained. These crystals melted at 140°, but showed their transformation at 107° instead of 125°.

Experiments with III. When an ethanolic solution of III was kept at −5° for several weeks, small spherical aggregates appeared which did not reduce Fehlings solution. Their optical activity varied between −5° and +20° and their nitrogen content between 13% and 14.6%. The homogeneity of these fractions was checked by reduction, followed by paper chromatography. All of them proved to be complex mixtures of 3 or 5 components. Unsuccessful fractionations were attempted from various solvents and solvent mixtures, including aqueous and dry methanol, acetone, dioxane, ethyl acetate, petrol ether, chloroform, carbon tetrachloride, ether, benzene, nitrobenzene, pyridine, and acetic acid.

When III was subject to low-pressure hydrogenolysis a sirup (VII) was formed reducing Fehling's solution rapidly, $[\alpha]_D^{17}$ +5°. By paper chromatography of VII, using a mixture of 25 parts of ethyl acetate, 8 parts of water, and 7 parts pyridine, six spots appeared after color reaction with resorcinol, anthrone, and α-naphthol. In relation to R_f of fructose = 1.00, the average distances travelled by these (R_f) spots were as follows: 0.32; 0.63; 0.84; 1.27; 1.34; 1.57. Owing to the diffuse character of the slower spots, further paper chromatographic separations were carried out with a mixture of butanol, water, and pyridine. Seven spots could be located after color reaction with resorcinol, their R_f values being as follows: (a) 0.35; (b) 0.50; (c) 0.67; (d) 0.92; (e) 1.12; (f) 1.25; (g) 1.35 (see Fig. 1). Three of these spots could be identified with well-defined compounds, namely: (a) diheterolevulosan I (di-D-fructopyranose 1,2′; 2,1′-dianhydride); (c) diheterolevulosan II (D-fructopyranose-D-fructofuranose 1,2′:2,1′-dianhydride); (e) difructose anhydride I (di-D-fructofuranose 1,2′:2,1′-dianhydride).

Quantitative chromatography of III. Five grams III were dissolved in 10 ml. of water, diluted by 190 ml. methanol and added to a column containing 1000 g. of a mixture of Florex XXX-celite (Hiflo) 5.1[7] (dimensions 310 × 90 mm.) prewetted by 1500 ml. ethanol 95%. The chromatogram was developed by 2500 ml. methanol 95%, followed by 2000 ml. of methanol 90%, 1000 ml. methanol 75% and 1000 ml. methanol 50%. The effluents were collected in portions of 25 ml. and their optical rotations measured

in a 4 dm. polarimetric tube. In this way the effluents could be divided into six fractions, each of which was shown by paper chromatography to contain 3–4 constituents.

These fractions, designated A (fastest moving), B, C, D, E, and F, were dried thoroughly *in vacuo* over phosphorus pentoxide. By addition of some dry ethanol to the horny residues, five crystalline substances were separated from A, B, C, and D at room temperature over a period of 10 weeks. From A and B small platelets (XI) could be isolated, which proved to be a condensation product of fructose and methylglyoxal, as will be described elsewhere; from the combined mother liquors diheterolevulosan I (IX) separated followed by small amounts of diheterolevulosan II (X). From C and D tiny amounts of strongly hygroscopic needles (XII) crystallized, $[\alpha]_D^{18}$ +270° (*c* 0.13 in methanol), m.p. 160° (dec.). So far the substance has not been obtained free from impurities. From D, E, and F some traces of small crystals (XIII) separated, $[\alpha]_D^{18}$ approx. −300° (*c* 0.10 in water). The amounts isolated were insufficient to permit purification and elementary analysis.

Nitration of D-*fructose by nitronium sulfate* (Method B): Three grams of D-fructose was dissolved with rapid stirring in 30 ml. of abs. nitric acid at 5° and this temperature kept during the entire procedure; 60 ml. of cold concentrated sulfuric acid was added over a period of 5 min., followed by 100 ml. of dry chloroform. After 2 min. of stirring, the upper chloroform layer was siphoned off, 50 ml. of fresh chloroform was added and the mixture was stirred for 2 min. This procedure was repeated once more and the combined chloroform extracts were repeatedly washed with 300 ml. portions of ice-cooled distilled water, until the aqueous layer was neutral towards litmus. After the first three washings, the chloroform layer was rapidly removed from the aqueous phase disregarding turbidity. To the almost colorless chloroform solution, 0.38 g. of recrystallized *p*-benzoquinone was added. The solution was dried for 4 hr. over anhydrous sodium sulfate and then concentrated *in vacuo* at 30°. There resulted 3.0 g. of a pale yellow sirup (XV) $[\alpha]_D^{18}$ −35° (c 2.0 in dioxan) (N = 13.1), which was dissolved in 15 ml. of dioxan, 20 ml. 95% ethanol were added, and the solution was reduced with 10 g. of palladium catalyst. After reduction a yellow sirup was obtained (XVI) that was subjected to paper chromatography (see Fig. 2).

Nitration of D-*fructose in an acetic anhydride mixture.*[3] Three grams of D-fructose was dissolved with rapid stirring in a mixture of 20 ml. abs. nitric acid, 15 ml. acetic acid, and 15 ml. acetic anhydride. The solution rapidly turned yellowish-brown; after 10 min. it was poured into 500 ml. of ice water. The product was extracted by three portions of 100 ml. ether, the combined yellow extracts were washed repeatedly with ice-cooled distilled water until neutral towards litmus. The ethereal solution was dried for 4 hr. over anhydrous sodium sulfate, 0.05 g. *p*-benzoquinone were added, and the ether distilled off. 5.70 g. of a deep yellow sirup (XVII) was obtained, $[\alpha]_D^{16}$ +30 (c 7 in methanol), N = 16. By hydrogenolysis of XVII a reddish-brown sirup was formed (XVIII). XVIII was subjected to paper chromatography (see Fig. 2).

Nitration of D-*fructose in presence of phosphorus pentoxide.*[11] Three grams of D-fructose was added to an ice-cooled mixture of 30 ml. abs. nitric acid, 30 ml. of dry chloroform and 6 g. of phosphorus pentoxide. After 5 min. of rapid stirring, 50 ml. of dry chloroform was added and the liquid part of the mixture siphoned off, leaving the phosphorus pentoxide in the reaction flask. The acid mixture was poured into 300 ml. of ice water, and shaken with an additional amount of 100 ml. of chloroform. The chloroform layer was removed and the turbid aqueous layer extracted twice with 100 ml. of ether. The mixed extracts were washed with ice-cooled distilled water until neutral, dried over anhydrous sodium sulfate, 0.02 g. of *p*-benzoquinone were added and the solvents evaporated *in vacuo*. 1.15 g. of an orange colored sirup (XIX) resulted, $[\alpha]_D^{17}$ −3.9°, N = 11.4. The reduction product (XX) of (XIX) was subjected to paper chromatography (see Fig. 2).

JERUSALEM, ISRAEL

[CONTRIBUTION FROM THE CHEMISTRY AND CHEMICAL ENGINEERING DIVISION OF THE MIDWEST RESEARCH INSTITUTE]

The Phenylation and Methylation of Alkoxychlorosilanes[1]

C. C. CHAPPELOW, JR., R. L. ELLIOTT, AND J. T. GOODWIN, JR.[2]

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The phenylation of diisopropoxydichlorosilane, triisopropoxychlorosilane, and triethoxychlorosilane with chlorobenzene and molten sodium was investigated. The effect of varying the reactant ratio on the yield of diphenyldiisopropoxysilane from the reaction of diisopropoxydichlorosilane, chlorobenzene, and molten sodium was studied. The methylation of triethoxychlorosilane and triisopropoxychlorosilane with methyl chloride and molten sodium was studied briefly. During this investigation, four new isopropoxychlorosilanes were prepared and characterized: diisopropoxydichlorosilane, triisopropoxychlorosilane, phenylisopropoxydichlorosilane, and phenyldiisopropoxychlorosilane.

Various modifications of the sodium method of preparing organosilicon compounds have been devised to control the degree of substitution. One approach[3] is based upon limiting the concentration of the organic halide in the reaction mixture by extreme dilution with an inert solvent. A two-stage synthesis[4] in which the organosodium reagent is prepared and treated separately allows much better control. Another approach to controlled substitution is based on the relative reactivities of the silicon-alkoxy and silicon-chlorine bonds toward the organosodium intermediate.

One objective of this study was to determine the effect on the phenylation and methylation reactions due to varying the type of alkoxy groups in the silane starting material. Another objective was to determine the effect of varying the reactant ratio

(1) This research was sponsored by the Ethyl Corporation, Baton Rouge, La.

(2) Present address: Corn Industries Research Foundation, Washington, D. C.

(3) E. G. Rochow, *Chemistry of the Silicones*, John Wiley and Sons, N. Y., 2nd Edition, p. 32, 1951.

(4) W. C. Schumb and C. M. Saffer, Jr., *J. Am. Chem. Soc.*, 63, 93 (1941).

TABLE I

PHENYLATION AND METHYLATION OF ALKOXYCHLOROSILANES

Reactants (mole)	Ratio RCl to Silane	Solvent (ml.)	Approx. Composition of Reaction Mixture (wt. %)[a]	Yield of Desired Product[b]
C_6H_5Cl + Na + $Cl_2Si(O\text{-}i\text{-}Pr)_2$ 0.71 1.50 0.35	2.03:1	Toluene 150	16% $Si(O\text{-}i\text{-}Pr)_4$, 14% $C_6H_5Si(O\ i\text{-}Pr)_3$, 23% $(C_6H_5)_2Si(O\text{-}i\text{-}Pr)_2$, 47% residue	15% $(C_6H_5)_2Si(O\ i\text{-}Pr)_2$
C_6H_5Cl + Na + $Cl_2Si(O\text{-}i\text{-}Pr)_2$ 0.71 1.50 0.35	2.03:1	Toluene 150	18% $Si(O\text{-}i\text{-}Pr)_4$, 14% $C_6H_5Si(O\text{-}i\text{-}Pr)_3$, 22% $(C_6H_5)_2Si(O\text{-}i\text{-}Pr)_2$, 46% residue	13% $(C_6H_5)_2Si(O\text{-}i\text{-}Pr)_2$
C_6H_5Cl + Na + $Cl_2Si(O\text{-}i\text{-}Pr)_2$ 0.61 1.30 0.35	1.75:1	Toluene 150	15% unchanged $Cl_2Si(O\text{-}i\text{-}Pr)_2$, 3% $C_6H_5Si(O\text{-}i\text{-}Pr)_2Cl$, 9% $C_6H_5Si(O\text{-}i\text{-}Pr)_3$, 57% $(C_6H_5)_2Si(O\text{-}i\text{-}Pr)_2$, 16% residue	61% $(C_6H_5)_2Si(O\text{-}i\text{-}Pr)_2$
C_6H_5Cl + Na + $Cl_2Si(O\text{-}i\text{-}Pr)_2$ 0.53 1.10 0.35	1.50:1	Toluene 150	18% unchanged $Cl_2Si(O\text{-}i\text{-}Pr)_2$, 9% $C_6H_5Si(O\text{-}i\text{-}Pr)_2Cl$, 7% $C_6H_5Si(O\text{-}i\text{-}Pr)_3$, 53% $(C_6H_5)_2Si(O\text{-}i\text{-}Pr)_2$, 13% residue	64% $(C_6H_5)_2Si(O\text{-}i\text{-}Pr)_2$
C_6H_5Cl + Na + $ClSi(O\text{-}i\text{-}Pr)_3$ 0.35 0.85 1.05	0.35:1	None	18% unchanged $ClSi(O\text{-}i\text{-}Pr)_3$ 76% $C_6H_5Si(O\text{-}i\text{-}Pr)_3$, 6% residue	72% $C_6H_5Si(O\text{-}i\text{-}Pr)_3$
C_6H_5Cl + Na + $ClSi(O\text{-}i\text{-}Pr)_3$ 0.35 0.85 1.05	0.35:1	None	20% unchanged $ClSi(O\text{-}i\text{-}Pr)_3$, 72% $C_6H_5Si(O\text{-}i\text{-}Pr)_3$, 8% residue	64% $C_6H_5Si(O\text{-}i\text{-}Pr)_3$
C_6H_5Cl + Na + $ClSi(OC_2H_5)_3$ 0.35 0.85 0.53	0.70:1	None	60% unchanged $ClSi(OC_2H_5)_3$, 39% $C_6H_5Si(OC_2H_5)_3$, 1% residue	40% $C_6H_5Si(OC_2H_5)_3$
CH_3Cl + Na + $ClSi(O\text{-}i\text{-}Pr)_3$ 0.70 0.85 0.35	2.00:1	Toluene 100	2% unchanged $ClSi(O\text{-}i\text{-}Pr)_3$, 73% $CH_3Si(O\text{-}i\text{-}Pr)_3$, 25% residue	38% $CH_3Si(O\text{-}i\text{-}Pr)_3$
CH_3Cl + Na + $ClSi(OC_2H_5)_3$ 1.5° 1.10 1.00	1.50:1	None	70% unchanged $ClSi(OC_2H_5)_3$, 10% $MeSi(OC_2H_5)_3$, 20% residue	13% $CH_3Si(OC_2H_5)_3$

[a] Not including solvent. [b] Yield calculations based on moles of limited reactant.

TABLE II

PHYSICAL PROPERTIES OF COMPOUNDS INVOLVED IN THIS STUDY

Compound	B.P. (°C/mm.)	n_D^{25}	d_4^{25}	MR_D Calcd.	MR_D Found
$Cl_2Si(O\text{-}i\text{-}Pr)_2$[a]	155/745	1.3960	1.0490	49.58	49.75
$ClSi(O\text{-}i\text{-}Pr)_3$[a]	177/734	1.3898	0.9496	59.97	60.07
$Si(O\text{-}i\text{-}Pr)_4$	62–64/5[b]	1.3844[c]	0.8744[d]	70.36	70.76
$C_6H_5Si(O\text{-}i\text{-}Pr)Cl_2$[a]	99–100/10	1.4868	1.1267	59.38	60.02
$C_6H_5Si(O\text{-}i\text{-}Pr)_2Cl$[a]	113–114/10	1.4669	1.0221	69.77	70.25
$C_6H_5Si(O\text{-}i\text{-}Pr)_3$	110–112/5[e]	1.4488[f]	0.9411[g]	80.16	80.46
$(C_6H_5)_2Si(O\text{-}i\text{-}Pr)_2$	152–154/5[h]	1.5120[i]	0.9973[j]	89.96	90.49
$CH_3Si(O\text{-}i\text{-}Pr)_3$	163/749[k]	1.3830[l]	0.8557	60.34	60.08
$ClSi(OC_2H_5)_3$	156–157/743[m]	1.3884	1.0124	46.08	46.35
$C_6HSi_5(OC_2H_5)_3$	122–124/15[n]	1.4590[o]	0.9904[p]	66.27	66.26
$CH_3Si(OC_2H_5)_3$	142–144/745[q]	1.3887[r]	0.9166[s]	46.45	45.97

[a] New compound. [b] 170°/16 mm.[11] [c] n_D^{20} 1.5136.[11] [d] d_4^{20} 0.9982.[11] [e] 136°/22.[11] [f] n_D^{20} 1.3852.[11] [g] d_4^{20} 0.8754.[11] [h] 170°/16 mm.[11] [i] n_D^{20} 1.5136.[11] [j] d_4^{20} 0.9982.[11] [k] 102°/100 mm.[12] [l] n_D^{25} 1.3869.[12] [m] 155–157°/760.[10] [n] 120°/14 mm.[11] [o] n_D^{20} 1.4611.[11] [p] d_4^{22} 0.9916.[11] [q] 143.5°/760 mm.[13] [r] n_D^{25} 1.3820.[13] [s] d_D^{25} 0.885.[13]

on the reaction of diisopropoxydichlorosilane and chlorobenzene in the presence of molten sodium. The results of this investigation are summarized in Table I.

The phenylation of alkoxychlorosilanes. The phenylation of tetramethoxysilane,[5] chlorotricyclohexoxysilane,[6] and dichlorodimethoxysilane[7] with chlorobenzene and sodium have been reported.

Our study of the phenylation of diisopropoxydichlorosilane by the molten sodium method revealed that higher yields of diphenyldiisopropoxysilane were obtained at lower chlorobenzene to silane molar ratio: 64% at 1.50 to 1; 61% at 1.75 to 1; 13–15% at 2.03 to 1.

The phenylation of trialkoxychlorosilanes was carried out in the absence of any solvent by adding chlorobenzene to molten sodium dispersed in the trialkoxychlorosilane. Higher yields of phenyltrialkoxysilane were obtained with triisopropoxy- (68%, average) than with triethoxychlorosilane (40%). An interaction between molten sodium and triethoxychlorosilane was observed which caused an induction period before the reaction was initiated. The exact nature of this interaction is not known. It may have been the formation of a sodium-silane complex or it may have been due to the cleavage of silicon-oxygen bonds. In the runs with triisopropoxychlorosilane, there was no appreciable molten sodium-silane interaction and the reactions were initiated immediately and easily carried to completion.

The methylation of alkoxychlorosilanes. The methylation of tetraethoxysilane,[8] trimethoxychlorosilane,[9] and dimethoxydichlorosilane[9] by the molten sodium method have been reported.

During this study, the methylation of triethoxychlorosilane and triisopropoxychlorosilane were carried out without the use of a catalyst, using molten sodium and methyl chloride. Reactions with both starting materials were difficult to initiate, and it was necessary to add small amounts of ethyl acetate at frequent intervals to sustain the reaction. The yield of methyltrialkoxysilane was higher when triisopropoxychlorosilane with solvent was used (38%) than when triethoxychlorosilane without solvent was used (13%).

The preparation of alkoxychlorosilanes. All of the alkoxychlorosilanes except triethoxychlorosilane which were involved in this work were prepared by the alcoholysis of chlorosilanes. By this procedure, four new alkoxychlorosilanes were prepared: diisopropoxydichlorosilane, triisopropoxychlorosilane, phenylisopropoxydichlorosilane, and phenyldiisopropoxychlorosilane. Triethoxychlorosilane[10] was prepared by the autoclave reaction of acetyl chloride and tetraethoxysilane. Other known[11–13] alkoxysilicon compounds included in this study were isolated from experimental reaction mixtures and characterized.

The physical properties of all the compounds involved in this study are listed in Table II.

EXPERIMENTAL[14]

Preparation of diisopropoxydichlorosilane. To 510 g. (3.0 mole) of tetrachlorosilane at 0° was added 306 g. (5.1 mole)

(5) C. W. Bondy and K. Reiser, British Patent No. 573,906 (1945).

(6) A. Bowman, *et al.*, British Patent No. 613,648 (1948).

(7) K. Hiratsuka, Japanese Patent No. 5,330 (1951).

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(9) C. W. Bondy, *et al.*, British Patent No. 612,822 (1948).

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of 2-propanol at a rate of 3 to 4 ml./min. The temperature of the reaction mixture was maintained at 0°. After the addition was complete, the reaction mixture was purged with nitrogen for approximately 15 min. while the temperature was gradually increased to 50°. The purged reaction mixture was distilled through a 45-plate, 3/4 in. i.d. Oldershaw column to give 190 g. (29.2%) of diisopropoxydichlorosilane, b.p. 155° at 745 mm., n_D^{25} 1.3960, d_4^{25} 1.0490, MR_D calcd. 49.58, found 49.75.

Anal. Calcd. for $SiC_6H_{14}O_2Cl_2$: Cl, 32.8. Found: Cl, 33.4.

Preparation of triisopropoxychlorosilane. To 748 g. (4.4 mole) of tetrachlorosilane was added 720 g. (12.0 mole) of 2-propanol in a manner similar to that in the preparation of diisopropoxydichlorosilane. Distillation gave 274 g. (26.0%) of triisopropoxychlorosilane, b.p. 177° at 734 mm., n_D^{25} 1.3898, d_4^{25} 0.9496, MR_D calcd. 60.07, found 59.97.

Anal. Calcd. for $SiC_9H_{21}O_3Cl$: Cl, 14.8. Found: Cl, 15.5.

A similar run using 816 g. (4.8 mole) of tetrachlorosilane and 732 g. (12.2 mole) of 2-propanol gave 250 g. (24.0%) of diisopropoxydichlorosilane, b.p. 154–156° and 515 g. (41.7%) of triisopropoxychlorosilane, b.p. 176–178°.

Another similar run using 1,020 g. (6.0 mole) of tetrachlorosilane and 900 g. (15.0 mole) of 2-propanol gave 307 g. (23.6%) of diisopropoxydichlorosilane, b.p. 154–156° and 692 g. (47.6%) of triisopropoxychlorosilane, b.p. 176–178°C.

Preparation of triethoxychlorosilane. A mixture of 157 g. (2.0 mole) of acetylchloride and 417 g. (2.0 mole) of tetraethoxysilane were placed in an autoclave and held at 160° for 1 hr. The resulting reaction mixture was flash distilled at reduced pressure to remove any metallic contamination picked up in the autoclave. Distillation gave 119 g. (30%) of triethoxychlorosilane, b.p. 156–157° at 743 mm., n_D^{25} 1.3884, d_4^{25} 1.0124, MR_D calcd. 46.08, found 46.35.

Preparation of phenylisopropoxydichlorosilane and phenyldiisopropoxychlorosilane. To 212 g. (1.0 mole) of phenyltrichlorosilane was added 90 g. (1.5 mole) of 2-propanol in the same general manner previously described. Fractionation of the reaction mixture yielded 45 g. (19.1%) of phenylisopropoxydichlorosilane, b.p., 99–100° at 10 mm., n_D^{25} 1.4868, d_4^{25} 1.1267, MR_D calcd. 59.38, found 60.02.

Anal. Calcd. for $SiC_9H_{12}CCl_2$: Cl, 30.15. Found: Cl, 29.66.

Further distillation gave 64 g. (23.8% yield) of phenyldiisopropoxychlorosilane, b.p., 113–114° at 10 mm., n_D^{25} 1.4669, d_4^{25} 1.0221, MR_D calcd. 69.77, found 70.25.

Anal. Calcd. for $SiC_{12}H_{19}O_2Cl$: Cl, 13.70. Found: Cl, 14.82.

The phenylation of diisopropoxydichlorosilane. To 34.5 g. (1.5 mole) of molten sodium in 150 ml. of toluene was added a mixture of 79.8 g. (0.71 mole) of chlorobenzene and 76 g. (0.35 mole) of diisopropoxydichlorosilane (the molar ratio of chlorobenzene to the silane was 2.03 to 1) at 110°. The addition of the reactant mixture resulted in an immediate temperature rise and a purple color development. The reaction temperature was maintained at 115° by controlling the rate of addition. After the addition was complete, the reaction mixture was maintained at 115° for 0.5 hr. A gelatinous precipitate was removed by centrifugation and washed with toluene, and the washings were added to the supernatant liquid. The solvent and most of the unchanged diisopropoxydichlorosilane were removed by atmospheric distillation. The concentrated reaction mixture was fractionated by a vacuum distillation through an 8 in. section of 3/4 in. i.d. column packed with 1/4 in. Berl saddles to give 16 g. (15.2%) of diphenyldiisopropoxysilane, b.p. 152–154° at 5 mm., n_D^{25} 1.5120, d_4^{25} 0.9973, MR_D calcd. 89.96, found 90.49, and the following: 11 g. of tetraisopropoxysilane, b.p. 62–64° at 5 mm., n_D^{25} 1.3844, d_4^{25} 0.8744, MR_D calcd. 70.36, found 70.76; 9.5 g. of phenyltriisopropoxysilane, b.p. 110–112° at 5 mm., n_D^{25} 1.4488, d_4^{25} 0.9411, MR_D calcd. 80.16, found 80.46; and 32 g. of an unidentified solid residue.

A duplicate run gave 14.0 g. (13.4%) of diphenyldiisopropoxysilane, b.p. 152–154° at 5 mm., n_D^{25} 1.5123, d_4^{25} 1.000, MR_D calcd. 89.96, found 90.10; 11.0 g. of tetraisopropoxysilane, b.p. 62–64° at 5 mm., n_D^{25} 1.3855, d_4^{25} 0.8718, MR_D calcd. 70.8, found 71.1; 9.0 g. of phenyltriisopropoxysilane, b.p. 110–112° at 5 mm., n_D^{25} 1.4464, d_4^{25} 0.9399, MR_D calcd. 80.7, found 80.1; and 28 g. of unidentified solid residue.

A similar run using 29.9 g. (1.3 mole) of sodium in 150 ml. of toluene, 68.6 g. (0.61 mole) of chlorobenzene, and 76 g. (0.35 mole) of diisopropoxydichlorosilane was carried out. The molar ratio of chlorobenzene to the silane was 1.75 to 1. The precipitate was removed by filtration, and the filtrate was fractionated as before to give 57.0 g. (61.3%) of diphenyldiisopropoxysilane, b.p. 150–152° at 5 mm., n_D^{25} 1.5101, d_4^{25} 0.9944, MR_D calcd. 89.96, found 90.20; 15.0 g. of unchanged diisopropoxydichlorosilane, 3.4 g. of phenylisopropoxydichlorosilane, 9.6 g. of phenyltriisopropoxysilane, b.p. 106–107° at 5 mm. and 16.0 g. of an unidentified solid residue.

A similar run using 25.3 g. (1.1 mole) of sodium in 150 ml. of toluene, 59.1 g. (0.525 mole) of chlorobenzene, and 76 g. (0.35 mole) of diisopropoxydichlorosilane was carried out. The molar ratio of chlorobenzene to the silane was 1.5 to 1. The reaction mixture was filtered easily and then fractionated as before to give: 50.0 g. (63.7%) of diphenyldiisopropoxysilane, b.p. 150–152° at 5 mm., n_D^{25} 1.5082, d_4^{25} 0.9952, MR_D calcd. 90.60, found 89.96; 17.1 g. of unchanged diisopropoxydichlorosilane, as calculated from chlorine analysis of the distillate from the atmospheric distillation; 8.5 g. of crude phenyldiisopropoxychlorosilane, collected in a b.p. range of 45–90° at 5 mm.; 6.5 g. of phenyltriisopropoxysilane, b.p. 106–107° at 5 mm., and 12.0 g. of an unidentified solid residue.

The phenylation of triisopropoxychlorosilane. To 19.5 g. (0.85 mole) of molten sodium in 253 g. (1.05 mole) of triisopropoxychlorosilane at 110° was added 39.5 g. (0.35 mole) of chlorobenzene. The reaction was initiated immediately upon addition of the chlorobenzene, and the reaction temperature was maintained at 115° by the rate of addition. Phenyltriisopropoxysilane was isolated in a manner similar to that of diphenyldiisopropoxysilane and was obtained in a 72 per cent yield (71.0 g.), b.p. 137–138° at 20 mm., n_D^{25} 1.4469, d_4^{25} 0.9428, MR_D calcd. 80.16, found 79.65. Also, 17.0 g. of unchanged triisopropoxychlorosilane and 6.0 g. of residue were obtained.

A duplicate run gave 63.0 g. (64%) of phenyltriisopropoxysilane, b.p. 122° at 10 mm., n_D^{25} 1.4482, d_4^{25} 0.9409; 17.0 g. of unchanged triisopropoxychlorosilane and 7.0 g. of residue.

The phenylation of triethoxychlorosilane. To 19.5 g. (0.85 mole) of molten sodium in a mixture of 1.04 g. (0.525 mole) of triethoxychlorosilane and 100 ml. of toluene at 110° was added 39.5 g. (0.35 mole) of chlorobenzene. About 10 ml. of chlorobenzene was added before the reaction was initiated, when there was a rapid temperature increase to 125°. The reaction mixture was cooled, then maintained at a temperature of 120° by the addition rate. After the addition of chlorobenzene was complete, the reaction mixture was maintained at 120° for 15 min. Phenyltriethoxysilane, isolated in a manner similar to that of the diphenyldiisopropoxysilane, was obtained in a 40.0% yield (35.5 g.), b.p. 122–124° at 15 mm., n_D^{25} 1.4590, d_4^{25} 0.9904, MR_D calcd. 66.27, found 66.26. Also, 54.0 g. of unchanged triethoxychlorosilane and 2.0 g. of residue were obtained.

The methylation of triisopropoxychlorosilane. A mixture of 19.5 g. (0.85 mole) of sodium, 84.0 g. (0.35 mole) of triisopropoxychlorosilane, and 100 ml. of toluene was heated to 110°. The methyl chloride (35.0 g., 0.70 mole) was introduced beneath the surface of the reaction mixture at a rate of 0.5 g./min. It was necessary to initiate and to maintain the reaction by the addition of 5 ml. of ethyl acetate (in 0.5 ml. portions) during a 3-hr. reaction period. After removal of the precipitate, the filtrate was distilled through a 10-plate, 1 in. i.d. Oldershaw column to give 27.0 g. (37.7% yield) of methyltriisopropoxysilane, b.p. 163° at 749 mm. n_D^{25} 1.3830,

d_4^{25} 0.8557, MR_D calcd. 60.34, found 60.08, 2.0 g. of unchanged triisopropoxychlorosilane and 7.0 g. of residue.

The Methylation of Triethoxychlorosilane. A run similar to that of the methyltriisopropoxysilane was carried out using 25.0 g. (1.1 mole) of sodium, 93.5 g. (0.5 mole) of triethoxychlorosilane, and 75.0 g. (1.5 mole) of methyl chloride. Again it was necessary to add ethyl acetate in small portions to maintain a reaction. Methyltriethoxysilane was obtained in 12.9% yield (11.5 g.), b.p. 142–144° at 745 mm., n_D^{25} 1.3887, d_4^{25} 0.9166, MR_D calcd. 46.45, found 45.97. Also, 80.5 g. of unchanged triethoxychlorosilane and 23.0 g. of residue were obtained.

KANSAS CITY 10, MO.

[CONTRIBUTION FROM EASTERN REGIONAL RESEARCH LABORATORY[1] AND TEMPLE UNIVERSITY]

Higher Alkyl Monoethers of Mono- to Tetraethylene Glycol[2a,b]

A. N. WRIGLEY,[3a] A. J. STIRTON,[3a] AND EDGAR HOWARD, JR.[3b]

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The mono-*n*-dodecyl, tetradecyl, hexadecyl, and octadecyl ethers of mono- to tetraethylene glycol, $R(OCH_2CH_2)_iOH$, were synthesized from alkyl halides or tosylates or by alkali-catalyzed reaction of alcohols with ethylene oxide. In the dodecyl, tetradecyl, and hexadecyl series, freezing-point minima occurred at i = 3. The distribution of products in oxyethylation of tetradecanol followed the equations of Weibull and Nycander, with a distribution constant of 3.0.

In view of the industrial importance of mixtures of monoalkyl ethers of polyethylene glycol, it would be useful to have available individual members of this class. One objective of this investigation was therefore to synthesize the mono-*n*-dodecyl, tetradecyl, hexadecyl, and octadecyl ethers of mono- to tetraethylene glycol and to report their characterizing constants.

Some of the members of this group of sixteen compounds have been previously reported. The Williamson reaction has been used to prepare glycol ethers for nicotine synergism studies.[4] Ethylene glycol mono-*n*-dodecyl ether was synthesized from the alkyl bromide and glycol[5] and ethylene glycol mono-*n*-octadecyl ether from the alkyl tosylate.[6] More recently the stepwise synthesis of mono- to tetraethylene glycol mono-*n*-dodecyl ethers by the acid-catalyzed addition of ethylene oxide to the next lower homolog was reported.[7] Alkali-induced oxyethylation,[8,9,10] common for the preparation of adducts having various average degrees of polymerization, has been seldom employed for the preparation of individual glycol ethers.[11]

Three methods of synthesis were used in the present work: the alkyl halide and alkyl tosylate methods and the alkali-catalyzed oxyethylation of alcohols.

Distribution of Products. The distribution of products is a point of interest in reactions like oxyethylation. When polymer chains are built up ideally from a fixed number of propagating units by a sequence of kinetically identical additions of monomer, size distribution has been shown by Flory[12] to be described by Poisson's formula:[13]

$$\frac{n_i}{n_\infty} = e^{-\nu}\frac{\nu^i}{i!} \qquad (1)$$

Although the conditions producing Poisson distribution are indeed found in the reaction of ethylene glycol with ethylene oxide,[14] reactions in which all steps are kinetically different, as in the ammonia-ethylene oxide reaction and the chlorination of methane, require much more complicated mathematics, as shown by Natta and Mantica.[15]

Regarding the assumption of kinetic identity of all steps as an oversimplification and the formulas of Natta as very cumbersome, Weibull and Nycander[14] suggested a compromise treatment for the reaction of an alcohol with ethylene oxide. They proposed that all hydroxyl groups bound to an oxy-

(1) A laboratory of the Eastern Utilization Research and Development Division, Agricultural Research Service, United States Department of Agriculture.

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(3) (a) Eastern Regional Research Laboratory, United States Department of Agriculture, Philadelphia 18, Pennsylvania. (b) Department of Chemistry, Temple University, Philadelphia 22, Pennsylvania.

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TABLE I

HIGHER *n*-ALKYL MONOETHERS OF MONO- TO TETRAETHYLENE GLYCOL

Glycol monoether	Method of preparation[a]	Yield %	B.P.	Mm.	F.P.	n^t_D	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
$C_{12}H_{25}OC_2H_4OH$[c]	C	18	137	2.2	20.3	1.4435^{25}	72.98	72.93	13.13	13.29
$C_{12}H_{25}O(C_2H_4O)_2H$[d]	B	80	127	0.010	19.0	1.4462^{25}	70.02	69.58	12.49	12.54
$C_{12}H_{25}O(C_2H_4O)_3H$[e]	B	62	153	0.035	17.2	1.4487^{25}	67.88	67.91	12.03	12.21
$C_{12}H_{25}O(C_2H_4O)_4H$[d]	B	78	166	0.02	20.5	1.4507^{25}	66.25	66.13	11.68	11.82
$C_{14}H_{29}OC_2H_4OH$	C	16	132	0.020	31.7	1.4330^{60}	74.36	74.49	13.26	13.22
$C_{14}H_{29}O(C_2H_4O)_2H$	B	80	146	0.02	28.5	1.4352^{60}	71.47	71.66	12.66	12.92
$C_{14}H_{29}O(C_2H_4O)_3H$	B	61	156	0.018	25.2	1.4373^{60}	69.31	69.11	12.22	12.15
$C_{14}H_{29}O(C_2H_4O)_4H$	B	70	183	0.018	28.5	1.4390^{60}	67.65	67.39	11.87	11.67
$C_{16}H_{33}OC_2H_4OH$	A	18	151	1.0	42.4–43.5[b]	1.4355^{60}	75.46	75.03	13.37	13.13
$C_{16}H_{33}O(C_2H_4O)_2H$	B	58	154	0.02	37.0	1.4373^{60}	72.67	72.86	12.81	12.74
$C_{16}H_{33}O(C_2H_4O)_3H$	B	63	172	0.013	30.5	1.4390^{60}	70.54	70.53	12.38	12.34
$C_{16}H_{33}O(C_2H_4O)_4H$	B	57	193	0.010	35.2	1.4407^{60}	68.85	69.08	12.04	12.27
$C_{18}H_{37}OC_2H_4OH$[f]	A	16	—	—	51.5–52.5[b]	1.4381^{60}	76.37	76.16	13.46	13.65
$C_{18}H_{37}O(C_2H_4O)_2H$	A	32	175	0.1	44.8–45.3[b]	1.4393^{60}	73.68	74.13	12.93	13.21
$C_{18}H_{37}O(C_2H_4O)_3H$	A	50	187	0.018	42.0	1.4407^{60}	71.59	71.51	12.52	12.78
$C_{18}H_{37}O(C_2H_4O)_4H$	B	76	214	0.05	40.8	1.4416^{60}	69.90	70.09	12.19	12.13

[a] A: etherification by *n*-alkyl *p*-toluenesulfonates; B: by alkyl bromides, C: by reaction of alcohols with ethylene oxide. [b] Melting points. [c–f] Previously reported: [c] Ref. 5, 7, 10, [d] Ref. 7, [e] Ref. 7, 10, [f] Ref. 6.

ethyl group have an equal ability to add ethylene oxide, differing, however, from that of the parent alcohol. This led to the following equations:

$$v = c \ln \frac{n_\infty}{n_0} - (c - 1)\left(1 - \frac{n_0}{n_\infty}\right) \qquad (2)$$

$$\frac{n_i}{n_\infty} = \frac{c^{i-1}}{(c-1)^i}\left\{\frac{n_0}{n_\infty} - \left(\frac{n_0}{n_\infty}\right)^c \sum_{j=0}^{i-1} \times \frac{1}{j!}\left[(c-1)\ln\frac{n_\infty}{n_0}\right]^j\right\} \qquad (3)$$

where

N_i = molecule with i added ethylene oxide molecules
m = number of moles of ethylene oxide consumed
n_∞ = number of moles of starting alcohol
n_0 = number of moles of surviving starting alcohol
n_i = number of moles of N_i in reaction product
k_i = velocity constant for reaction of N_i with ethylene oxide
k_0 = velocity constant for reaction of starting alcohol with ethylene oxide
c = k_i/k_0 = distribution constant
v = m/n_∞ = average number of moles of ethylene oxide per mole of starting alcohol

For the alkali-catalyzed reactions of ethylene glycol and of ethanol with ethylene oxide they found distribution constants c of 1 and 2.2 respectively.

Fractional distillation performed in the present preparation of ethylene glycol monotetradecyl ether provided data on the distribution of products for comparison with those required by the Poisson and the Weibull-Nycander equations.

EXPERIMENTAL

Materials. Good commercial grades of 1-dodecanol, tetradecanol, hexadecanol, and octadecanol were purified by fractional distillation and crystallization. *n*-Octadecyl and *n*-hexadecyl *p*-toluenesulfonates were made by the tosyl chloride–pyridine method[16] from the alcohols. Eastman grade *n*-dodecyl, tetradecyl, hexadecyl, and octadecyl bromides were found to have satisfactory purities and were used without further purification. Mono- to tetraethylene glycols were fractionally redistilled, and middle fractions with satisfactory refractive indices were used in synthesis. Commercial ethylene oxide of stated 99.5% purity was used.

Etherification by means of tosylates. For four ether alcohols the method of Shirley, Zietz and Reedy[6] was employed except that a higher ratio of glycol to alkyl tosylate was used. For ethylene glycol mono-*n*-hexadecyl ether, di- and tri-ethylene glycol mono-*n*-octadecyl ether, 10 mol. of glycol were used per mole of tosylate; for ethylene glycol mono-*n*-octadecyl ether, 5 mol.

Etherification by means of alkyl bromides. The preparation of *tetraethylene glycol mono-n-octadecyl ether* will serve as an example. With stirring, under a blanket of nitrogen, 8.28 g. (0.36 g.-atom) of sodium was dissolved, one small piece at a time, in 583 g. (3 mol.) of tetraethylene glycol at about 100°. After immersion of the flask in a 140° bath, 100 g. (0.3 mol.) of *n*-octadecyl bromide was added during 40 min. with vigorous stirring. After 5.5 hr. at this temperature, the reaction mixture diluted with xylene was neutralized and washed five times with hot water. Vacuum distillation through a Vigreux column gave a 76% yield of tetraethylene glycol mono-*n*-octadecyl ether. As noted in Table I, ten ethers were prepared by this method. The method has since provided intermediates for the synthesis of individual ether alcohol sulfates.[17]

Etherification by reaction of alcohols with ethylene oxide. Ethylene glycol mono-n-tetradecyl ether. In a 1 l., three necked flask,[9] 1.06 g. of sodium was dissolved with heating at 80–185° under a nitrogen atmosphere in 428.76 g. (2 mol.) of *n*-tetradecanol. At a temperature of 170–175°, this solution was stirred in an atmosphere of ethylene oxide for 3 hr., when weight increase indicated the reaction of 92.9 g. of ethylene oxide, or 1.055 mol. of ethylene oxide per mole of tetradecanol.

The reaction mixture was neutralized with the calculated amount of concentrated hydrochloric acid, dried, and filtered to give a colorless liquid, 481.5 g. of which was vacuum distilled through a protruded packing column having about 35 theoretical plates.[18] Refractive indices at 60° were

(16) D. A. Shirley and W. H. Reedy, *J. Am. Chem Soc.* **73**, 458 (1951).

(17) J. K. Weil, R. G. Bistline, Jr., and A. J. Stirton, *J. Phys. Chem.*, **62**, 1083 (1958).

(18) M. S. Peters and M. R. Cannon, *Ind. Eng. Chem.*, **44**, 1452 (1952).

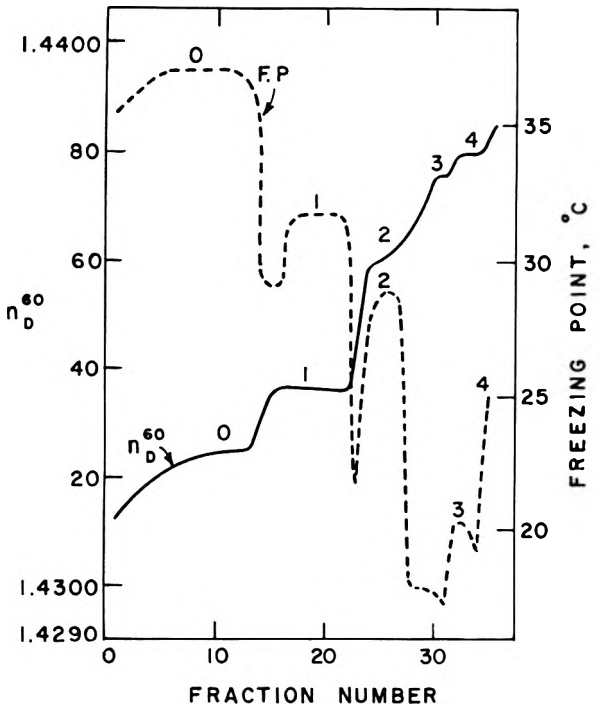


Fig. 1. Fractional distillation of oxyethylated tetradecanol (v = 1.055): refractive index and freezing point *vs* fraction number

measured on a refractometer having a precision of about 0.00003, and freezing points were measured in the cylindrical tubes used as fraction receivers.

From the curves of refractive index and freezing point plotted against fraction number (Fig. 1), fractions 16 to 22 were considered to be almost entirely ethylene glycol mono-*n*-tetradecyl ether, amounting to 74.7 g. (16% yield based on tetradecanol and adjusted for use of less than total reaction product in the distillation).

Distribution of products from oxyethylation. In order to examine the results of the reaction in the manner of Weibull and Nycander, it was first necessary to adjust the weights of reactants to reflect the fact that the fractional distillation was applied to 481.5 g. rather than to the entire reaction product, exclusive of sodium, of 521.7 g.

The weights (and number of moles) of the major components of the mixture resulting from oxyethylation of tetradecanol were estimated with the help of the plot of refractive index and freezing point *vs.* fraction number (Fig. 1). In general, the composition of intermediate fractions was estimated by interpolation of refractive indices; in a few cases assignments were somewhat arbitrary. The estimated amounts of uncombined tetradecanol and the mono-, di-, and triethylene glycol mono-*n*-tetradecyl ethers are collected in Table II.

The distribution constant c is calculated from both equation 2 (when it is designated c′) and from equation 3 (when designated c″). Thus, for v = 1.0549 and n_0/n_∞ = 0.5183, $c' = 3.2668 \simeq 3.27$.

For the calculation of c″, i is taken as having the value 1, and equation 3 reduces[19] to:

$$c'' = 1 + \frac{n_0}{n_1} - \frac{n_0}{n_1}\left(\frac{n_0}{n_\infty}\right)^{c''} - 1 \qquad (4)$$

which can be solved by successive approximations, as $c'' = 2.8186 \simeq 2.82$.

The values 3.27 for c′ and 2.82 for c″ suggest a mean value of about 3.0 for the distribution constant.

(19) B. Weibull, private communication.

TABLE II

COMPOSITION OF FRACTIONS: AMOUNT OF COMPONENTS, $RO(CH_2CH_2O)_iH$, INDICATED IN DISTILLATION OF TETRADECANOL–ETHYLENE OXIDE REACTION PRODUCT

	Fraction		Individual component, $RO(CH_2CH_2O)_iH$		
i	No.	Wt., g.	Wt., g.	n_i	n_i/n_∞
0	1–5	72.7	65.43		
	6–13	132.7	132.70		
	14	10.8	5.94		
	15	11.6	1.04		
				0.9568	0.5183
1	14	10.8	4.86		
	15	11.6	10.56		
	16–22	74.70	74.70		
	23	10.59	4.24		
	24	11.19	0.45		
				0.3669	0.1988
2	23	10.59	6.35		
	24	11.19	10.74		
	25–26	32.24	32.24		
	27	13.16	11.71		
	28	4.46	3.21		
	29	4.28	2.01		
	30	4.75	1.14		
	31	4.00	0.84		
				0.2256	0.1222
3	27	13.16	1.45		
	28	4.46	1.25		
	29	4.28	2.27		
	30	4.75	3.61		
	31	4.00	3.16		
	32–34	8.69	8.69		
	35	14.84	12.47		
				0.0949	0.0514
4	35	14.84	2.37		
	—	—	—		
				—	—

Using this value for c, a theoretical value of $\frac{n_0}{n_\infty} = 0.5062$ is found by successive approximation in equation 2, and is used in equation 3 to permit calculation of theoretical values of n_1/n_∞, n_2/n_∞, and n_3/n_∞ for inclusion in Table III.

DISCUSSION

Physical constants. The boiling points, freezing points, and refractive indices found for the sixteen ether alcohols synthesized in this study are collected in Table I.

In Fig. 2 the freezing points (in three cases the melting points) are plotted against the number of oxyethyl groups, i, added to a given alkyl group. In the dodecyl, tetradecyl, and hexadecyl series, minimum freezing points occur for the triethylene glycol derivative. The apparent leveling off in the plot of the octadecyl series suggests that a minimum freezing point in that series may occur at or shortly after the fourth member.

Solubility of the glycol monoethers. At the arbitrary ratio of 0.10 g. of glycol ether to 2.5 ml. of solvent, three typical products, glycol monooctadecyl, triglycol monotetradecyl, and tetraglycol monododecyl ether, were insoluble in water, both at room temperature and at 75°, but soluble in ben-

TABLE III

ALKALI-CATALYZED OXYETHYLATIONS OF FATTY ALCOHOLS, DISTRIBUTION OF COMPOUNDS IN REACTION PRODUCT

n-Fatty Alcohol:	Tetradecanol			Dodecanol	Hexadecanol
Wt., ROH, g.	395.72			369	112
Ethylene oxide, g.	85.74			101	60
Catalyst	0.978 g. Na			1.85 g. KOH	0.56 g. KOH
Temperature	170–175°			155–160°	130–150°
v	1.055			1.15	3.0
Experimental or Theoretical	Exptl.	Theoretical[a] WN	FP	Exptl.	Exptl.
n_0/n_∞	0.518	0.506	0.348	0.46	0.24
n_1/n_∞	0.199	0.188	0.367	0.21	
n_2/n_∞	0.122	0.150	0.194	—	
n_3/n_∞	0.051	0.090	0.068		
$\sum \frac{n_i}{n_\infty}$	0.890	0.934	0.977	0.67	0.24
$\sum \frac{in_i}{vn_\infty}$	0.566	0.717	0.909	0.18	0.000
c′	3.27			2.5	3.4
c″	2.82			2.5	
c		3.0	(1)	2.5	

[a] Theoretical distributions are calculated by Weibull-Nycander and by Flory-Poisson equations as indicated

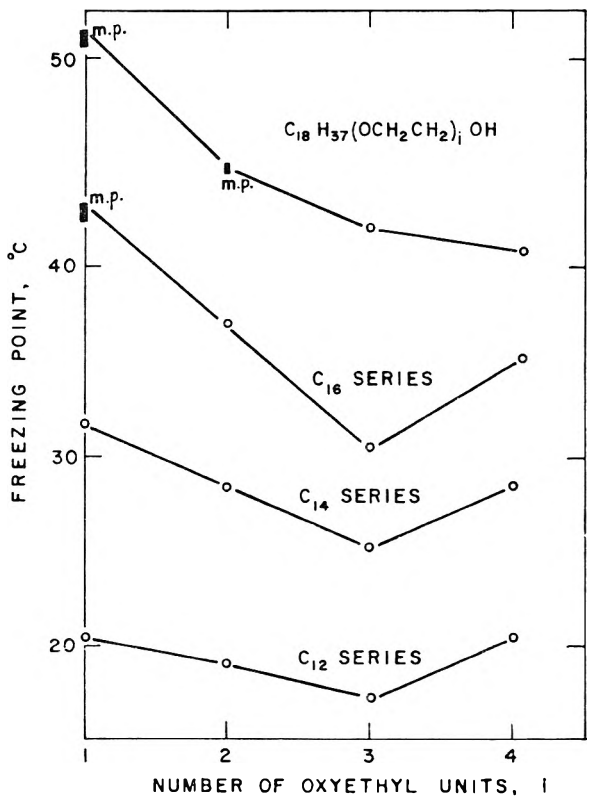


Fig. 2. Freezing points (or melting points, m.p.) of mono- to tetraethylene glycol mono-*n*-dodecyl, tetradecyl, hexadecyl, and octadecyl ethers

zene, carbon tetrachloride, and ethanol. In isooctane, clear solutions were obtained except for glycol monooctadecyl ether at room temperature and tetraglycol monododecyl ether at 75°.

Dilute mixtures (0.025 to 0.30%) of tetraethylene glycol monododecyl ether and water became clear when cooled to temperatures near 0°, and cloud points[20] of 9.5 to 5.2° were found. Clarification by cooling is probably related to the strengthening of hydrogen bonds between ether-alcohol and water.

Infrared spectra. Infrared spectra of the sixteen mono- to tetraethylene glycol monoethers synthesized in this study possessed major bands corresponding to the structures expected and found in related work.[7]

By dipole measurements evidence has been adduced for the coexistence of both *trans* and *gauche* forms of mono- to heptaethylene glycol,[21] and Kuroda and Kubo[22,23] have reported that certain infrared bands between 800 and 1000 cm.$^{-1}$ (measured on the pure liquids) reflect these *trans* and *gauche* conformations. A comparison made in Table IV of values from the work cited and appropriate spectra of the present glycol monododecyl ether series suggests that these ethers also exist in the liquid state in both *gauche* and *trans* conformations.

Distribution of products from oxyethylation. It is evident from Table III and Fig. 3, that there is disagreement between the experimental distribution of products from the alkali-catalyzed oxyethylation of tetradecanol to an average of 1.055 oxyethyl groups and the Flory-Poisson distribution calculated for the same degree of polymerization. Whereas the Poisson formula predicts slightly more

(20) J. M. Cross, *Proc. Chem. Specialties Mfrs. Assoc.*, 135 (June, 1950).

(21) T. Uchida, Y. Kurita, N. Koizumi, and M. Kubo, *J. Polymer Sci.*, 21, 313 (1956).

(22) Y. Kuroda and M. Kubo, *J. Polymer Sci.*, 26, 323 (1957).

(23) Y. Kuroda and M. Kubo, *J. Polymer Sci.*, 36, 453 (1959).

TABLE IV

COMPARISON OF SPECTRAL BANDS DUE TO CH_2 ROCKING FREQUENCIES OF MONO- TO TETRAETHYLENE GLYCOL[a] WITH BANDS FOUND IN INFRARED SPECTRA OF THE CORRESPONDING MONO-*n*-DODECYL ETHERS (LIQUID STATE)[b]

	Gauche Form		Trans Form	
i	A	B	A_u	B_g
$H(OCH_2CH_2)_iOH$[a]				
1	—	883	863	—
2	922	896	816	1000
3	934	888	830	1000
4	942	889	831	1000
(7)	(947)	(887)	(844)	(1000)
$n\text{-}C_{12}H_{25}(OCH_2CH_2)_iOH$				
1	920[c]	894	865[c]	—
2	935	890	830[d]	—
3	937	888	844[c]	(—)
4	940	885	841[d]	1000[c]

[a] Data of Kuroda and Kubo.[22] [b] Frequencies given in cm.$^{-1}$. [c] Shoulder. [d] Weak.

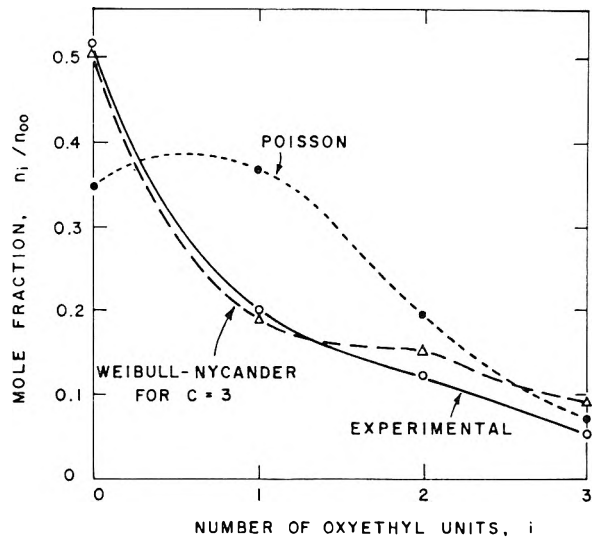


Fig. 3. Experimental distribution of products in oxyethylation of tetradecanol to v = 1.055 compared with theoretical Poisson distribution and with Weibull-Nycander distribution calculated for c = 3

ethylene glycol monotetradecyl ether than recovered parent alcohol, there was actually found over 50 mole per cent of the parent and only 20 mole per cent of the first glycol ether.

Treated in the Weibull-Nycander way, the experimental results suggest distribution constants c′ and c″ of 3.27 and 2.82. The experimental distribution agrees fairly well with a theoretical Weibull-Nycander distribution calculated for c = 3.0. The agreement is good for i = 0 and 1 and, though less close, still fairly satisfactory at i = 2 and 3. Excessive pot temperatures in the equipment employed prevented continuing the distillation much into the i = 4 region.

The sum of experimental values of n_i/n_∞ for i = 0 to 3 amounts to 0.89, whereas theoretical recovery at the same stage would be 0.93 if calculated by the Weibull-Nycander equations and 0.98 by the Poisson formula. For the sum of values of in_i/vn_∞ the experimental is again closer to the Weibull-Nycander than to the Poisson total. Discrepancies, magnified in this second test, may reflect incomplete recovery of derivatives having i = 2 and 3. In spite of the imperfections noted, it seems reasonable to recognize a Weibull-Nycander distribution and to accept a distribution constant in the neighborhood of 3 for the alkoxide-catalyzed reaction of tetradecanol with ethylene oxide under the conditions employed.

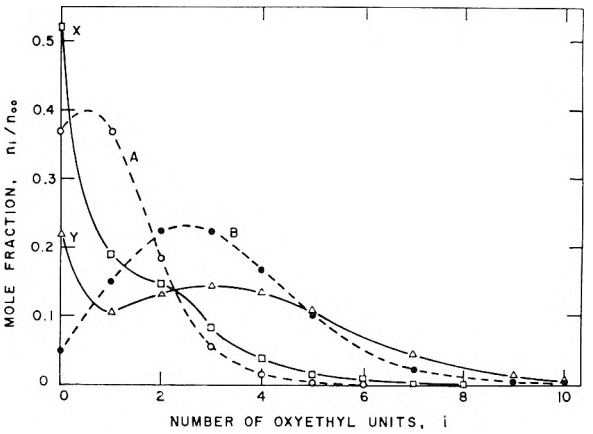


Fig. 4. Theoretical distribution of products of oxyethylation calculated by equations of Weibull and Nycander for c = 3, and v = 1 (solid curve X) or 3 (solid curve Y). Dotted curves A and B show distributions required by Flory-Poisson equation for v = 1 or 3

For comparative purposes the table lists some data available from distillations incidental to the preparation of ethylene glycol mono-*n*-dodecyl ether and of a parent-alcohol-free oxyethylate of *n*-hexadecanol. The indicated distribution constants of 2.5 and 3.4 support the order of magnitude found for the tetradecanol experiment.

Flory-Poisson distribution has been found valid for oxyethylation of ethylene glycol,[14] phenols,[24,25] and stearic acid,[26] in the last two cases because of the preferential combination of the parent compound with ethylene oxide before significant further reaction of the ether alcohols.[9,27] The present results indicate, however, that oxyethylation of long-chain primary alcohols results in Weibull-Nycander distribution as established for ethanol[14] rather than Poisson distribution as assumed for lauryl alcohol.[28]

(24) S. A. Miller, B. Bann, and R. D. Thrower, *J. Chem. Soc.*, 3623 (1950).

(25) R. L. Mayhew and R. C. Hyatt, *J. Am. Oil Chemists' Soc.*, 29, 357 (1952).

(26) R. L. Birkmeier and J. D. Brandner, *Agric. and Food Chem.*, 6, 471 (1958).

(27) L. Schechter and J. Wynstra, *Ind. Eng. Chem.*, **48**, 86 (1956).

(28) J. V. Karabinos and E. J. Quinn, *J. Am. Oil Chemists' Soc.*, **33**, 223 (1956).

Comparison of theoretical Weibull-Nycander and Poisson distributions. It is of interest, therefore, to compare, in Fig. 4, theoretical distributions calculated by the two methods at degrees of oxyethylation of 1 and 3. In a Poisson distribution (c by definition equal to 1), even at v = 1 the predicted fraction of surviving parent compound (n_0/n_∞) is no higher than that of any oxyethylated derivative. In fact, on passing to v = 3, n_0/n_∞ is smaller than n_{1-5}/n_∞.

By contrast, Weibull-Nycander distribution (with c = 3, let us say) requires that the fraction of surviving alcohol in each case exceed that of any oxyethylated descendant. The maxima of the curves are broader and weaker than for the Poisson formula. There are minima, or a tendency toward a minimum, at $i = 1$, reflecting the preferential consumption of the oxyethylated derivatives compared to the parent alcohol.

Acidity and Nucleophilicity. In alkaline-catalyzed reactions the distribution constant has been regarded as the product of two factors, one measuring the acidity of the derivative hydroxyl groups compared to the parent, the other, the relative reactivity of derivative and parent anions toward ethylene oxide.[14] Ethoxyethanol has been shown to have a relative acidity of 12 compared to 0.95 for ethanol.[29] A reversal of the order of relative nucleophilic reactivities of derived and parent anions is to be expected, and initial rates of oxyethylation were indeed higher for ethanol than for ethoxyethanol.[14] Preliminary attempts by the present authors to measure the separate oxyethylation reactivities of dodecanol and diethylene glycol monododecyl ether, catalyzed by potassium alkoxide at 120°, suggest a ratio of 1.5 to 1 in favor of the former.

Acknowledgment. We are grateful to Miss Ruth Fitz for elemental analyses, and to Dr. C. R. Eddy and Mr. C. T. Leander, Jr., for infrared spectra and discussions concerning them.

PHILADELPHIA, PA.

(29) J. Hine and M. Hine, *J. Am. Chem. Soc.*, **74**, 5266 (1952).

Notes

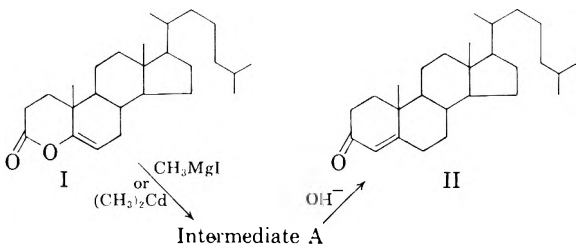
A department for short papers of immediate interest.

An Intermediate in the Grignard Reaction[1]

GEORGE I. FUJIMOTO[2] AND KENNETH D. ZWAHLEN[3]

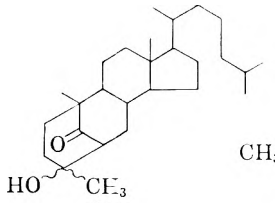
Received September 30, 1959

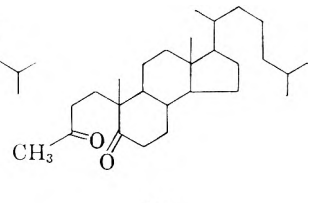
In the Grignard reaction for the introduction of isotopic carbon into the cholestenone nucleus we obtained a crystalline intermediate (A), melting at 174–178°, which gave an analysis corresponding to a methyl adduct to the enol lactone (I).[4] This intermediate was obtained after mild hydrolysis of the Grignard product in almost quantitative yield. Infrared data indicated the presence of a hydroxyl (3600 cm.$^{-1}$) and a ketone (1720 cm.$^{-1}$) group. Treatment with acid or alkali converted it to cholestenone (II).

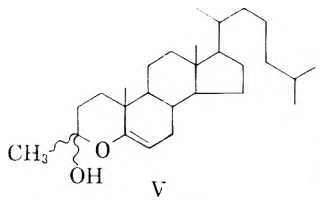


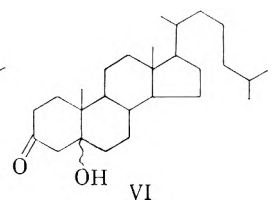
The identical intermediate (A) was obtained upon treatment of the enol lactone I with excess dimethylcadmium, although in lesser yield. It would appear that the mode of addition of the methyl Grignard reagent and of dimethylcadmium to the enol lactone and rearrangement is similar.

The following are the several formulations for the intermediate (A) which are considered on the basis of our findings and those of several other investigators. The evidence establishes structure III (3-hydroxy-4,5-seco-3,6-cyclocholestan-5-one) for this methyl adduct.[5] Our studies with model systems for this reaction further substantiate this structure.[6]









The diketone IV has been synthesized by Schmid and Kagi[7] by an independent method and also isolated by Heard and Ziegler[8] and shown to have quite different properties (a colorless oil, $[\alpha]_D^{19}$ +60° in chloroform) from intermediate A. These findings and the fact that this structure could not account for the presence of a hydroxyl peak in the infrared would eliminate structure IV as the intermediate A.

The hemiacetal structure V has been proposed by Heard and Ziegler[8] who also prepared this intermediate by the Grignard method (they reported m.p. 164–175°, $[\alpha]_D^{23}$ +10° in chloroform). They based their structure on the evidence of a positive tetranitromethane test indicating presence of unsaturation and on conversion of this intermediate to the diketone IV on vacuum distillation. They ascribed the ketone peak in the infrared spectrum of this intermediate to contamination mainly by the diketone IV.

When we purified our sample of intermediate A further by chromatography and recrystallization, we obtained material melting at 176–178°, $[\alpha]_D^{24}$ +14.5 in chloroform. The ketone and hydroxyl peaks in the infrared remained pronounced. A tetranitromethane test on this sample was negative. This indicated that the compound does have both hydroxyl and carbonyl functions and lacks unsaturation. Further evidence against structure V lies in the absence of an enol ether peak in the region of 1665 cm.$^{-1}$ in the infrared spectrum.[9]

The arguments against structure VI for intermediate A are two-fold. A steroid 3-ketone would

(1) Presented at the Meeting-in-Miniature of the New York Section, American Chemical Society, March 20, 1959. This investigation was supported in part by research grants from the National Institutes of Health, Public Health Service.

(2) Inquiries should be sent to the Albert Einstein College of Medicine, Yeshiva University, New York 61, N. Y.

(3) Present address: Shell Chemical Company, Modesto, Calif.

(4) G. I. Fujimoto, *J. Am. Chem. Soc.*, **73**, 1856 (1951).

(5) Evidence for this structure was first presented at the XIVth International Congress of Pure and Applied Chemistry, Zurich, Switzerland, July 1955.

(6) K. D. Zwahlen, W. J. Horton, and G. I. Fujimoto, *J. Am. Chem. Soc.*, **79**, 3131 (1957).

(7) H. Schmid and K. Kagi, *Helv. Chim. Acta*, **33**, 1582 (1950).

(8) R. D. H. Heard and P. Ziegler, *J. Am. Chem. Soc.*, **73**, 4036 (1951).

(9) H. Rosenkrantz and M. Gut, *Helv. Chim. Acta*, **36**, 1000 (1953).

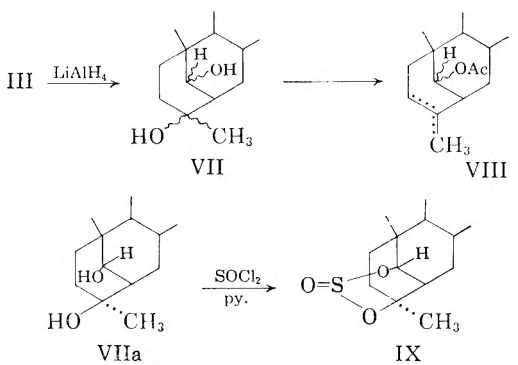
be expected to form derivatives fairly readily.[10] This has not been our experience with intermediate A. It failed to form either a semicarbazone or an oxime under the usual mild conditions[11] and only the starting substance (A) was recovered

When the ketone function in intermediate A was reduced with lithium aluminum hydride, a dihydroxy product was obtained which could not be acetylated when treated with acetic anhydride and pyridine (*vide infra*). If a steroid 3α- or 3β-hydroxyl group had been formed, it would have been expected to acetylate readily under these conditions.[10]

Structure III does satisfy the experimental observations for the intermediate A. Molecular model of structure III shows that the ketone is in a somewhat hindered, bridged position and would not be expected to form derivatives easily. This would account for the failure to form a semicarbazone or an oxime.

The hindered nature of the hydroxyl groups in the product (mixture of isomers VII) of the lithium aluminum hydride reduction of intermediate A is consistent with formulation III. As mentioned above, the diols VII failed to acetylate on standing overnight in acetic anhydride and pyridine. However, when the diols were treated with *p*-toluenesulfonic acid in benzene and acetic anhydride, an oil was obtained from which was isolated in over 50% yield an unsaturated acetate (VIII, m.p. 74.5–75.5°). This substance gave a positive tetranitromethane test.

A cyclic sulfite ester (IX) of the type obtained in our previous work[6] resulted from treatment of the diol mixture VII with thionyl chloride in benzene and pyridine. Efforts to obtain optimal yields of IX were not attempted, but indications are that the isomer VIIa is probably a major product of the hydride reduction. It appears that both III and VII consist of a mixture of 3α- and 3β-hydroxyl isomers and that the 3β-hydroxyl is the preponderant one.



(10) See for example Fieser & Fieser, *Natural Products Related to Phenanthrene*, Reinhold Publishing Corp., New York, N. Y., 1949, p. 125.

(11) *Cf.* Shriner and Fuson, *Identification of Organic Compounds*, 3rd Edit., J. Wiley & Sons, Inc., New York, 1948, pp. 170 and 202.

Further support for the structure III comes from the interpretation of the nuclear magnetic resonance spectrum of this intermediate.[12] This spectrum indicates that:

1. The resonance peak for a proton on a double bond (as would be required for structure V) is absent.

2. The C-19 methyl peak is shifted appreciably from the position for the corresponding peak in cholesterol, although the C-18 methyl peak is in the identical position for both. This would favor structure III over VI since the C-19 methyl in VI would be expected to have a peak like cholesterol.

3. An additional methyl peak to the number found in cholesterol is present in the spectrum. When the sample is dissolved in pyridine this chloroform-*d* methyl peak shifts towards lower field about 8 c.p.s., while dissolving cholesterol in pyridine has only a slight effect on the positions of the methyl peaks.

4. This extra methyl group is attached to a carbon bearing no protons.

The above findings are consistent only with structure III.

EXPERIMENTAL[13]

3-Hydroxy-4,5-seco-3,6-cyclocholestan-5-one (III). Dimethylcadmium in benzene was prepared according to Cason[14] from methylmagnesium bromide (0.24 g. of magnesium) and 1.00 g. of cadmium chloride. A solution of 1.00 g. of 5-hydroxy-3,5-seco-A-norcholest-5-en-3-oic acid lactone (I) in 25 ml. of benzene was added, and the mixture was refluxed for 3 hr. with stirring. It was then allowed to stand overnight at room temperature. To it was added 50 ml. of ice water and 3 ml. of dilute hydrochloric acid, the layers were separated and the aqueous solution extracted with ether. The organic solutions were combined and washed several times with water, dried over sodium sulfate, and the solvents distilled. The pale yellow oil (0.92 g.) obtained was dissolved in hexane and chromatographed on 40 g. of silica. The fraction in the 10% butanone in hexane eluate weighed 0.30 g. (29%) m.p. 140–174°. A single crystallization from acetone gave a melting point of 174–176° and material for analysis melted at 176–178°, undepressed when mixed with III from the Grignard reaction.[4]

4,5-Seco-3,6-cyclocholestan-3,5-diol (VII). A suspension of 3.00 g. of III in 50 ml. of ether was added to a slurry of 0.50 g. of lithium aluminum hydride in 50 ml. of ether. After 1 hr. a slight excess of water was added dropwise, the ether was decanted, and the salts were washed several times with ether. Distillation of the ether *in vacuo* and crystallization of the residue from acetone–methylene chloride gave 1.59 g. of VII (53%) m.p. 188–193°. After several crystallizations from ether-acetone a sample melted at 189–194°.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.14; H, 11.95. Found: C, 80.24; H, 12.02.

Dehydration and acetylation of VII *to yield* VIII. A solution of 0.50 g. (1.25 mmol.) of VII and 0.24 g. of *p*-toluenesulfonic acid monohydrate in 10 ml. of benzene and 10 ml. of

(12) The assistance of Dr. J. N. Shoolery of Varian Associates in obtaining and interpreting the NMR spectrum is gratefully acknowledged. The sample was run in chloroform-*d* and also in pyridine at 60 Mc.

(13) Melting points have been taken on a Kofler hot stage and are corrected.

(14) J. Cason, *J. Am. Chem. Soc.*, 68, 2079 (1946).

acetic anhydride was allowed to stand at room temperature overnight. After addition of 0.21 g. (2.5 mmol.) of sodium acetate the solvents were removed *in vacuo*. The residue was collected in ether and the ether was filtered and evaporated. The residual oil crystallized from acetone at −80°; m.p. 50–56° (0.30 g., 57%). After crystallization from methanol VIII melted at 71–74°. Further crystallization from the same solvent gave a sample melting at 74.5–75.5°.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 80.98; H, 11.31.

The test for unsaturation with tetranitromethane was positive. When the diols VII was allowed to stand in pyridine–acetic anhydride overnight, only unchanged VII was recovered.

Cyclic sulfite ester IX *of* VIIa. A solution of 1.20 g. of diol VII in 45 ml. of benzene with 1 ml. of thionyl chloride and 3 drops of pyridine was allowed to stand 2 hr. at room temperature. Removal of the solvents *in vacuo* gave a dark brown tar. From an ethanol extract of the tar a pale yellow oil was obtained which was chromatographed on 50 g. of silica. The benzene eluate weighed 0.130 g. and melted at 136–139°. Several crystallizations from methanol-acetone and finally from acetone gave a sample of IX melting at 139–141.5°.

Anal. Calcd. for $C_{27}H_{46}O_3S$: C, 71.95; H, 10.29. Found: C, 72.42; H, 10.17.

Treatment of IX with alcoholic potassium hydroxide regenerated the diol VIIa.

Departments of Biochemistry
Albert Einstein College of Medicine
Yeshiva University
Eastchester Road and Morris Park Avenue
New York 61, N. Y.
and
University of Utah College of Medicine
Salt Lake City, Utah

Structure of a Supposed Tetraphenylcyclobutane

Thomas S. Cantrell and John L. Kice

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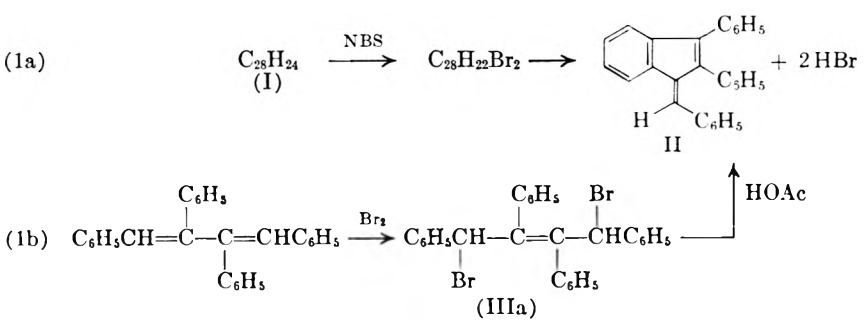
Recently Morton, Flood, and Bright[1] reported the isolation of a hydrocarbon $C_{28}H_{24}$ (I) which they believed to be a previously unreported isomer of 1,2,3,4-tetraphenylcyclobutane. We were interested in investigating the reaction of such cyclobutanes with *N*-bromosuccinimide, and by chance, we happened to choose their compound for study rather than the other previously reported isomers.[2,3]

Compound I readily underwent reaction with two moles of *N*-bromosuccinimide in refluxing carbon tetrachloride to yield a very labile dibromide which decomposed on further refluxing of the solution to afford hydrogen bromide and a brilliant yellow hydrocarbon, $C_{28}H_{20}$ (II). II was obtained in about 40% yield and was shown to be 1-benzylidene-2,3-diphenylindene by comparison with an authentic sample of this benzofulvene prepared from tetraphenylbutadiene by the usual route[4] (Eq. 1b). Although this result (Eq. 1a) is not mechanistically incompatible with the formulation of I as a tetraphenylcyclobutane, as witness Eq. 2, some question arose concerning the structure of I when we learned from Dr. Emil White[5] that the other isomers[2,3] of 1,2,3,4-tetraphenylcyclobutane do not behave in this fashion.

The reported[6] m.p. of one of the geometric isomers of 1,2,3,4-tetraphenyl-1-butene is the same as that of I, and since treatment of this tetraphenylbutene with two moles of N-bromosuccinimide might be expected to give the dibromide (III) which yields II on decomposition, we synthesized[6] a sample of this olefin for comparison with I. The synthetic sample of 1,2,3,4-tetraphenyl-1-butene was identical in every respect with I. It is thus clear that I is one of the geometric isomers of 1,2,3,4-tetraphenyl-1-butene rather than a tetraphenylcyclobutane.

Morton, Flood, and Bright[1] isolated I (15%) as a by-product of the formation of stilbene (80%) from the reaction of benzyl chloride with excess potassium amide in liquid ammonia. It seems possible that I may arise from some such side reaction as 3:



(1) J. M. Morton, E. A. Flood, and N. F. H. Bright, *Can. J. Chem.*, **35**, 1097 (1957).

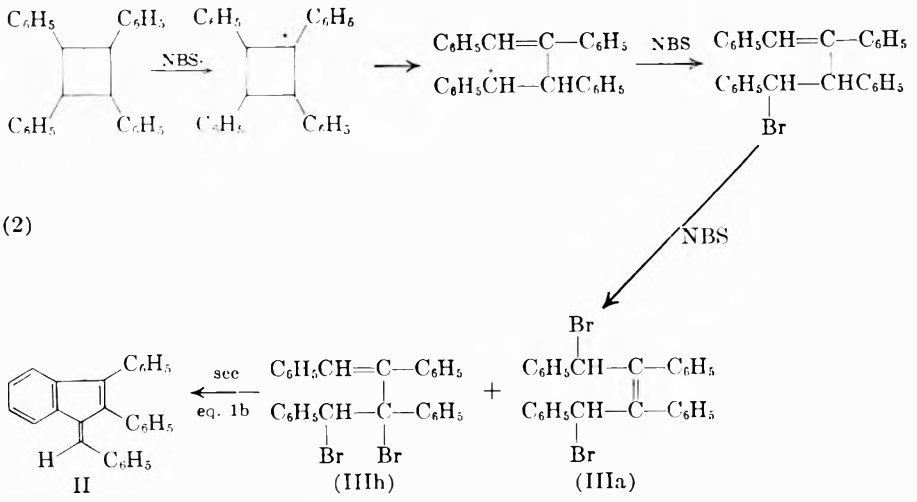
(2) M. Pailer and U. Müller, *Monatsh.*, **79**, 615 (1948).

(3) J. D. Fulton and J. D. Dunitz, *Nature*, **160**, 161 (1947).

(4) A. Orechoff, *Ber.*, **47**, 89 (1914).

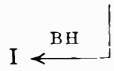
(5) E. H. White, private communication.

(6) E. Bergmann, D. Winter, and W. Schreiber, *Ann.*, **500**, 122 (1933).



(2)

(3)



EXPERIMENTAL

Preparation of I. The reaction of benzyl chloride with excess potassium amide was carried out in the manner described by Morton, Flood, and Bright.[1] We found it less tedious to separate I from the majority of the stilbene formed by fractional sublimation rather than fractional crystallization as used by the Canadian authors. Sublimation of 5-g. batches of the hydrocarbon mixture at 0.5 mm. (furnace temp., 130°) removed the major portion of the stilbene. Recrystallization of the partially purified I so obtained from ethanol gave pure I, m.p. 149–150° (lit.[1] 149–150°). The ultraviolet absorption spectrum of I in isooctane showed λ_{max} = 260 mμ (log ϵ, 4.19).[7]

Reaction of I *with N-bromosuccinimide.* In 20 ml. of carbon tetrachloride was dissolved 1.50 g. of I, 1.50 g. of *N*-bromosuccinimide, and about 20 mg. of benzoyl peroxide. The solution was refluxed for 6 hr. under nitrogen. A slow stream of nitrogen was passed through the solution during the reaction, and the exit tube of the condenser was connected to a trap containing acidic aqueous silver nitrate. No hydrogen bromide was evolved during the first hour of reflux, but after about 1.5 hr. hydrogen bromide began to be evolved. At the end of 5 hr. hydrogen bromide evolution had ceased. At the end of the reflux period the solution was cooled, the succinimide removed by filtration, and the solvent removed under reduced pressure. The viscous residue was chromatographed on 80 g. of acid-washed alumina. Elution with 2:1 hexane-benzene gave 0.92 g. of orange solid. Recrystallization of this material from benzene-hexane gave 0.59 g. (40%) of II, m.p. 172–173°. An additional recrystallization gave purer II, brilliant yellow needles, m.p. 176–177°.

Anal. Calcd. for $C_{28}H_{20}$: C, 94.34; H, 5.66. Mol. wt. 356. Found: C, 94.17; H, 5.80. Mol. wt. (Signer) 360. Ultraviolet absorption spectrum in isooctane: λ_{max} 332 mμ, 286 mμ, 240 mμ (log ϵ 4.03, 4.32, 4.38).

In another experiment the solution was refluxed for only 1 hr. instead of 6. The solution was then cooled, the succinimide filtered off, and the solvent removed under reduced pressure. The semisolid residue was recrystallized from hexane-benzene, pale yellow needles, m.p. 153° (dec.). Analysis for bromine indicated this rather labile substance was a dibromide (although apparently not entirely pure since the analysis showed somewhat less than the calculated amount of bromine). Refluxing a solution of this dibromide in toluene for 1 hr. gave a quantitative conversion to II.

Preparation of 1-benzylidene-2,3-diphenylindene and comparison with II. 1,2,3,4-Tetraphenyl-1,3-butadiene, prepared by the method of Smith and Hoehn,[8] was brominated to give III, and III was subsequently cyclized to 1-benzylidene-2,3-diphenylindene by the procedures described by Orechoff.[4] After recrystallization the benzofulvene melted at 183–184°. The infrared and ultraviolet absorption spectra of this authentic sample of 1-benzylidene-2,3-diphenylindene were identical with those of II. The slightly lower melting point of II (176–177°) is apparently due to the presence of an impurity in the benzofulvene prepared by the *N*-bromosuccinimide route, since a mixture of II and authentic 1-benzylidene-2,3-diphenylindene also melted at 176–177°. This fact together with the identity of the spectra seems to establish clearly that II and 1-benzylidene-2,3-diphenylindene are indeed the same compound.

Preparation of 1,2,3,4-tetraphenyl-1-butene and comparison with I. A sample of the 150°-melting isomer of this olefin was prepared by the method described by Bergmann, Winter, and Schreiber.[6] This involves the addition of benzylmagnesium chloride to α-benzyldesoxybenzoin, followed by dehydration of the resulting carbinol. The 150°-isomer is separated from the other olefins formed by fractional crystallization. It was recrystallized from ethanol, m.p. 148–149°, mixed m.p. with I, 148–149°. The infrared spectra of I and the tetraphenylbutene were completely superimposable as were the ultraviolet absorption spectra. It is thus definite that Morton *et al.*'s tetraphenylcyclobutane (I) is in fact one of the geometric isomers of 1,2,3,4-tetraphenyl-1-butene.

(7) The identity of the ultraviolet spectra of I as prepared by us and as reported by Morton *et al.*[1] leaves no doubt that despite our slightly different method of purification we are dealing with the same compound. The Canadian authors mentioned that the extinction coefficient for I seemed anomalously high for a tetraphenylcyclobutane. On the other hand it is perfectly reasonable for a tetraphenylbutene. The position of the λ_{max} for I (260 mμ) is undoubtedly due to the fact that coplanarity of the phenyl groups is sterically prevented in both the geometric isomers of 1,2,3,4-tetraphenyl-1-butene.

(8) L. I. Smith and H. H. Hoehn, *J. Am. Chem. Soc.* **63**, 1184 (1941).

The α-benzyldesoxybenzoin required in the above synthesis was prepared by alkylation of desoxybenzoin with benzyl chloride in the presence of sodamide in liquid ammonia using the general procedure developed by Hauser[9] for such alkylations.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF SOUTH CAROLINA
COLUMBIA, S. C.

(9) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **81**, 1161 (1959).

Diels-Alder Reactions with Dihydronaphthalenes[1]

N. C. DENO AND HARRY CHAFETZ

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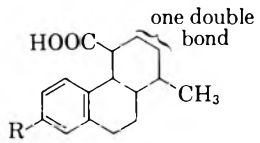
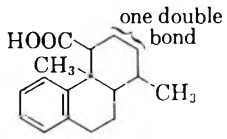
It had been shown that 1,2-dihydronaphthalene reacts with 2,4-hexadienoic acid (sorbic acid) to give a phenanthrene derivative I in 18% yield.[2] This reaction has now been extended to 7-methoxy-1,2-dihydronaphthalene and 1-methyl-3,4-dihydronaphthalene. In both cases the Diels-Alder reaction with 2,4-hexadienoic acid gave low yields of noncrystalline gums. These two products were shown to be primarily structures II and III respectively by degradation of II to 1-methyl-7-methoxyphenanthrene and III to 1-methylphenanthrene. The crude products may have been mixtures of isomers. The position of the double bond was not determined.



I. R = H
II. R = CH_3O



III

The structural isomer formed in these reactions is analogous to that formed when 2,4-hexadienoic acid reacts with styrene and its derivatives.[2] In all of these reactions, the number two carbon atom of 2,4-hexadienoic acid bonds to the α-carbon of the phenylolefin system and the number five carbon atom bonds to the β-carbon of the phenylolefin.

EXPERIMENTAL

7-Methoxy-1,2-dihydronaphthalene plus 2,4-hexadienoic acid. 7-Methoxy-1,2-dihydronaphthalene was prepared by the following sequence: β-Naphthol was hydrogenated to 1,2,3,4-tetrahydro-6-hydroxynaphthalene by the method of Stork.[3] The conversion to the methyl ether was effected with methyl sulfate.[4] Oxidation with lead tetraacetate and thermal removal of acetic acid gave 7-methoxy-1,2-dihydronaphthalene.[5]

7-Methoxy-1,2-dihydronaphthalene was treated with 2,4-hexadienoic acid in a manner similar to that used with 1,2-dihydronaphthalene.[2] Dimethylaniline was added to the extent of one-fourth the total weight of the reactants and 2% by weight of hydroquinone was also added. An atmosphere of carbon dioxide was employed. Variation in the ratio of reactants from equimolar to 1:2 and 2:1 seemed to have little effect. Raising the temperature of the reaction from 140° to 190° increased the yield of distillable product from 6 to 12.5% and lowered the yield of acidic copolymer from 35 to 12%. The runs were held at these temperatures for 100 to 150 hr.

The product II was collected as a hard, yellow gum, b.p. 150–200° (1 mm.). The neutral equivalent was 274, which agrees with 272 which is that calculated for $C_{17}H_{20}O_3$.

The carbon skeleton of the adduct was indicated by its degradation to 1-methyl-7-methoxyphenanthrene. A mixture of 0.95 g. of adduct and 0.4 g. of 10% palladium-carbon catalyst was heated for 20 min. at 300–315° in a carbon dioxide atmosphere. The crude product was dissolved in acetone and the catalyst was removed by filtration. The acetone was replaced by benzene and the solution washed with aqueous alkali. After evaporative distillation and recrystallization of the distillate from methanol, 40 mg. (5%) of white plates, m.p. 134–135°, were isolated. The melting point was not depressed when mixed with an authentic sample of 1-methyl-7-methoxyphenanthrene.[6]

1-Methyl-3,4-dihydronaphthalene plus 2,4-hexadienoic acid. 1-Methyl-3,4-dihydronaphthalene was prepared by the method of English and Cavaglieri.[7]

A mixture of 35 g. of this compound, 22.4 g. of 2,4-hexandienoic acid, 5 ml. of dimethylaniline, and 1.5 g. of hydroquinone was heated at 190° for 100 hr. in a carbon dioxide atmosphere. An ether solution of the reaction mixture was extracted with 5% potassium hydroxide solution and the aqueous extract precipitated with dilute hydrochloric acid. Evaporative distillation of the precipitated acid at 170–210° (1 mm.) gave 6.2 g. (12%) of distillate and 6.4 g. (12.5%) of acidic copolymer. The distillate was a hard yellow, acidic gum and is believed to possess structure III. The position of the double bond is uncertain.

The carbon skeleton of III was indicated by its degradation to 1-methylphenanthrene. The experimental conditions were identical with those used in the degradation of II to 1-methyl-7-methoxyphenanthrene. The yield of 1-methylphenanthrene, m.p. 117–119°, was 30%. The melting point was not depressed when mixed with an authentic sample of 1-methylphenanthrene and the identity was further checked by preparation of the picrate, m.p. 134–137°.

DEPARTMENT OF CHEMISTRY
PENNSYLVANIA STATE UNIVERSITY
UNIVERSITY PARK, PA.

(1) Grateful acknowledgment is made for the support of this research by the Bristol Laboratories Inc., Syracuse, N. Y.

(2) N. Deno, *J. Am. Chem. Soc.*, **72**, 4057 (1950).

(3) G. Stork, *J. Am. Chem. Soc.*, **69**, 576 (1947).

(4) V. C. Burnop, G. M. Elliot, and R. P. Linstead, *J. Chem. Soc.*, 727 (1940).

(5) W. S. Johnson J. M. Anderson, and W. E. Shelberg, *J. Am. Chem. Soc.*, **66**, 218 (1944).

(6) This sample was kindly supplied by Dr. Andre S. Dreiding of the Detroit Institute for Cancer Research.

(7) J. English, Jr., and G. Cavaglieri, *J. Am. Chem. Soc.*, **65**, 1085 (1943).

Preparation of Some Bicyclic Nitriles by the Diels-Alder Reaction

MEYER SCHWARZ AND MILLARD MAIENTHAL

Received August 24, 1959

As part of a program to relate the dielectric properties of some nitriles to their structures it

became necessary to prepare some bicyclic nitriles of established configuration.

Alder and co-workers[1] have recently reported that acrylonitrile and cyclopentadiene react to give a mixture that is 60% 5-*endo*-cyano-2-norbornene and 40% 5-*exo*-cyano-2-norbornene. They found that this ratio of isomers was not greatly affected by changing the temperature of the reaction. They also found that the reaction between acrylonitrile and 1,3-cyclohexadiene gave about equal amounts of the 5-*exo*-cyano- and 5-*endo*-cyano-bicyclo[2.2.2]oct-2-ene. Thus, their results showed that the cyano group has little or no directing influence in the Diels-Alder reaction.

Gillois-Doucet[2], Yashunskii *et al.*[3] and Trapp[4] prepared the adduct of methacrylonitrile and cyclopentadiene without assigning a structure to it. Trapp hydrolyzed the adduct to an amide which was identical with the amide prepared from 5-*endo*-methyl-2-norbornene-5-*exo*-carboxylic acid.[5] A suggestion that this adduct is principally the *endo*-methyl *exo*-nitrile was made by Boehme *et al.*[6]

We dehydrated the amide obtained from hydrolysis of the adduct of methacrylonitrile and cyclopentadiene to yield 5-*exo*-cyano-5-*endo*-methyl-2-norbornene. The infrared spectrum of this latter compound was identical with that of the nitrile prepared directly by the Diels-Alder reaction, indicating that there was no *endo*-cyano isomer formed in this reaction.

The adduct from ethacrylonitrile and cyclopentadiene was shown to be 5-*exo*-cyano-5-*endo*-ethyl-2-norbornene since hydrolysis yielded only one amide, which proved to be identical with 5-*endo*-ethyl-2-norbornene-5-*exo*-carboxamide identified by Boehme and co-workers[6] after preparation from the corresponding acid.

When methacrylonitrile and 1,3-cyclohexadiene reacted, the adduct could not be separated from cyclohexadiene dimer by distillation. The reaction mixture was hydrolyzed to yield, exclusively, 5-*endo*-methylbicyclo[2.2.2]oct-2-ene-5-carboxamide which has been prepared by Boehme *et al.*[6] from the acid chloride of known configuration. Dehydration of the amide with phosphorous pentoxide yielded pure 5-*exo*-cyano-5-*endo*-methylbicyclo[2.2.2]oct-2-ene.

Similarly, when ethacrylonitrile and 1,3-cyclohexadiene reacted, the adduct was contaminated with cyclohexadiene dimer. Upon hydrolysis, only one amide was isolated; it was dehydrated to give a pure nitrile. Since methacrylonitrile gave the *exo*-cyano adducts with both cyclopentadiene and cyclohexadiene, and since ethacrylonitrile gave the *exo*-cyano adduct with cyclopentadiene, the adduct of ethacrylonitrile and cyclohexadiene probably also has the *exo*-cyano structure.

Chemical proof is lacking because the corresponding *endo*- and *exo*-acids are not available. The amide proved to be extremely resistant to hydrolysis, preventing proof of structure *via* the iodo lactone method.

These results indicate that alkyl groups must have considerable directing influence in Diels-Alder reactions. While it was shown by Alder *et al.*[1] that acrylonitrile reacted with cyclopentadiene to yield an adduct of a three to two *endo-exo* ratio, the present experiments showed that α-methacrylonitrile and α-ethacrylonitrile yielded the *exo*-cyano form exclusively.

The same conclusion can be drawn from the preparation of the adducts of 1,3-cyclohexadiene. In the acrylonitrile -1,3-cyclohexadiene adduct prepared by Alder *et al.*[1], the *endo-exo* ratio was about one to one. However, the adduct formed from methacrylonitrile and 1,3-cyclohexadiene was the *exo*-cyano derivative. Since only one amide could be isolated from the adduct of ethyl acrylonitrile and 1,3-cyclohexadiene, the *exo*-cyano structure has been assigned to it.

This same directing influence of alkyl groups has been observed in the reaction of α-substituted acrylic acids with cyclopentadiene. The acrylic acid–cyclopentadiene adduct has been shown to comprise a three to one mixture of *endo*- and *exo*-isomers[7], the α-methacrylic acid–cyclopentadiene adduct a one to three *endo-exo* mixture[5], and the α-ethacrylic acid–cyclopentadiene adduct almost exclusively the *exo* acid.[6]

The unsaturated nitriles were reduced catalytically to the corresponding saturated compounds.

The infrared spectra of the bicylic nitriles showed certain properties in common. The nitrile absorption was found at 4.5 μ, and the unsaturated nitriles exhibited maxima at 6.1 and 6.2–6.4 μ. Both 2-cyano-2-methylbicyclo-octane and 2-cyano-2-ethyl bicyclo-octane had maxima at 3.8 μ.[8] This maximum was absent in the corresponding bicyclo-octenes.

EXPERIMENTAL

5-exo-Cyano-5-endo-methyl-2-norbornene. A mixture of 377 g. (5.7 moles) of cyclopentadiene and 377 g. (5.7 moles) of methylacrylonitrile was refluxed for 8 hr. until the temperature reached 120°. The mixture was then distilled. After methacrylonitrile and cyclopentadiene dimer were removed, there was obtained 178 g., 22%, of 5-*exo*-cyano-5-*endo*-methyl-2-norbornene, b.p. 98–100°/30 mm., m.p. 61–63°

(1) K. Alder, K. Heimbach, and R. Reubke, *Chem. Ber.*, **91**, 1516 (1958).

(2) J. Gillois-Doucet, *Ann. Chim. (Paris)*, **10**, 497 (1955).

(3) V. G. Yashunskii, A. P. Terent'ev, and Ya. G. Neklin, *Zhur. Obsheĭ Khim.*, **26**, 723 (1956).

(4) W. B. Trapp, Thesis, University of Colorado, 1952.

(5) J. S. Meek and W. B. Trapp, *J. Am. Chem. Soc.*, **79**, 3909 (1957).

(6) W. R. Boehme, E. Schipper, W. G. Scharpf, and J. Nichols, *J. Am. Chem. Soc.*, **80**, 5188 (1958).

(7) C. D. VerNooy and C. S. Rondestvedt, Jr., *J. Am. Chem. Soc.*, **77**, 3583 (1955).

(8) J. Hine, J. A. Brown, L. H. Zalkow, W. E. Gardner, and M. Hine, *J. Am. Chem. Soc.*, **77**, 597 (1955).

(lit.[3] m.p. 55° and 30–32°[4]). Infrared absorption maxima: 10.25(s), 10.58(s), 10.62(s), 10.88(s), 11.05(s), 11.65(s), 11.78(s), 11.81(m), 12.22(s), 13.00(s), 13.75(s), 14.30(s) μ.

Anal. Calcd. for $C_9H_{11}N$: C, 81.16; H, 8.33. Found: C, 81.0; H, 8.5.

In order to prove the configuration of the nitrile, it was first hydrolyzed in alcoholic potassium hydroxide to 5-*endo*-methyl-2-norbornene-5-*exo*-carboxamide which after recrystallization from benzene melted at 157° (lit.[5] m.p. 157.5–158.5°). The infrared spectrum of this amide was identical with that of an authentic sample of 5-*endo*-methyl-2-norbornene-5-*exo*-carboxamide.[9] The amide obtained by hydrolysis was dehydrated with phosphorus pentoxide by the method of Boehme *et al.*[6] to give a 45% yield of 5-*exo*-cyano-5-*endo*-methyl-2-norbornene, b.p. 98°/28 mm., m.p. 63–64°. The spectrum of this nitrile was identical with the spectrum of the original adduct.

2-exo-Cyano-2-endo-methylnorbornane. 5-*exo*-Cyano-5-*endo*-methyl-2-norbornene (23.8 g., 0.18 mole) in 200 ml. of ethanol was hydrogenated in the presence of platinum oxide catalyst under about 20 lb. pressure at room temperature. After removal of catalyst and solvent, the residue was distilled, to yield 15 g., 62%, of 2-*exo*-cyano-2-*endo*-methylnorbornane, b.p. 116–117°/45 mm., m.p. 47–48°.

Anal. Calcd. for $C_9H_{13}N$: C, 79.95; H, 9.69. Found: C, 80.2; H, 9.6.

5-exo-Cyano-5-endo-ethyl-2-norbornene. A mixture of 84 g. (1.04 moles) ethacrylonitrile and 135 g. (2.05 moles) of cyclopentadiene was refluxed about 3.5 hr. until its temperature had risen to 140°. The product was distilled to yield 62 g., 40.5%, of 5-*exo*-cyano-5-*endo*-ethyl-2-norbornene, b.p. 101°/15 mm., n_D 1.4775, m.p. 9.5–12°. Infrared absorption maxima: 10.0(s), 10.5(s), 10.9(s), 11.32(s), 11.75(s), 12.2(s), 12.8(s), 13.75(s), 14.3(s) μ.

Anal. Calcd. for $C_{10}H_{13}N$: C, 81.58; H, 8.90. Found: C, 81.23; H, 8.6.

This nitrile was hydrolyzed in alcoholic potassium hydroxide to yield 5-*endo*-ethyl-2-norbornene-5-*exo*-carboxamide, which on recrystallization from benzene-*n*-heptane melted at 94–95° (lit.[6] 97–98°).

2-exo-Cyano-2-endo-ethylnorbornane. A solution of 30 g. (0.22 mole) of 5-*exo*-cyano-5-*endo*-ethyl-2-norbornene in 50 ml. of alcohol was hydrogenated at 40 lb. pressure at room temperature in the presence of platinum oxide catalyst. After removal of catalyst and solvent the residue was distilled to yield 26 g., 79%, of 2-*exo*-cyano-2-*endo*-ethylnorbornane b.p. 103–104°/13 mm. The analytical sample was redistilled, b.p. 96°/10 mm., $n_D^{25.5}$ 1.4708. Infrared absorption maxima: 10.0(w), 10.45(s), 10.6(m), 10.7(m), 11.45(s), 11.9(s), 12.7(s), 12.98(m), 13.12(m) μ.

Anal. Calcd. for $C_{10}H_{15}N$: C, 80.48; H, 10.13. Found: C, 80.8; H, 10.3.

5-endo-Methylbicyclo[2.2.2]oct-2-ene-5-exo-carboxamide. A mixture of 44.5 g. (0.55 mole) of 1,3-cyclohexadiene and 38 g. (0.58 mole) of methacrylonitrile was placed in a steel bomb and heated in an oil bath at 190° for 6.5 hr. Distillation of the reaction mixture gave some unchanged methacrylonitrile and 37.0 g. of crude adduct b.p. 95–100°/10 mm. The product thus obtained solidified at room temperature, but on standing overnight some liquid separated from it. It is assumed that at this stage the adduct was contaminated with some bicyclohexadiene which has nearly the same soiling point. Several attempts to purify this adduct by distillation failed to give a sample that had a satisfactory analysis.

The crude adduct was hydrolyzed with alcoholic potassium hydroxide to yield 5-*endo*-methylbicyclo[2.2.2]oct-2-ene-5-*exo*-carboxamide, which on recrystallization from ethanol-water, melted at 127–128° (lit.[6] m.p. 125–126°).

5-exo-Cyano-5-endo-methylbicyclo[2.2.2]oct-2-ene. The above amide was dehydrated by the procedure of McElvain.[10] A mixture of 62.0 g. (0.38 mole) of 5-*endo*-methylbicyclo[2.2.2]oct-2-ene-5-*exo*-carboxamide, 175 ml. of benzene, 102 g. of triethylamine, and 95 g. of phosphorus pentoxide was heated with stirring until the reaction began. After the initial exothermic reaction had subsided, the mixture was refluxed for an additional 0.5 hr. The liquid was decanted from the inorganic layer and the residue washed several times with benzene. The combined organic extracts were distilled yielding 35 g., 63% of 5-*exo*-cyano-5-*endo*-methylbicyclo[2.2.2]oct-2-ene, b.p. 127–129°/50 mm. A sample for analysis was sublimed *in vacuo* and melted at 98–99°. Infrared absorption maxima: 9.98(w), 10.22(s), 10.48(s), 10.72(s), 10.88(s), 11.49(s), 11.83(s), 12.3(s), 13.95(s), 14.2(s) μ.

Anal. Calcd. for $C_{10}H_{13}N$: C, 81.58; H, 8.90. Found: C, 81.6; H, 9.1.

2-Cyano-2-methylbicyclo[2.2.2]octane. A mixture of 15 g. (0.1 mole) of 5-*exo*-cyano-5-*endo*-methylbicyclo[2.2.2]oct-2-ene, 100 ml. of alcohol, and 0.1 g. of platinum oxide was hydrogenated under 20 lb. pressure. After removal of the catalyst, the solution was poured into water, precipitating the product which was dried over phosphorus pentoxide, yielding 13 g., 87%, of 2-cyano-2-methylbicyclo[2.2.2]octane melting at 108–109°. A sample for analysis was sublimed *in vacuo*, m.p. 108–109°. Infrared absorption maxima: 3.8(m), 9.85(w), 10.10(s), 10.29(w), 10.53(m), 10.69(m), 11.1(s), 11.35(s), 11.62(m), 11.96(m), 12.8(s), 12.48(m), 12.85(m), 14.8(m) μ.

Anal. Calcd. for $C_{10}H_{15}N$: C, 80.48; H, 10.13. Found: C, 80.4; H, 10.2.

5-endo-Ethylbicyclo[2.2.2]oct-2-ene-5-exo-carboxamide. A mixture of 50 g. (0.63 mole) of 1,3-cyclohexadiene and 40 g. (0.5 mole) of ethacrylonitrile was heated in a steel bomb to 190° for 8 hr. The reaction mixture was distilled and after a forerun of unchanged starting material there was obtained 14.5 g. of crude adduct, b.p. 133–140°/35 mm. Fractionation of this product failed to yield a pure sample of nitrile.

A mixture of 39 g. of the crude adduct, 50 g. of potassium hydroxide, 100 ml. of ethylene glycol, and 10 ml. of water was refluxed 8 hr. The cooled reaction mixture was dissolved in water and extracted with benzene. The extract was steam-distilled to remove the benzene and most of the unhydrolyzed starting material. The residual aqueous mixture was kept at 0° overnight and the solid collected by filtering. Several recrystallizations from methanol-water yielded 5-*endo*-ethylbicyclo[2.2.2]oct-2-ene-5-*exo*-carboxamide, m.p. 92°.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56. Found: C, 74.0; H, 9.6.

5-exo-Cyano-5-endo-ethylbicyclo[2.2.2]oct-2-ene. A mixture of 28 g. (0.15 mole) of 5-*endo*-ethylbicyclo[2,2,2]oct-2-ene-5-*exo*-carboxamide, 400 ml. of benzene, 100 g. of triethylamine, and 50 g. of phosphorus pentoxide was stirred and refluxed for 1.5 hr. The cooled mixture was extracted several times with benzene. The combined benzene extracts were dried and distilled to yield 19.5 g., 77.5%, of 5-*exo*-cyano-5-*endo*-ethylbicyclo[2.2.2]oct-2-ene, b.p. 75–80°/3 mm., $n_D^{22.4}$ 1.4876. Infrared absorption maxima: 10.08(w), 10.35(s), 11.01(w), 11.6(s), 12.4(s), 12.75(s), 12.95(s) μ.

Anal. Calcd. for $C_{11}H_{15}N$: C, 81.94; H, 9.36. Found: C, 81.9; H, 9.4.

2-Cyano-2-ethylbicyclo[2.2.2]octane. The unsaturated nitrile was reduced in alcohol with hydrogen in the presence of platinum oxide under 25 lb. pressure to yield 2-cyano-2-ethylbicyclo[2.2.2]octane, b.p. 105°/8 mm., n_D^{25} 1.4824. Infrared absorption maxima: 3.81(w), 10.1(w), 10.39(s), 10.72(m), 11.0(w), 11.32(w), 11.7(s), 12.15(s), 12.48(w), 12.8(m), 12.98(m) μ.

Anal. Calcd. for $C_{11}H_{17}N$: N, 8.58. Found: N, 8.3.

(9) The authors are indebted to Dr. J. S. Meek for this spectrum.

(10) S. M. McElvain and R. C. Clarke, *J. Am. Chem. Soc.*, 69, 2657 (1947).

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DIAMOND ORDNANCE FUZE LABORATORIES
WASHINGTON 25, D. C.

Reaction of Cyanogen with Organic Compounds. XIV. Compounds Containing Hydrogen Activated by Neighboring Groups[1]

HENRY M. WOODBURN AND THOMAS J. DOLCE[2]

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Previous papers in this series[3] have described many reactions of cyanogen with the hydrogen of functional groups. However, little has been done with the cyanogen reactions of hydrogen activated by neighboring groups. Traube[4] has reported on malonic ester, acetoacetic ester, and acetylacetone and Langenbeck[5] showed that acetaldehyde reacts with cyanogen. However, the structure of the product indicates that hydrolysis was an accompanying step:

$$CH_3CHO \rightleftharpoons CH_2{=}CHOH \xrightarrow[H_2O]{(CN)_2} (CH_2{=}CHOC(=NH){-}CONH_2)(H_2O)$$

The present study was undertaken to discover other active hydrogen compounds which would react with cyanogen. Table I lists the compounds with which some measure of success was obtained. In every case the product consisted of a substance in which one molecule of the organic reagent had added to one molecule of cyanogen.

Other compounds which were studied but were recovered unchanged were nitromethane, 2-nitropropane, 1-nitrobutane, phenylacetonitrile, succinonitrile, benzaldehyde, and cyclopentadiene.

Attempts were made without success to add a second molecule of cyanogen to the condensation products of cyanogen with acetylacetone and with acetoacetanilide. In addition the following compounds, all of which contain but one active hydrogen, failed to react: ethyl butylmalonate, 3-chloroacetylacetone, ethyl α-acetylacetoacetate, triphenylmethane, and 4-pyridyldiphenylmethane.

In no case was it possible to obtain products in which the ratio of organic reagent to cyanogen was 2:1 instead of 1:1

EXPERIMENTAL

Pure, compressed cyanogen in cylinders was supplied by the American Cyanamid Company. The gas was led from the cylinder into a trap cooled by Dry-Ice-acetone where it became solid and permitted the tube to be weighed before and after a reaction. The rate of vaporization was easily controlled by warming or cooling the tube.

Except for nitroparaffins and aldehydes where the nature and strength of a basic solvent appeared to be critical, all the successful reactions took place in the presence of alcohol and a small amount of sodium. Three procedures illustrative of the above are given.

TABLE I

REACTION OF CYANOGEN WITH COMPOUNDS CONTAINING ACTIVE HYDROGEN

Reagent	Product	M.P.	Yield, %	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$C_2H_5NO_2$	$CH_3CHNO_2C(=NH)CN$	117–119	7.5	37.8	4.0	33.1	37.9	4.4	33.3
$C_2H_5CH_2NO_2$	$C_2H_5CHNO_2C(=NH)CN$	67–69	4.7	42.6	5.0	29.8	42.6	4.9	30.4
C_6H_5NHCO | CH_2COCH_3	$C_6H_5NHCOCHC(=NH)CN$ | $COCH_3$	204–205	43.0	62.0	4.8	18.3	62.4	5.1	18.1
$CH_2CNCO_2C_2H_5$	$CHCNCO_2C_2H_5$ | $C(=NH)CN$	168–170	2.4	50.9	4.3	25.4	50.7	4.5	25.2
$CH_2(CN)_2$	$(CN)_2CHC(=NH)CN$	171	6.5	50.8	1.7	47.5	50.4	2.2	47.2
$(CH_3)_2CHCHO$	$(CH_3)_2C{=}CHOC(=NH)$ | $CONH_2{\cdot}H_2O$	108–110	22.7	45.0	7.6	17.5	45.2	7.5	17.0
C_3H_7CHO	Gummy product			Infrared spectrum closely resembled that from isobutyraldehyde product					

Reaction with nitroethane. A solution of 22.1 g. (0.29 mole) of nitroethane was prepared in 200 ml. of 1*N* aqueous sodium hydroxide and cooled to 0°. Three-tenths of a mole (15.6 g.) of cyanogen was bubbled into the solution. The mixture darkened quite rapidly and after a short time a small amount of crystalline material formed. When all the cyanogen had been added, the dark mixture was extracted immediately with 200 ml. of ether and the extract dried over anhydrous magnesium sulfate while standing in the ice chest. Evaporation of the ether left 2.8 g. (7.5% yield) of yellow solid. Recrystallization from ether with decolorizing carbon present gave pure material forming yellow needles which melted at 117–119°.

(1) From the dissertation presented by Thomas J. Dolce in partial fulfillment of the requirements for the Ph.D. degree, February 1958. The financial assistance of Research Corporation is gratefully acknowledged.

(2) Present address: Research Laboratory, Celanese Corporation, Summit, N. J.

(3) Paper No. 1 of this series appeared in *J. Org. Chem.*, **14**, 555 (1949).

(4) W. Traube, *Ber.*, **31**, 2938 (1898).

(5) W. Lagenbeck, *Ann.*, **469**, 16 (1929).

Reaction with acetoacetanilide. In 290 ml. of 95% ethanol which contained a catalytic amount of sodium (less than 0.1 g.) was dissolved 62.0 g. (0.35 mole) of acetoacetanilide. The solution was cooled to 0° and treated with 18.2 g. (0.35 mole) of cyanogen. Crystals began to separate almost immediately and continued to do so as the reaction proceeded. Filtered immediately and dried, the solid weighed 34.5 g. (43% yield). Recrystallized from acetone the product formed minute, light yellow needles which melted at 204–205°.

Reaction with isobutyraldehyde. Twenty-four g. (0.33 mole) of isobutyraldehyde was placed in a 500-ml. flask fitted with a stirrer, and 70 ml. of 2% sodium carbonate solution was added. The aldehyde was insoluble in the carbonate solution, but the presence of the base appeared necessary to cause a reaction. With the flask cooled by an ice bath, 17.2 g. (0.33 mole) of cyanogen was passed in. Vigorous stirring was needed since the product which began to form after a few minutes was gummy and tended to clog the addition tube. The gummy material gradually became a light tan foamy mass. This was filtered with some difficulty, and placed in a vacuum desiccator overnight to dry. It became a light yellow, crusty solid weighing 12.0 g. (22.7% yield).

Recrystallized from ethanol with decolorizing carbon present, a solid was obtained which melted at 108–110° with decomposition.

Department of Chemistry
University of Buffalo
Buffalo 14, N.Y.

Reaction of Diazoethane and 1-Diazopropane With Aliphatic Aldehydes

Richard F. Smith

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The major products obtained in the reaction of aldehydes with diazomethane are the methyl ketone or the oxide. As pointed out by Gutsche, in an excellent review article, aromatic and aliphatic aldehydes most frequently react to give mixtures of both ketones and oxides. In the few cases studied however,[1] aromatic aldehydes reacted with higher diazoalkanes to yield the ketones as the major products in good yields.

Because of the selective formation of ketones in the higher diazoalkane–aromatic aldehyde reaction, it seemed of interest to study the reaction of higher diazoalkanes with aliphatic aldehydes. It was found that ketones (see Table I) were formed in 51–78% yields from the reaction of the readily available[2] diazoethane and 1-diazopropane with five simple aliphatic aldehydes. Widely boiling foreruns were obtained in many cases, but were not examined for oxide content.

From the few cases studied, it would appear that the reaction of higher diazoalkanes with aliphatic aldehydes may provide a convenient synthetic method for the small scale conversion of aliphatic aldehydes to the corresponding alkyl ketones.

Experimental

Boiling points and melting points are uncorrected.

General method of reaction of aldehydes with diazoalkanes. The diazoalkanes were prepared from the nitrosoalkylurethanes by the method of Wilds and Meader.[2] Ethereal solutions of diazoethane (from 0.15 mole[3] of the urethane) or 1-diazopropane (from 0.20 mole of the urethane) were treated with 0.1 mole of the aldehyde. The reaction was allowed to proceed overnight at room temperature. The ether and excess diazoalkane were removed by distillation and the products were obtained by distillation through a 12″ Vigreux column.

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TABLE I

Reactions with Diazoethane

Aldehyde	Product	Yield, %	B.P., °C. Found	B.P., °C. Lit.	Derivative,[a] M.P., °C. Found	Derivative,[a] M.P., °C. Lit.
Propionaldehyde	3-Pentanone	62	99–100	102[b]	155–157D	156[b]
n-Butyraldehyde	3-Hexanone	56	122–125	121–123[c]	129–130D	130[d]
Isobutyraldehyde	2-Methyl-3-pentanone	58	109–113	111–113[e]	110–111D	111–113[f]
n-Valeraldehyde	3-Heptanone	72	144–147	148[g]	100–102S	103[g]
n-Heptaldehyde	3-Nonanone	71	185–190	187[h]	109–111S	111–112[i]
	Reactions with 1-Diazopropane					
Propionaldehyde	3-Hexanone	51[j]	121–123	121–123[c]	129–130D	130[d]
n-Butyraldehyde	4-Heptanone	74	141–144	144[g]	131–132S	132[g]
Isobutyraldehyde	2-Methyl-3-hexanone	64	131–133	134–136[k]	116–118S	119[k]
n-Valeraldehyde	4-Octanone	74	164–167	170[l]	94–95S	96[l]
n-Heptaldehyde	4-Decanone	78	204–207	202–206[m]	117–118H	117–119[n]

[a] D = 2,4-dinitrophenylhydrazone; S = semicarbazone; H = hydantoin. [b] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, John Wiley & Sons, New York, 4th ed., p. 316. [c] L. I. Smith, H. E. Ungnade, W. M. Lauer, and R. M. Leekley, *J. Am. Chem. Soc.*, 61, 3079 (1939). [d] R. B. Wagner and H. D. Zook, *Synthetic Organic Chemistry*, John Wiley & Sons, New York, 1953, p. 352. [e] F. C. Whitmore and L. P. Block, *J. Am. Chem. Soc.*, 64, 1619 (1942). [f] H. Fournier, *Bull. soc. chim.*, 7, 836 (1910). [g] M. L. Sherrill, *J. Am. Chem. Soc.*, 52, 1982 (1930). [h] A. I. Vogel, *J. Chem. Soc.*, 610 (1948). [i] Ref. *d.*, p. 354. [j] The yield of distilled product was 41%. An additional 10% was isolated as the 2,4-dinitrophenylhydrazone by treatment of a forerun (b.p. 96–120°) with excess of Brady's solution. [k] B. E. Hudson and C. R. Hauser, *J. Am. Chem. Soc.*, 63, 3163 (1941). [l] L. Boueveault, *Bull. soc. chim. France* (3) 35, 629 (1906). [m] P. Karrer, B. Shibata, A. Wettstein, and L. Jacubowicz, *Helv. Chim. Acta*, 13, 1292 (1930). [n] M. S. Kharash and H. N. Friedlander, *J. Org. Chem.*, 14, 248 (1949).

tion of the State University of New York. The author also wishes to express his thanks to the Foundation for a Summer Research Fellowship.

CHEMISTRY DEPARTMENT
STATE UNIVERSITY OF NEW YORK
NEW YORK STATE COLLEGE FOR TEACHERS
ALBANY, N. Y.

(1) C. D. Gutsche, *Org. Reactions*, VIII, 364 (1954).

(2) A. H. Wilds and A. L. Meader, Jr., *J. Org. Chem.*, **13**, 763 (1948).

(3) The molar quantities were chosen to give a slight excess (about 10%) of the diazoalkane (based on the average yields of diazoalkane given by Wilds and Meader[2]). In an experiment conducted by Mr. E. Otremba in these laboratories, it was established that 3-pentanone does not react with etheral diazoethane at room temperature. Thus, it was assumed that the ketonic product would not react with excess diazoalkane. A polar solvent is evidently necessary to promote the reaction of acyclic ketones with diazoalkanes (ref. 1, p. 375).

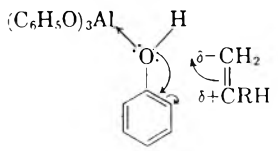
Reaction of Aluminum Phenoxide with Nitriles

H. W. JOHNSTON

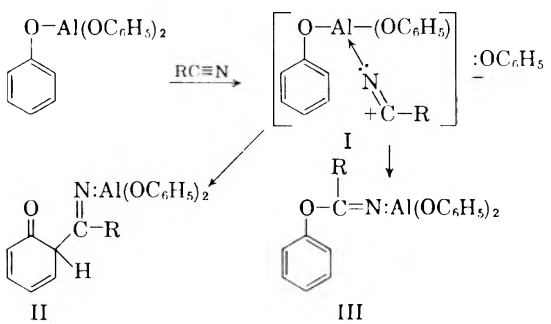
Received November 2, 1959

In a previous report it was shown that the cyanoethylation of phenol in the presence of anhydrous aluminum chloride and dry hydrogen chloride gave a small amount of the *ortho-* addition product, the δ-lactone of β-(*o*-hydroxyphenyl) propionic acid.[1] Our interest in the possibility of increasing the yield of this *ortho-* isomer was prompted by the work of Kolka, Napolitano, and Ecke, who found that alkylation of the phenolic salt of aluminum with alkenes at temperatures of 240° to 320° and pressures of 200 to 800 p.s.i. gave unusually high yields of *ortho-* alkylated products.[2] However, in our laboratory when acrylonitrile and aluminum phenoxide were caused to react together under similar conditions, a resin was obtained as the principal reaction product, and neither dihydrocoumarin nor *p*-hydroxyphenylpropionitrile were isolated. An infrared spectral examination of the resin showed that the cyano-group had completely disappeared, and strong aromatic carbonyl bands appeared, indicating that, under these relatively severe reaction conditions, polymerization of the olefin had taken place with considerable cross linking of the resin through the formation of carbonyl groups linked to the aromatic ring. Bands corresponding to both *ortho-* and *para-* substitution were noted. That cross linking of the polymer took place in a Hoesch-type reaction of the nitrile was confirmed in an experiment in which acetonitrile was substituted for acrylonitrile in the reaction with aluminum phenoxide. *o*-Hydroxyacetophenone and *p*-hydroxyacetophenone were recovered in yields of 3 and 4%, respectively based upon equivalents of aluminum consumed.

In the alkylation of phenol with ethylene or propylene the suggestion is advanced that a cyclic concerted mechanism operates, in which aluminum phenoxide is coordinated with excess phenol with simultaneous attack of the olefin upon the *ortho-* position of the benzene ring:[2]



However, this mechanism as constructed here implies an electron shift toward the ring though opposed by both the coordination of aluminum and the proton of phenol. A suggested mechanism more applicable to the aluminum phenoxide-nitrile system might be the displacement of a phenoxide ion from aluminum phenoxide by the nitrogen atom and its electron pair. An attack is then possible upon the *ortho-* position of the new phenoxide complex (I) to give an *ortho-* substituted dienone (II) or, alternately, upon the oxygen atom of the displaced phenoxide ion to form an imidic ester complex (III). Cleavage of the latter would permit amidation of the *para-* position of phenol.



An interesting study of the Fries rearrangement parallels the above suggestion. Cullinane and Edwards[3] have studied the rate of rearrangement of substituted phenyl acetates and have found that the kinetics were consistent with a mechanism which assumes the displacement of the acyl group from the oxygen atom by a second mole of catalyst. The acyl carbonium ion attack upon the *ortho-* or *para-* position of the phenolic moiety is said to be irreversible, contrary to the results obtained by Rosenmund and Schnurr.[4]

Finally, in some experiments with aluminum phenoxide and ethyl acrylate a small amount of β-phenoxypropionic acid was isolated indicating

(1) H. W. Johnston and F. J. Gross, *J. Org. Chem.*, **22**, 1264 (1957).

(2) H. J. Kolka, J. P. Napolitano, and G. Ecke, *J. Org. Chem.*, **21**, 712 (1956).

(3) W. M. Cullinane and B. F. R. Edwards, *J. Chem. Soc.*, 434 (1958) and *J. Chem. Soc.*, 3016 (1957).

(4) K. W. Rosenmund and W. Schnurr, *Ann.*, **460**, 56 (1928).

the definite possibility of 1,4-addition of phenoxide ion to the acrylic ester. Also, in the presence of diphenyl ether as a solvent instead of excess phenol, phenyl acrylate was isolated in 20% yield based on consumed phenol. This ester-interchange reaction tends to support the proposal that in the analogous reaction of aluminum phenoxide and acrylonitrile the nitrilo-group displaces phenoxide ion from the aluminum complex.

EXPERIMENTAL

Reaction of acetonitrile with aluminum phenoxide. Eighteen g. (0.67 mole) of aluminum turnings was added in small portions over a period of 3 hr. to 184 g. (2 moles) of freshly distilled phenol held at 172–185° under an atmosphere of nitrogen gas. The addition of aluminum metal was carried out conveniently in glass apparatus until a temperature of 185° was noted for the molten mass, at which time it was transferred to a 1-l. stainless steel bomb. The bomb was heated to 195° with the remaining aluminum until no more phenol was lost through the vent.

The bomb was cooled to room temperature and opened. Eighty-two g. (2 moles) of freshly distilled acetonitrile was added and the bomb-head replaced. Air was purged from the bomb by means of nitrogen after which the reaction mixture was heated to 185° with constant mechanical shaking for a period of 6 hr. A maximum pressure of 115 p.s.i. was noted. Heating and shaking were continued for an additional 2 hr. at 220° and 165 p.s.i., after which the bomb was cooled to room temperature and opened. The mixture, consisting of a watery liquid and a brittle crystalline solid, was poured over 1 kg. of cracked ice containing 150 ml. of concentrated hydrochloric acid (*d*, 1.2). (Two g. of unreacted aluminum was recovered at this point.)

The organic phase was separated and steam-distilled. The distillate was shaken with sodium chloride and the oils were recovered by extraction with three 50-ml. portions of toluene. The hydrocarbon solution was washed three times with 50-ml. portions of saturated sodium chloride, separated, and distilled through a 100-cm. modified Claisen column. One hundred and thirty g. of phenol (0.57 mole) was recovered at 89° and 24 mm. after which the residue was transferred to a Claisen flask of 10 ml. capacity. Three g. (0.04 mole) of colorless liquid was recovered at 95–99° at 18 mm. which was identified as *o*-hydroxyacetophenone (oxime, m.p. 114–116° uncorr., which is in agreement with the literature).[5]

The residual tar which was involatile in steam was taken up in ether and separated from the aqueous phase. Benzene was added and the solvents distilled until a thick oil was obtained. A small amount of hot 3:1 alcohol-benzene mixture was added and crystallization took place upon standing in an ice chest. Seven g. (0.05 mole) of *p*-hydroxyacetophenone, m.p. 104–106°, was obtained.[6]

Reaction of acrylonitrile with aluminum phenoxide. In a procedure similar to that described for acetonitrile and aluminum phenoxide, 9 g. (0.37 mole) of aluminum turnings was caused to react with 282 g. (3 moles) of phenol at 170–172° under nitrogen. Since an excess of phenol was present as a solvent it was unnecessary to transfer the mixture to the bomb until all the aluminum has been dissolved. Fifty-three g. (1 mole) of freshly distilled phenol was added and the mixture was held with continual shaking at 172–180° for 9 hr. From the dark red oil 177 g. (1.2 moles) of phenol was recovered and a viscous dark brown resin remained which was undistillable.

Examination of the infrared spectrum of a resin-potassium bromide-pellet showed practically complete disappearance of the nitrile bond at 2251 cm.$^{-1}$ and the appearance of strong aromatic ketone bands at 1578, 1641, 1223, and 1169 cm.$^{-1}$

Reaction of ethyl acrylate with aluminum phenoxide. In a procedure similar to that employed for the reaction of phenol and acrylonitrile 282 g. (3 moles) of phenol, 9.0 g. (0.37 mole) of aluminum turnings and 900 g. of ethyl acrylate gave a yellow oil from which ethyl acrylate and phenol were removed by distillation. The residue consisted of rubbery red crumbs. Extraction with toluene followed by vacuum stripping of this solvent gave 9 g. of a tan fusible residue, which was recrystallized from hot water to a melting point of 85–93°. Further recrystallization from benzene gave needles of β-phenoxyproprionic acid, m.p. 93–96°,[7] identified by conversion into the semicarbazone of 4-chromanone, m.p. 223–226°. Louden and Razden[8] report a melting point of 227° for this derivative.

In a second experiment, 18 g. (0.67 mole) aluminum turnings was caused to react with 184 g. (2 moles) of phenol in 75 ml. of diphenyl ether. Two hundred g. (2 moles) of ethyl acrylate was added to the salt and held at 175–182° for 11 hr. under pressures of 40 to 60 p.s.i. Decomposition of the reaction mixture in acid followed by isolation of distillable products as described above gave 52 g. (0.35 mole) of phenyl acrylate, b.p. range, 65° at 15 mm. to 71° at 14 mm. Redistillation of this fraction at ordinary pressures gave a product of b.p. 106–168° at 712 mm., sp. gr., 0.975 20°/4°. Infrared analysis showed strong bands at 1610, 1590, 1500, 1480, 1300, 1240, 1180, 1120, 1050, 690 cm.$^{-1}$ A ferric chloride test was negative; bromine was strongly absorbed.

In addition, 24 g. of phenol was recovered to complete recovery of the diphenyl ether. A gelatinous material, presumably polyethyl acrylate and its cross-linked phenolic derivatives, was noted.

Acknowledgments. The author wishes to express his appreciation to Mr. Andrew Man-Kuen Tsoi, undergraduate research assistant at Whitworth College, for technical aid and to Dr. Gardner W. Stacy, Chemistry Department, Washington State College, who kindly secured the infrared analyses. The support of the Research Corporation (Frederick Gardner Cottrell Grant 2814) and of the National Institute of Health (R.G.-5965(A)) is gratefully acknowledged.

DEPARTMENT OF CHEMISTRY
WHITWORTH COLLEGE
SPOKANE, WASH.

(5) A. C. Cope, *J. Am. Chem. Soc.*, **57**, 574 (1934).

(6) E. M. Huntress and S. P. Mulliken, *Identification of Pure Organic Compounds, Order I*, John Wiley and Sons, nc., New York, N. Y., 1941, p. 229.

(7) S. G. Powell, *J. Am. Chem. Soc.*, **45**, 2710 (1923).

(8) J. D. Louden and R. K. Razden, *J. Chem. Soc.*, 4289 (1954).

An Attempted Synthesis of Dipyrazolo[*def*, *qrs*]flavanthrene-8,16-dione

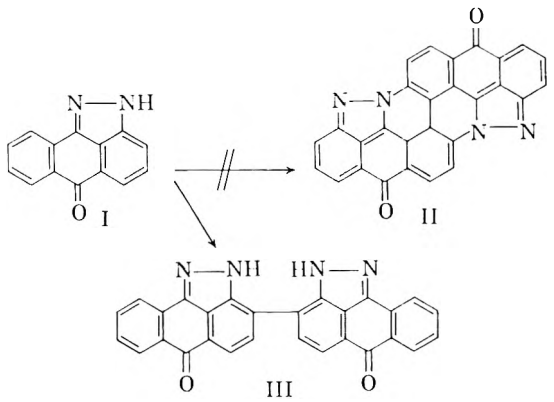
W. L. MOSBY AND W. L. BERRY

Received September 8, 1959

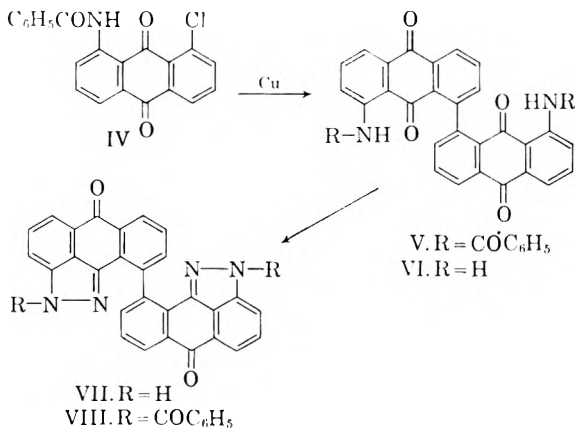
Fusion of pyrazolanthrone (I) with alkali produces a dye known as "pyrazolanthrone yellow," for which, at one time, structure II was proposed.[1]

(1) F. Mayer and R. Heil, *Ber.*, **55**, 2155 (1922).

Although the dye is now recognized[2] to have structure III, no synthesis of the interesting compound dipyrazolo[*def*, *qrs*]flavanthrene-8,16-dione (II) has been reported. Following is an account of an attempt to prepare II, and of its failure in the final step.



Treatment of 1 - benzamido - 8 - chloroanthraquinone (IV) with copper powder in a solvent resulted chiefly in dehalogenation, giving 1-benzamidoanthraquinone. However, when the volume of solvent was drastically reduced, a good yield of the bianthraquinonyl compound V was produced. Acid hydrolysis readily afforded the free amine (VI).



The diamine VI was tetrazotized, reduced and cyclized to produce VII in a manner analogous to the synthesis[3,4] of pyrazolanthrone from 1-aminoanthraquinone. Unfortunately, no way was found to convert either VII, or its dibenzoyl derivative (VIII) into the desired quinone II. Under acidic conditions (heating with aluminum chloride in pyridine or nitrobenzene or in an aluminum chloride–sodium chloride melt) VII was recovered unchanged. Heating VII with potassium hydroxide and methanol yielded a small amount of insoluble, alkali-sensitive pale orange dye (bright green vat solution), probably produced by bimolecular coupling in the 3,3′-positions analogous to the formation of III from I. Introduction of manganese dioxide into a caustic melt with VII afforded a product readily soluble in dilute base, which in behavior and color reactions resembles the *o*-carboxyphenylindazoles obtained[5] under similar conditions from I and III. These two undesired products were not investigated further.

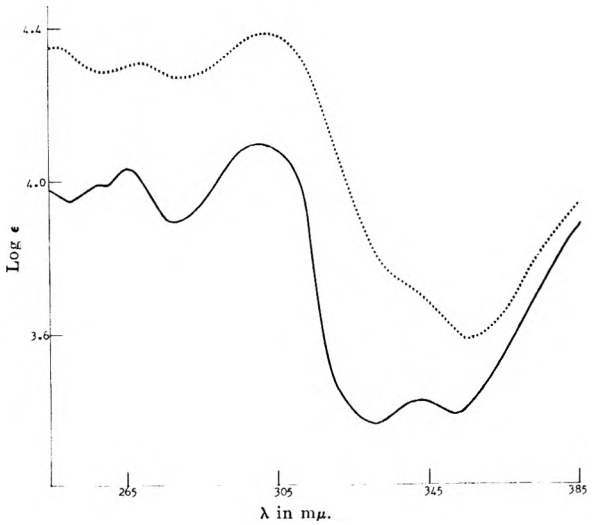


Fig. 1. Ultraviolet spectra in dimethylformamide solution of pyrazolanthrone (——) and of compound VII (- - -).

One obstacle to the facile conversion of VII into II may be noted from an examination of the ultraviolet spectrum of VII (Fig. 1). From the virtual superimposability of the curves of VII and I (with doubling of the extinction coefficient) it appears that the plane of the upper half of the molecule of VII is approximately orthogonal to that of the lower half. This barrier to coplanarity plus the need to lose four hydrogen atoms (two as hydride ions), doubtless indicate a high activation energy for the transformation of VII into II, and permit one of the possible side reactions to occur preferentially.

A curious difference in the reactivity of 1-chloro-8-nitroanthraquinone was encountered in treating it with hydrazine and with *p*-toluenesulfonamide. Reaction with hydrazine occurred with displacement of the nitro group, giving the known[3] 10-chloropyrazolanthrone, while 1-nitro-8-(*p*-toluenesulfonamido)-anthraquinone resulted from reaction with *p*-toluenesulfonamide.

EXPERIMENTAL

8,8′-Dibenzamido-1,1′-bianthraquinonyl (V). A mixture of 16.0 g. of 1-benzamido-8-chloroanthraquinone (m.p. 226.5–

(2) A. Lüttringhaus, P. Nawiasky, and A. Krause, Ger. Patent **457,182**; *Frdl.*, **16**, 1371 (1931). U. S. Patent **1,817,995**.

(3) R. Möhlau, *Ber.*, **45**, 2233 (1912).

(4) *B.I.O.S. Final Report No. 987*, p. 128.

(5) W. Bradley and K. W. Geddes, *J. Chem. Soc.*, 1636 (1952).

228.5°), 10 ml. of *o*-dichlorobenzene, and 16.0 g. of copper powder was stirred and heated under reflux to 150–160° and held there for 4 hr. The cooled, dark brown reaction product was transferred to a Soxhlet thimble and extracted with 700 ml. of chlorobenzene for 16 hr. Upon cooling, the chlorobenzene solution deposited 10.10 g. of V (70% yield), m.p. 345–349°. Two recrystallizations from chlorobenzene gave bright yellow plates, m.p. 347–349°.

Anal. Calcd. for $C_{42}H_{24}N_2O_6$: C, 77.45; H, 3.71; N, 4.30; O, 14.72. Found: C, 76.70; H, 3.61; N, 4.25; O, 14.60.

8,8'-Diamino-1,1'-bianthraquinonyl (VI) was obtained from the dibenzamido compound (V) by warming it with concentrated sulfuric acid at 100°. The crude product was crystallized twice from chlorobenzene, giving an 84% yield of shiny red plates, m.p. >350°.

Anal. Calcd. for $C_{28}H_{16}N_2O_4$: C, 75.66; H, 3.63; N, 6.30; O, 14.40. Found: C, 74.80; H, 3.60; N, 6.42; O, 13.90.

10,10'-Dipyrazolanthronyl (VII). A solution of 4.66 g. of the diamine (VI) in 50 ml. of concentrated sulfuric acid was converted into the tetrazo derivative by treatment with 1.70 g. of sodium nitrite. The addition of approximately 40 g. of ice caused the diazonium sulfate to precipitate, and this was filtered off and added to a solution of 11.6 g. of sodium bisulfite, 12 g. of ice, 14 ml. of 28% sodium hydroxide, and 14 ml. of water. The resulting suspension was heated to 80° and held there 45 min., during which time a further 18 ml. of 28% sodium hydroxide and 5.0 g. of sodium bisulfite were added. The initial yellow color of the solution changed to red. Then 20 g. of sodium chloride was added and the solution was cooled. The red precipitate was filtered, pressed dry, and added to 75 ml. of 99.5% sulfuric acid at 40–50°. The temperature of the solution was then raised slowly to 90–98°, where it was held for 1.5 hr. Pouring the solution onto ice gave a yellow precipitate, which after filtration, washing, and drying weighed 3.90 g. (85% yield). A sample recrystallized twice from nitrobenzene melted above 350° and had λ_{max} 268 and 300 mμ (ϵ 20,500 and 24,200).

Anal. Calcd. for $C_{28}H_{14}N_4O_2$: C, 76.70; H, 3.22; N, 12.78. Found: C, 76.20; H, 3.50; N, 12.30.

The *dibenzoyl derivative* (VIII), obtained from VII by treatment with benzoyl chloride in pyridine, crystallized from chlorobenzene in pale yellow plates, m.p. >350°.

Anal. Calcd. for $C_{42}H_{26}N_4O_4 \cdot {}^1/_4C_6H_5Cl$: C, 77.00; H, 4.02; Cl, 1.31; N, 8.28; O, 9.42. Found: C, 77.30; H, 3.49; Cl, 1.62; N, 8.42; O, 9.50.

10-Chloropyrazolanthrone. The reaction of 1-chloro-8-nitroanthraquinone (m.p. 263°) with hydrazine hydrate in pyridine yielded a purple solid which was triturated with 10% sodium hydroxide solution and filtered. Acidification of the basic filtrate gave a light yellow solid, which was crystallized from *o*-dichlorobenzene, giving a 71% yield of the known 10-chloropyrazolanthrone, m.p. 346–347° (lit. 346–347°[5]; >360°[3]), identified by comparison of melting point and infrared spectrum with those of an authentic sample.

1-Amino-8-nitroanthraquinone. 1-Chloro-8-nitroanthraquinone was treated with *p*-toluenesulfonamide, sodium acetate, and cuprous chloride in boiling amyl alcohol, giving a 95% yield of crude 1-toluenesulfonamido-8-nitroanthraquinone. A sample after crystallization from acetic acid melted at 255.0–256.5°. This tosyl derivative was hydrolyzed in 81% yield to the amine by warming it in concentrated sulfuric acid for a few minutes, and pouring the resulting solution into water. Crystallization from *o*-dichlorobenzene gave red needles, m.p. 298–299° (dec.) (lit. 294°[6] and 283–284°[7]).

(6) F. Ullmann, *Enzyklopädie der technischen Chemie* Urban & Schwarzenberg, Berlin, 2er. Aufl., 1928, Bd. I, p. 493.

(7) E. Hefti, *Helv. Chim. Acta*, **14**, 1404 (1931).

Acknowledgment. The authors are indebted to Mr. O. E. Sundberg and his associates for the microanalyses, to Mrs. C. M. Jorgensen for the infrared spectra, and to Mr. F. C. Dexter for the ultraviolet spectra.

RESEARCH DEPARTMENT
ORGANIC CHEMICALS DIVISION
AMERICAN CYANAMID CO.
BOUND BROOK, N. J.

N-Substituted Imides. II. Potassium Naphthalimide as a Reagent for the Identification of Alkyl Halides[1]

SISTER MARY AMBROSE DEVEREUX, S.N.J.M.,[2,3] AND HUGH B. DONAHOE

Received August 17, 1959

Many reagents have been suggested for the identification of alkyl halides.[4] Recent studies have included *N*-substituted phthalimides[5] and saccharins.[6] Continuing work in this laboratory concerned with *N*-substituted imides possessing physiological activity suggested that potassium naphthalimide might be a satisfactory reagent for this purpose.

The derivatives were prepared by condensing potassium naphthalimide and the appropriate alkyl halide using dimethylformamide as solvent. The reaction went smoothly for primary and secondary chlorides, bromides, and iodides but yields were low with the secondary halides. Tertiary halides did not react.

The crude products were recrystallized from various alcohols or alcohol-water mixtures. In each case a white crystalline solid with a sharp melting point was obtained. Attempts to determine saponification equivalents were unsuccessful as the imide linkage resisted all attempts at hydrolysis.

Although the melting points of the products (Table I) were close together in the higher members of the series, all were solids and could be used as derivatives. Only *N*-methyl- and *N*-ethyl naphthalimide have been previously reported.[7]

(1) Paper I, J. D. Commerford and H. B. Donahoe, *J. Org. Chem.*, **21**, 583 (1956).

(2) Taken from a portion of the Ph.D. Dissertation of Sister Mary Ambrose Devereux, S.N.J.M. (1957).

(3) Present address: College of the Holy Names, Oakland, California.

(4) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, New York, N. Y., 1956, p. 242.

(5) J. H. Billman and R. V. Cash, *J. Am. Chem. Soc.*, **76**, 1944 (1954).

(6) E. E. Reid, L. M. Rice, and C. H. Grogan, *J. Am. Chem. Soc.*, **77**, 5628 (1955).

(7) G. F. Jaubert, *Ber.*, **28**, 360 (1895).

TABLE I[a]

N-ALKYLNAPHTHALIMIDES

N-Alkyl Substituent	Yield,[b] %	M.P.	Solvent[c]	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	92	206.5[d]	A	$C_{13}H_9NO_2$		
Ethyl	88	154[e]	A	$C_{14}H_{11}NO_2$		
Propyl	90	158–159	B	$C_{15}H_{13}NO_2$	5.86	6.14
Isopropyl	12	163–164	C	$C_{15}H_{13}NO_2$	5.86	5.63
Butyl	95	96.5–97	B	$C_{16}H_{15}NO_2$	5.53	5.27
sec-Butyl	4	111–112	C	$C_{16}H_{15}NO_2$	5.53	5.43
Amyl	55	86	C	$C_{17}H_{17}NO_2$	5.24	5.10
Isoamyl	57	104–105	C	$C_{17}H_{17}NO_2$	5.24	5.11
1-Methylbutyl	4	69	D	$C_{17}H_{17}NO_2$	5.24	5.50
Hexyl	75	81.5–82.5	B	$C_{18}H_{19}NO_2$	4.97	5.24
Heptyl	90	70.5–71.5	C	$C_{19}H_{21}NO_2$	4.74	4.79
Octyl	43	42.5–43.5	A	$C_{20}H_{23}NO_2$	4.52	4.50
Nonyl	95	56.5–57	C	$C_{21}H_{25}NO_2$	4.33	4.01
Decyl	95	52	A	$C_{22}H_{27}NO_2$	4.19	4.29
Undecyl	80	53–53.5	C	$C_{23}H_{29}NO_2$	3.98	3.99
Dodecyl	95	56–57	E	$C_{24}H_{31}NO_2$	3.83	3.85
Benzyl	82	95–96	B	$C_{19}H_{13}NO_2$	4.87	5.01

[a] All melting points are corrected. [b] Crude yield based on potassium naphthalimide. [c] Recrystallizing solvent: A = 95% ethanol; B = isopropanol; C = isopropanol-water; D = methanol-water; E = methanol. [d] G. F. Jaubert, *Ber.*, **28**, 360 (1895) reported m.p. 205°. [e] G. F. Jaubert, *op. cit.*, reported m.p. 148°.

EXPERIMENTAL

N-Alkylnaphthalimides. In a small flask fitted with an efficient reflux condenser were placed 2.35 g. (0.01 mol.) of potassium naphthalimide,[8] the appropriate alkyl halide (0.01 mol.), and 15 ml. of dimethyl formamide. The mixture was refluxed on a steam bath for 1 hr. and cooled, and the precipitated potassium bromide was removed by filtration. Cold water was added to the filtrate and the precipitated *N*-alkyl naphthalimide was removed and dissolved in ether. Any ether insoluble material was removed and the ether evaporated to give the crude product which was recrystallized.

DEPARTMENT OF CHEMISTRY
ST. LOUIS UNIVERSITY
ST. LOUIS 4, MO.

(8) A. M. Mattocks and O. S. Hutchinson, *J. Am. Chem. Soc.*, **70**, 3474 (1948).

Tetrazole-Azidoazomethine Equilibrium. II. Amino- and Hydroxypyridotetrazoles[1]

J. H. BOYER AND H. W. HYDE

Received October 2, 1959

The predicted absence[2] of tetrazole-azidoazomethine tautomerism for derivatives of pyridotetrazole with certain strong electron donating substituents has been established by examination of 6- and 8-hydroxy- and 8-aminopyridotetrazole. On treatment with sodium azide in the presence of hydrochloric acid in refluxing aqueous ethanol, 2-chloro-3-amino- and 2-chloro-3-hydroxypyridine are transformed into 8-amino- (I) and 8-hydroxypyridotetrazole (II) respectively. A similar reaction with 2-chloro-5-aminopyridine occurs with the unexpected replacement of the amino group with the hydroxyl group. It is assumed that the functional group has not migrated to another position

TABLE I

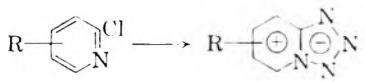
INFRARED ABSORPTION (cm.$^{-1}$) FROM KBr DISKS (% TRANSMITTANCE)

8-Aminopyridotetrazole (I)	8-Hydroxypyridotetrazole (II)	6-Hydroxypyridotetrazole (III)
3401 (35.0)	3059 (18.0)	3448 (51.8)
3300 (32.5)	2994 (18.2)	2564 (27.0)
3195 (34.9)	2793 (25.6)	1923 (51.7)
3096 (39.6)	2660 (24.0)	1786 (55.6)
1639 (30.5)	2475 (40.0)	1656 (48.0)
1570 (39.3)	1894 (74.8)	1570 (49.4)
1497 (36.9)	1835 (79.2)	1553 (40.7)
1414 (42.6)	1764 (78.6)	1515 (28.5)
1381 (43.2)	1631 (34.5)	1431 (23.7)
1361 (45.0)	1585 (6.5)	1350 (29.0)
1318 (48.6)	1502 (18.9)	1311 (23.7)
1232 (56.5)	1429 (15.7)	1259 (37.6)
1220 (37.7)	1393 (30.0)	1211 (24.0)
1156 (40.7)	1321 (15.0)	1147 (37.7)
1107 (40.0)	1239 (28.9)	1106 (23.0)
1076 (36.5)	1206 (21.0)	1095 (25.3)
1067 (42.9)	1159 (14.0)	1028 (41.5)
938 (50.0)	1104 (34.3)	964 (49.0)
841 (39.0)	1067 (45.4)	873 (27.6)
716 (28.0)	1044 (47.2)	815 (19.4)
701 (46.5)	1016 (24.6)	793 (26.5)
693 (47.4)	952 (71.0)	768 (32.4)
	880 (44.5)	696 (46.4)
	849 (68.7)	
	794 (44.0)	
	774 (26.0)	
	744 (21.3)	
	696 (30.0)	

(1) Partial support of this work by National Institutes of Health Grant Nos. H-2295 and CY-2895 and Office of Ordnance Research, U. S. Army, Contract No. DA-01-009-ORD-699 is gratefully acknowledged.

TABLE II

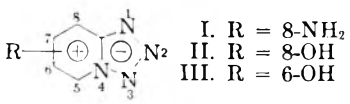
PREPARATION OF PYRIDOTETRAZOLES FROM 2-CHLOROPYRIDINES



Chloropyridine R	Pyridotetrazole R	M.P. (dec.)	Yield, %	Molecular Formula	Analysis: Carbon, % Calcd. Found	Analysis: Nitrogen, % Calcd. Found	Analysis: Nitrogen, % Calcd. Found
3-NH_2	8-NH_2 (I)[a]	180–183	32[b]	$C_5H_5N_4$	44.43 44.34	3.73 3.86	51.86 52.30
3-$N(COCH_3)_2$[c]	8-NHCOCH$_3$	207–210[d]	3[e]	$C_7H_7N_5O$	47.45 47.66	3.99 4.22	39.74 39.23
3-OH[c]	8-OH (II)[a,f]	>220	22	$C_5H_4N_4O$	44.11 44.18	2.95 3.15	41.26 41.40
5-NH_2	6-OH (III)[a]	215–220	19[h]	$C_5H_4N_4O$	44.11 44.39	2.95 3.01	41.26 40.70

[a] Samples in ethanol gave ultraviolet absorption recorded by a Beckman Quartz Spectrophotometer, Model DK. [b] Based on 70% recovery of starting material. [c] Ref. 6. [d] Also obtained for the product from I and acetic anhydride. [e] Based on the transformation of 55% starting material into 2-chloro-3-acetamidopyridine. [f] From 8.5 g. (0.066 mol.) of 2-chloro-3-pyridinol, m.p. 164–165°, II is obtained in 22% yield with 4.4 g. of an unidentified product, m.p. 184–186° (dec.). *Anal.* Found: C, 46.26; H, 3.38; N, 12.34. [g] A. Binz and O. v. Schickh, *Ber.*, **68**, 315 (1935). [h] Based on 50% recovery of starting material.

and that the product is 6-hydroxypyridotetrazole (III).



I. R = 8-NH_2
II. R = 8-OH
III. R = 6-OH

Similar attempts to obtain the other five unknown hydroxy- and aminopyridotetrazoles from corresponding halopyridines have been unsuccessful. Halogen in 2-bromo-4-nitropyridine, 2-chloro-3-acetamidopyridine, 2-bromo-4-aminopyridine and 2-bromo-6-aminopyridine resists displacement by the azido group in acid solutions of hydrogen azide. Chlorine in 2-chloro-3-acetamidopyridine is unreactive to silver azide and in 2-chloro-3-aminopyridine is unreactive to hydrazine.

Infrared absorption (Table I) in the region 1100 to 1000 cm.$^{-1}$ for I (three bands), II (four bands) and III (three bands) in potassium bromide disks may be characteristic of the tetrazole ring;[3] however, absorption in the region 770 to 730 cm.$^{-1}$ in which tetrazole absorption has been found,[3] is less consistent.

Since each of the three compounds is transparent in the region 2160–2120 cm.$^{-1}$ [2] in either potassium bromide disks or *N,N*-dimethylformamide solution it is concluded that tautomeric azide structures are not present in either the solid state or in certain solutions.

Ultraviolet absorption for 8-aminopyridotetrazole in ethanol at 288 mμ (log ε 3.17) and for 8-hydroxypyridotetrazole in ethanol at 270 mμ (log ε 3.70) represents expected bathochromic shifts from absorption at 260 mμ (log ε 3.72) for pyridotetrazole in ethanol. Two bands for 6-hydroxypyridotetrazole in ethanol, one at 292 mμ (log ε 2.49) the other at 260 mμ (log ε 2.50), are assigned to the tetrazole (III) rather than tautomeric 2-azido-5-hydroxypyridine[4] in agreement with its lack of infrared absorption in the region 2160 to 2120 cm.$^{-1}$

EXPERIMENTAL[5]

8-Aminopyridotetrazole. A solution of 1.0 g. (0.009 mol.) of 3-amino-2-chloropyridine m.p. 80–81°,[6] 40 ml. of ethanol, and 10 ml. of water was added to a solution of 1.0 g. (0.016 mol.) of sodium azide, 7 ml. of ethanol, and 15 ml. of water. After addition of 5.0 ml. (0.024 mol.) and 4.8 *N* hydrochloric acid, the solution was refluxed for 96 hr. and evaporated to bring about precipitation of a solid which recrystallized from benzene as colorless needles, m.p. 180–183° (dec.), 0.10 g. (32%, based on recovered 3-amino-2-chloropyridine). Repeated recrystallization raised the melting point to 184–185° (dec.). Neutralization of the original filtrate gave 0.7 g. of crude 3-amino-2-chloropyridine, m.p. 77–79°. Analytical data and other similar preparations are described in Table II.

Acknowledgment We are indebted to Mr. R. T. O'Connor, Southern Regional Research Laboratory for infrared absorption data.

CHEMISTRY DEPARTMENT
TULANE UNIVERSITY
NEW ORLEANS 18, LA.

(2) J. H. Boyer and E. J. Miller, Jr., *J. Am. Chem. Soc.*, **81**, 4671 (1959).

(3) E. Lieber, D. Levering, and L. Patterson, *Anal. Chem.*, **23**, 1594 (1951) report that tetrazoles absorb between 1100 and 1000 cm.$^{-1}$ where up to three bands may occur and in the 763 to 758 cm.$^{-1}$ and 741 to 735 cm.$^{-1}$ regions.

(4) Absorption at 285 mμ (log ε 2.1) has been reported for phenyl azide in ethanol (yu. N. Sheĭnker and M. V. Lomonosar, *Doklady Akad. Nauk S.S.S.R.*, **77**, 1043 (1951). *Chem. Abstr.*, **45**, 6927 (1951).

(5) Semimicro analyses by Alfred Bernhardt, Max Planck Institut Mülheim (Ruhr), Germany. Melting points are uncorrected.

(6) O. v. Schickh, A. Binz, and A. Schulz, *Ber.*, **69**, 2593 (1936).

The Reaction of Two Oxazolo(4′,5′-3,4)-coumarins with Alkali

CHARLES H. STAMMER

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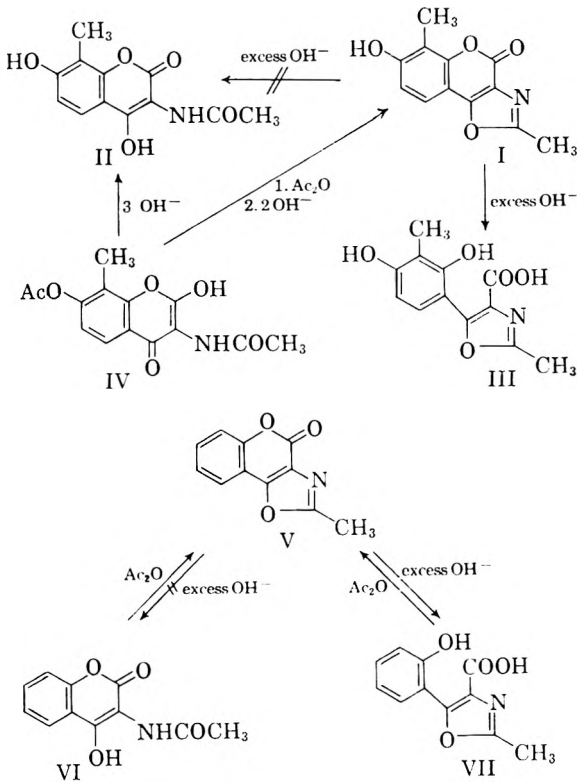
In connection with structure studies on the antibiotic novobiocin,[1,2] we examined the reaction of the substituted oxazole I with alkali. Because of



Arndt's[3] report that the unsubstituted oxazole V was converted to the coumarin VI by alkali, we expected I to be converted into the known coumarin[4] II. However, II was not the product obtained. Present evidence discussed in this paper indicates that the acid III was the product.

We prepared the oxazole I by the conversion of IV[2] into *O*-acetyl I[1] with boiling acetic anhydride. Deacetylation of this material with two equivalents of alkali gave the phenol I in 62% yield over-all. When I was treated with excess alcoholic sodium hydroxide at room temperature, the product was more acidic (pK'_a 4.2) than II (pK'_a 5.3) and its ultraviolet and infrared spectra were different from those of II. In view of the considerable stability of the oxazole ring to alcoholic alkali,[5] it seemed likely that the *lactone* ring of I had been opened giving the carboxylic acid III. The physical properties of III were consistent with this formulation. Sublimation of V at 200° did not reform the lactone ring, but treatment with boiling acetic anhydride did cause lactonization to *O*-acetyl I.

In view of these results, we examined the reaction of the unsubstituted oxazole V with alkali. The coumarin VI was prepared by the procedure of Huebner and Link[6] and was converted into the oxazole V with boiling acetic anhydride. When V was allowed to react with excess alcoholic sodium hydroxide at room temperature, the product was *not* VI but an isomeric compound more acidic (pK'_a 4.4) than VI (pK'_a 5.0). The ultraviolet and infrared spectra of the new acid, formulated as VII, were different from those of VI and were consistent with structure VII. As in the case of the acid III, VII could be sublimed at 150° unchanged. However, lactonization occurred readily in boiling acetic anhydride to give VII.

The results outlined above show that the oxazole rings of III and VII were not opened by alkali forming an acetamido 4-hydroxycoumarin. The available data indicate that the lactone rings were cleaved giving oxazole carboxylic acids such as III and VII.

EXPERIMENTAL

7-Acetoxy-8-methyl-2-methyloxazolo (4′,5′-3,4)coumarin (O-acetyl I). A mixture of 1.0 g. of 3-acetamido-7-acetoxy-4-hydroxy-8-methylcoumarin (IV) and 20 ml. of acetic anhydride was refluxed for 2 hr. during which time the solid dissolved. The solution was allowed to stand at room temperature overnight. The crystalline precipitate, 0.64 g. (66%), m.p. 211–212°,[7] was collected on a filter and dried. This product, 7-acetoxy-8-methyl-2-methyloxazolo(4′,5′-3,4)coumarin, was the same as that obtained by refluxing a solution of novobiocic acid in acetic anhydride.[1] Obtained by the latter method and recrystallized from ethyl acetate, the compound melted at 208–209° and showed $\lambda_{max}^{CH_3OH}$ 321 mμ (ε 9330), shoulder 314 (ε 10,700), 307 (ε 12,200), 284 (ε 12,800), shoulder 275 (ε 10,800), 212 (ε 24,000).

Anal. Calcd. for $C_{14}H_{11}NO_5$: C, 61.64; H, 4.06; N, 5.13. Found: C, 61.34; H, 3.84; N, 5.37.

7-Hydroxy-8-methyl-2-methyloxazolo(4′,5′-3,4)coumarin (I). A slurry of 546 mg. (2 mmoles) of 7-acetoxy-8-methyl-2-methyloxazolo(4′,5′-3,4)coumarin in 5 ml. of ethanol was cooled in an ice bath and four 1-ml. portions of 1*N* sodium hydroxide were added at 5-min. intervals. The solid did not dissolve until the solution was diluted to 20 ml. with water. The final *p*H of the solution was 10.5–11.0. The solution was filtered and the filtrate was acidified to *p*H 4 with 2.5*N* hydrochloric acid. The white precipitate, 437 mg. (95%), m.p. 310–317° (dec.), was collected on a filter and dried.

(1) J. W. Hinman, E. L. Caron, and H. Hoeksema, *J. Am. Chem. Soc.*, **79**, 3789 (1957).

(2) C. H. Stammer, E. Walton, A. N. Wilson, R. W. Walker, N. R. Trenner, F. W. Holly, and K. Folkers, *J. Am. Chem. Soc.*, **80**, 137 (1958).

(3) F. Arndt, L. Louve, R. Un, and E. Ayca, *Ber.*, 319 (1951).

(4) Compound IV is written in the chromone rather than the coumarin form for reasons discussed in ref. 2.

(5) R. H. Wiley [*Chem. Revs.*, **37**, 401 (1945)] states that 2-methyl-5-phenyloxazole, analogous to I, is stable to alcoholic potassium hydroxide at 200°.

(6) C. F. Huebner and K. P. Link, *J. Am. Chem. Soc.*, **67**, 99 (1945).

(7) All melting points were taken on a Kofler Micro Hot Stage.

The product was recrystallized from 1:5 water–dimethylformamide giving 341 mg., m.p. 295–303° (dec.), of 7-hydroxy-8-methyl-2-methyloxazolo(4′,5′-3,4)coumarin (I). An analytical sample was prepared by recrystallization of a small sample from 1:3 water–dimethylformamide and 1:1 water–dimethylformamide successively.

Anal. Calcd. for $C_{21}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.22; H, 3.89; N, 6.51.

Other physical properties of I were: $\lambda_{max}^{CH_3OH}$ 316 mμ (ε, 18,500), shoulder 295 (ε, 9450), shoulder 249 (ε, 10,150), 2440 (ε, 10,500); $pK_a'^{8}$ 9.6; λ_{max}^{Nujol} 5.72 (C=O), 6.03.

(8) All pK_a' values are $pH\ ^1/_2$ values obtained by potentiometric titration of the compounds in 70% acetone-water mixtures.

4-Carboxy-5-(2,4-dihydroxy-3-methylphenyl)-2-methyloxazole (III). To a slurry of 231 mg. (1 mmole) of 7-hydroxy-8-methyl-2-methyloxazolo(4′,5′-3,4)coumarin (I) in 5 ml. of ethanol was added 10 ml. of 0.6*N* sodium hydroxide. The yellow-green solution was allowed to stand overnight at room temperature and then evaporated *in vacuo* to about 3 ml. The solution was diluted to about 8 ml. with water and acidified with 2.5*N* hydrochloric acid. The precipitate weighed 273 mg. When this material was heated on the Micro Hot Stage, it changed crystal form at 115–125°, sublimed at 180°, and decomposed at 290–300°. Two crystallizations of this product from water gave 88 mg. of 4-carboxy-5-(2,4-dihydroxy-3-methylphenyl)-2-methyloxazole, transition 228–233°, 290–300° (dec.).

Anal. Calcd. for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.59; H, 4.40; N, 6.17.

Other physical properties were $\lambda_{max}^{CH_3OH}$ 300 mμ (ε, 13,200), 222 (ε, 20,400); pK_a' 4.2; λ_{max}^{Nujol} 5.89 (C=O), 6.17.

For comparison with II, we here record our physical data on 3-acetamido-4,7-dihydroxy-8-methylcoumarin (II): m.p. 280–281°: λ_{max}^{MeOH} 316 mμ (ε, 5270), 292 (ε, 2660), shoulder 249 (ε, 3160), 245 (ε, 3210); pK_a' 5.3; λ_{max}^{Nujol} 6.09, 6.18.

When III was sublimed at 200–220° and *ca.* 0.1 mm., the crystalline sublimate melted at 315–325° (dec.) with a transition 220–230°. Apparently no lactonization to I had occurred. Refluxing acetic anhydride, however, converted III into *O*-acetyl I in 40 min. The crude product obtained melted at 200–204° and its mixture with authentic *O*-acetyl I melted at 204–209°.

4-Carboxy-5-(2-hydroxyphenyl)-2-methyloxazole (VII). A slurry of 380 mg. (2 mmoles) of the 2-methyloxazolo(4′,5′-3,4)coumarin[6] V (m.p. 195–196°) in 10 ml. of ethanol was treated with 20 ml. of 0.6*N* sodium hydroxide. A yellow-green color formed in the solution and the oxazole slowly dissolved. After 16 hr. at room temperature, the solution was evaporated *in vacuo* to a volume of about 2 ml. and acidified with concentrated hydrochloric acid. The crude product, 380 mg. (92%), melted at 165–170°. After one recrystallization from ethyl acetate, the 4-carboxy-5-(2-hydroxyphenyl)-2-methyloxazole (VII), 175 mg., melted at 170–173°. After one further recrystallization from ethyl acetate, the product had m.p. 171–174°; $\lambda_{max}^{CH_3OH}$ 295 mμ (ε, 5400), 262 (ε, 8240), pK_a' 4.4; λ_{max}^{Nujol} 6.01, 6.18.

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.44; H, 4.38; N, 6.47.

We obtained the following physical data on 3-acetamido-4-hydroxycoumarin (VI) in order to compare it with the acid VII obtained above: m.p. 229–230°, $\lambda_{max}^{CH_3OH}$ 316 mμ (ε, 11,700), shoulder 295 (ε, 9450), 282 (ε, 8320); pK_a' 5.0; λ_{max}^{Nujol} 5.93 (C=O), 6.13.

When the acid VII was sublimed at 150–160° and *ca.* 0.05 mm., the sublimate melted at 175–178°. Apparently no lactonization to V, m.p. 195–196°, had occurred. However, when VII was treated with refluxing acetic anhydride for 30 min., a 64% yield of oxazole V crystallized from the solution.

MERCK SHARP & DOHME RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
RAHWAY, N. J.

The Isomerization of Some Aziridine Derivatives. III. A New Synthesis of 2-Imidazolines

HAROLD W. HEINE AND HOWARD S. BENDER

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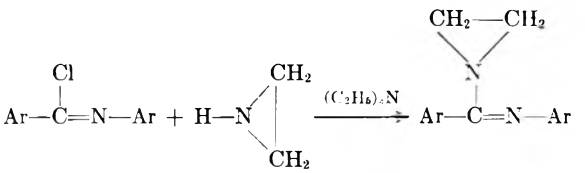
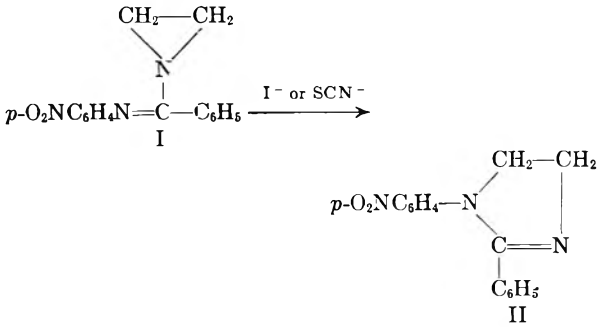
Previous work in this laboratory has been concerned with the isomerization of 1-aroylaziridines.[1,2] For example, 1-*p*-nitrobenzoyl-2,2-dimethylaziridine has been selectively isomerized to 2-*p*-nitrophenyl-4,4-dimethyl-2-oxazoline, 2-*p*-nitrophenyl-5,5-dimethyl-2-oxazoline, or *N*-(β-methallyl)-*p*-nitrobenzamide by sodium iodide in acetone, concentrated sulfuric acid, or refluxing heptane respectively. We now wish to report the synthesis and isomerization of a new class of aziridine derivatives, the 1-(*N*-arylbenzimidoyl)aziridines.

The 1-(*N*-*p*-nitrophenylbenzimidoyl)aziridine (I) and the 1-(*N*-phenyl-*p*-nitrobenzimidoyl)aziridine used in the present study were prepared by reaction of the corresponding *N*-arylbenzimidoyl chloride with aziridine in benzene containing triethylamine:



The *N*-*p*-nitrophenylbenzimidoyl chloride reacted much faster with aziridine than did *N*-phenyl-*p*-nitrobenzimidoyl chloride. Evidently *N*-arylbenzimidoyl chlorides are much less susceptible to nucleophilic attack when a strong electron-withdrawing group is attached to the benzimidoyl moiety than when it is attached to the *N*-aryl moiety.

The 1-(*N*-arylbenzimidoyl)aziridines in acetone solutions containing iodide ion or thiocyanate ion smoothly undergo isomerization to 2-imidazolines. Thus I was converted in over 90% yield to 1-*p*-nitrophenyl-2-phenyl-2-imidazoline (II):



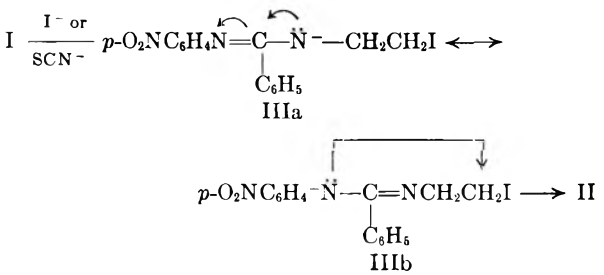
The structure of II was confirmed by comparison of infrared spectra and by mixed melting point

(1) H. W. Heine and Z. Proctor, *J. Org. Chem.*, **23**, 1554 (1958).

(2) H. W. Heine, M. E. Fetter and E. M. Nicholson, *J. Am. Chem. Soc.*, **81**, 2202 (1959).

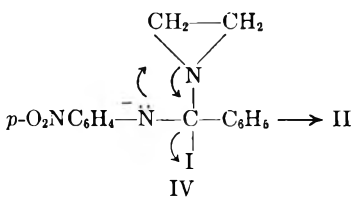
with an authentic sample of II prepared by the method of Partridge and Turner.[3] In an analogous experiment 1-(*N*-phenyl-*p*-nitrobenzimidoyl)aziridine was converted into 1-phenyl-2-nitrophenyl-2-imidazoline.

The 2-imidazoline is probably formed by a two step process involving first a nucleophilic attack of iodide or thiocyanate ion on the methylene group of the aziridine ring to form an amidino ion IIIa as an intermediate. This step is quite similar to the opening of the ethylene oxide ring by iodide ion[4,5] or thiocyanate ion[6] to form the corresponding β-substituted alkoxide ions. The second step of the process is the displacement of the iodide ion or thiocyanate ion by the negatively charged nitrogen of the resonance hybrid IIIb:



This mechanism requires the displacement of thiocyanate ion from carbon which, while unusual, is not entirely without analogy.[7,8,9]

Alternatively, the isomerization may also take place by the addition of the iodide or thiocyanate ion to the benzimidoyl carbon to give the intermediate IV which subsequently cyclizes to the imidazoline:



2-Propanol can also be used as a solvent for carrying out the isomerization. Thus I rearranged to II in over 94% yield in 2-propanol containing iodide ion. Under these same experimental conditions, 1-*p*-nitrobenzoylaziridine isomerized to 2-*p*-nitrophenyl-2-oxazoline in high yield. The latter result was contrasted with methanolic solutions containing iodide ion whereupon 1-*p*-nitrobenzoylaziridine formed methyl *p*-nitrobenzoate in 95% yield.[2]

Acid catalyzed methanolysis of 1-(*N*-*p*-nitrophenylbenzimidoyl)aziridine and 1-*p*-nitrobenzoylaziridine gave, as expected, *N*-*p*-nitrophenyl-*N'*-2-methoxyethylbenzamidine and *N*-2-methoxyethyl-*p*-nitrobenzamide respectively. The structures of these two products were confirmed by independent syntheses.

EXPERIMENTAL

1-(N-p-nitrophenylbenzimidoyl)aziridine. To a 300 ml. flask equipped with a stirrer, drying tube and dropping funnel was added 1.1 g. of aziridine, 5.05 g. triethylamine and 70 ml. of dry benzene. Over the course of 1 hr. a solution of 6.52 g. of *N*-*p*-nitrophenylbenzimidoyl chloride[10] (m.p. 113–114.5°) in 100 ml. of benzene was added. The mixture was stirred at room temperature for 12 hr., the triethylamine hydrochloride filtered, and the solvent evaporated. A crude yield of 6.6 g. melting at 116–120° was obtained. The substituted aziridine was recrystallized in small portions from 2-propanol to give material melting at 132–134°.

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: N, 15.71. Found: N, 15.80.

1-(N-phenyl-p-nitrobenzimidoyl)aziridine. To a mixture of 2.2 g. of aziridine, 10.1 g. of triethylamine, and 70 ml. of benzene was added slowly (1 hr.) a solution of 13.1 g. of *N*-phenyl-*p*-nitrobenzimidoyl chloride[11] in 100 ml. of benzene. The mixture was heated to 40° and stirred for 43 hr. The triethylamine hydrochloride was filtered and the solvent evaporated to give 13.1 g. of crude product melting at 81–84°. Recrystallization twice and in small portions from cyclohexane gave product melting 94–96°.

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: N, 15.71. Found: N, 15.75.

Isomerization of 1-(N-p-nitrophenylbenzimidoyl)aziridine (I). One hundred milligrams of I was added to 50 ml. of acetone containing 274 mg. of sodium iodide. The mixture was refluxed 3.5 hr., the solvent evaporated, and the residue washed with water and filtered. The crude 1-*p*-nitrophenyl-2-phenyl-2-imidazoline weighed 98 mg., turned slightly amber on heating, and melted at 172–175°. A mixed melting point with an authentic sample of the 2-imidazoline[3] showed no depression of melting point. An infrared spectrum of the crude product was identical with the spectrum of the authentic sample. Other experiments using smaller quantities of sodium iodide (*e.g.* 20 mg.) and the same reaction time gave only slight conversion. However, a 93% yield of crude imidazoline was obtained using 100 mg. I, 50 ml. acetone, and 20 mg. sodium iodide with a reflux period of 76 hr.

Isomerization of I by potassium thiocyanate. To a solution of 50 ml. of acetone and 1 g. of potassium thiocyanate was added 100 mg. of I. The mixture was refluxed for 47 hr., the solvent evaporated, and the residue washed with water and filtered. The crude 1-*p*-nitrophenyl-2-phenyl-2-imidazoline weighed 94 mg. and melted at 169–174°.

Rearrangement of 1-(N-phenyl-p-nitrobenzimidoyl)aziridine (V). One hundred milligrams of V was added to 50 ml. of acetone containing 250 mg. of sodium iodide. The reaction mixture was refluxed 3 hr. and worked up as described above. A crude yield of 96 mg. of 1-phenyl-2-*p*-nitrophenyl-2-imidazoline melting at 102–104° was obtained. Mixed melting point determinations of the isomerized product with a sample of authentic 1-phenyl-2-*p*-nitrophenyl-2-imidazoline melted 102–108°. Infrared spectra of the two samples were identical.

1-Phenyl-2-p-nitrophenyl-2-imidazoline. To a 200 ml. round-bottom flask equipped with a condenser and drying

(3) M. W. Partridge and H. A. Turner, *J. Chem. Soc.*, 1308 (1949).

(4) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Company, Inc., New York, 1940, pp. 301–302.

(5) J. N. Bronsted, M. Kilpatrick, and M. Kilpatrick, *J. Am. Chem. Soc.*, **51**, 428 (1929).

(6) P. L. Nichols, Jr., and J. D. Ingham, *J. Am. Chem. Soc.*, **77**, 6547 (1955).

(7) L. Hagelberg, *Ber.*, **23**, 1083 (1890).

(8) H. P. Kaufmann, E. Gindsberg, W. Rottig, and R. Salchow, *Ber.*, **70**, 2519 (1937).

(9) J. R. Siegel and D. H. Rosenblatt, *J. Am. Chem. Soc.*, **80**, 1753 (1958).

(10) O. Mumm, *Ber.*, **43**, 892 (1910).

(11) R. C. Shah and J. S. Chanbal, *J. Chem. Soc.*, 651 (1932).

tube were added 5.75 g. of phosphorus pentachloride and 6.85 g. of *N*-2-bromoethyl-*p*-nitrobenzamide.[12] The mixture was heated for 120 hr. To this mixture was added 2.33 g. of aniline dissolved in 70 ml. of benzene. After an additional 24 hr. of refluxing, the phosphorus oxychloride which was formed and benzene were evaporated by means of a water aspirator and water bath. The resulting brown oil was poured into 250 ml. of hot water, the solution neutralized with ammonium hydroxide, and the organic material extracted with chloroform. The chloroform extracts were filtered through a norit pad and evaporated. The yellow crystalline residue was recrystallized twice from 50% aqueous ethanol and melted at 109–111°. A crude yield of 3.1 g. was obtained.

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: N, 15.71. Found 15.71.

Acid methanolysis of I. To a mixture of 50 ml. of methanol and 36 mg. of concentrated sulfuric acid was added 100 mg. of I. The mixture was refluxed 3 hr., neutralized with several drops of 30% sodium hydroxide, the solvent evaporated, and the residue washed with water and filtered. A yield of 98.9 mg. of crude *N p*-nitrophenyl-N'-2-methoxyethylbenzamidine melting at 87–89° was obtained. An infrared spectrum of the crude product was identical with spectrum of an authentic sample of the amidine. Recrystallization of the crude product from cyclohexane gave crystals melting 95–97°.

N-p-nitrophenyl-N'-2-methoxyethylbenzamidine. To 3.25 g. of *N*-*p*-nitrophenylbenzimidoyl chloride was added 1.60 g. of 60% aqueous 2-methoxyethylamine. After the reaction subsided, the mixture was allowed to cool to room temperature and 40 ml. of water was added. The mixture after standing overnight gave 3.4 g. of material melting at 80–85°. Recrystallization from cyclohexane gave crystals melting at 95–97°.

Anal. Calcd. for $C_{16}H_{17}N_3O_3$: N, 14.04. Found 14.51.

Acid methanolysis of 1-p-nitrobenzoylaziridine. To a solution of 14 mg. of 98% sulfuric acid in 60 ml. of methanol was added 384 mg. of 1-*p*-nitrobenzoylaziridine. The reaction mixture was allowed to stand 13 hr. at room temperature, the solvent was then evaporated, and the residue was washed and filtered. A yield of 422 mg. of *N*-2-methoxyethyl-*p*-nitrobenzamide melting at 109–113° and having an infrared identical with an authentic sample[13] was obtained.

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DEPARTMENT OF CHEMISTRY
BUCKNELL UNIVERSITY
LEWISBURG, PENNSYLVANIA

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(13) H. W. Heine, *J. Am. Chem. Soc.*, **79**, 907 (1957).

"1-Phenylazetidine" and an Unusual Hofmann-Martius Reaction

A. FISCHER, R. D. TOPSOM, AND J. VAUGHAN

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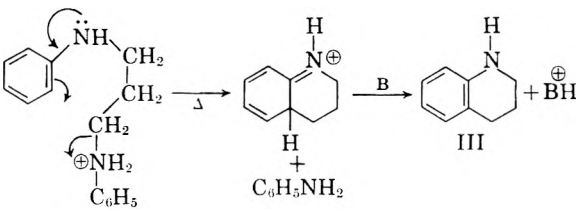
In 1899 Scholtz[1] claimed to have prepared 1-phenylazetidine [*N*-phenyltrimethyleneimine (I)] by the reaction of 1,3-dibromopropane with aniline. Not only is this the sole recorded preparation of an azetidine from the reaction of a dihalide with an amine,[2] but on no other occasion has the isolation of any *N*-aryl derivative of this ring been claimed. Scholtz obtained the compound, in small yield, as a low-boiling fraction when distilling his main reaction product, which was *N,N'*-diphenyltrimethylenediamine (II). Hanssen[3] had previously prepared the diamine (II) by this method but failed to distill it owing to extensive decomposition. Veer[4] later carried out the same preparation. He differed from Hanssen in distilling the diamine (II) quite readily, and differed from Scholtz in obtaining only aniline, and no trace of the cyclic compound (I), in the very small first runnings of his distillation.

In repeating Scholtz's preparation, we found that during the distillation of diamine (II), the "low-boiling" fraction could be separated into aniline, and a material answering to Scholtz's description of the azetidine (I). This description, however, also fits the secondary amine 1,2,3,4-tetrahydroquinoline (III), with which the compound was readily identified.

When the diamine (II) was carefully freed from acid (following Veer's[4] procedure of repeated water and ether extractions) it could, indeed, be distilled unchanged, but the monohydrobromide of II was found to break down smoothly at 230–250° into aniline and the reduced quinoline (III). With smaller amounts of hydrobromic acid present, decomposition of II was less rapid and although breakdown was still perceptible with "catalytic" quantities, it was found convenient to use 0.1 mol. hydrobromic acid. Under these conditions the yield of purified III, over several runs, was 50% of theory (on scheme below), with an apparently quantitative yield of aniline.

It seems likely that formation of the compound (III) is the result of an interesting Hofmann-Martius reaction:



On this scheme, the results obtained by Hanssen, Scholtz, and Veer are understandable, because incomplete removal of acid from the diamine (II) should result, at distillation temperature, in reaction of the type postulated. It is of interest that Scholtz prepared the *o*-tolyl analog of II. His predistillation treatment of this compound resembled that of Veer and consequently no breakdown products of distillation were reported. We find that addition of 0.1 mol. hydrobromic acid to this

(1) M. Scholtz, *Ber.*, **32**, 2252 (1899).

(2) S. A. Ballard and D. S. Melstrom, in *Heterocyclic Compounds* (ed. Elderfield), John Wiley & Sons, Inc., New York, 1950, Vol. 1, p. 87.

(3) A. Hanssen, *Ber.*, **20**, 781 (1887).

(4) W. L. C. Veer, *Rec. Trav. Chim.*, **57**, 989 (1938).

diamine leads to smooth decomposition at 240° to give 8-methyl-1,2,3,4-tetrahydroquinoline in 50–60% yield. The recovery of *o*-toluidine appears to be somewhat above that expected on the simple reaction scheme.

It may be added that in the initial preparation of II by Hanssen's route,[3] yield of the diamine could be increased to 85% by use of excess aniline, recovery of which was satisfactory.

EXPERIMENTAL

N,N'-diphenyltrimethylenediamine (II). On our scale of preparation, high yields proved possible when the ratio of aniline:1,3-dibromopropane was *ca.* 10:1. Aniline (128.0 g.) and dibromopropane (25.0 g.) were heated together on a steam bath. After 30 min., solid aniline hydrobromide suddenly appeared in mass. The material was diluted with 300 ml. diethyl ether and shaken with ammonia. The ethereal extract was then washed with water, dried over anhydrous potassium carbonate, and ether removed by distillation at normal pressure. Distillation at 20 mm. allowed recovery of aniline (102.2 g. = 97% of initial excess) and further fractionation of the residue at 0.1 mm. gave 23.8 g. of the required compound (II) (85% theory, b.p. 189–192° at 1 mm.; n_D^{14} 1.6257).

Rearrangement of II. It was found convenient to work with a molar ratio of hydrobromic acid:*N,N'*-diphenyltrimethylenediamine of 1:10. To 14.3 g. of II was added 0.5 ml. hydrobromic acid (S.G. 1.7) and the mixture was heated (oil bath) in a simple Claissen distillation apparatus under 12 mm. pressure. Between 230° and 240° (oil bath temperature), nearly all the reaction material decomposed to give 13.1 g. of distillate. This distillate was carefully fractionated under reduced pressure to yield 6 g. aniline and 4.3 g. of III (51% of theory; b.p. 122–124°/15 mm., 130°/21 mm.; hydrochloride m. 180–181°; benzoylated under Schotten-Baumann conditions to give benzoyl derivative m.p. 76°): lit. b.p. of 1,2,3,4-tetrahydroquinoline, b.p. 245–250° at 755 mm.: hydrochloride, m.p. 181°; benzoyl derivative, m.p. 76°.

Rearrangement of N,N'-di-o-tolyltrimethylenediamine. To 16.3 g. of this diamine (prepared, in similar manner to II, in 78% yield) was added 0.5 ml. hydrobromic acid in 25 ml. ether. After shaking well, the ether was removed, and the residual liquid decomposed as for compound II. Rearrangement took place smoothly at 240–250° (oil bath), giving 14.6 g. distillate. Fractionation of this distillate finally gave 7.75 g. *o*-toluidine and 4.85 g. of 8-methyl-1,2,3,4-tetrahydroquinoline (53% yield). The reduced quinoline (n_D^{15} 1.5870) was fully characterized by a benzoyl derivative m.p. 108.5°, hydrochloride m.p. 215°, and by dehydrogenation (standard procedure using sulphur) to 8-methylquinoline (n_D^{23} 1.6148, picrate m.p. 205° unchanged by addition of authentic sample).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CANTERBURY
CHRISTCHURCH, N. Z.

The Rate of Hydrolysis of 1,2-Naphthoquinone-1-imine

CHARLES C. IRVING

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Although the ease of hydrolysis of quinone imines to quinones has been recognized qualitatively,[1,2] no quantitative data are available concerning the rate of this reaction, as quinone imines generally cannot be obtained sufficiently pure for rate measurements. However, the availability of the pure *o*-quinone imine, 1,2-naphthoquinone-1-imine,[3] has permitted a determination of its rate of hydrolysis in aqueous solvents.

1,2-Naphthoquinone-1-imine was stable for several hours in 95% ethanol but was rapidly hydrolyzed to the *o*-quinone in alcohol–water mixtures which contained less than 75% ethanol. The first order rate constants for the hydrolysis of 1,2-naphthoquinone-1-imine are listed in Table I. After 1,2-naphthoquinone-1-imine had been completely hydrolyzed (thirty minutes in 10% ethanol), only 1,2-naphthoquinone could be detected in the solution by ultraviolet spectrophotometry.

TABLE I

RATE CONSTANTS FOR THE HYDROLYSIS OF 1,2-NAPHTHOQUINONE-1-IMINE IN AQUEOUS ETHANOL AT 25°

Ethanol concentration (% by volume)	$10^4 k_{obs}$ (sec.$^{-1}$)
95	0.57
75	1.3
55	4.8
40	8.7
25	14.9
10	34.8

In contrast to the moderate stability of 1,2-naphthoquinone-1-imine in 95% ethanol, 1,2-naphthoquinone-1-benzimide was unstable in this solvent. The instability of 1,2-naphthoquinone-1-benzimide in 95% ethanol was not due to its hydrolysis but to the formation of an adduct, *N*-(x-ethoxy-2-hydroxy-1-naphthyl)benzamide, m.p. 160–161°. The isolation of this adduct has been reported previously.[4]

Nevertheless, *N*-acylated derivatives of 1,2-naphthoquinone-1-imine were more resistant towards hydrolysis in aqueous systems than the *o*-quinone imine itself. 1,2-Naphthoquinone-1-benzimide was stable for as long as two hours in 20% aqueous dioxane. The quinone imide was also stable in mixtures of 0.1 *M* phosphate buffer–dioxane (8:2, by volume) of *p*H 6.1 and 7.3 for a minimum of twenty minutes, this being the longest time interval over which observations were

(1) L. F. Fieser and M. Fieser, *Organic Chemistry*, 3rd Ed., Reinhold Publishing Corporation, New York, N. Y., 1956, p. 715.

(2) N. V. Sidgwick, T. W. J. Taylor, and W. Baker, *The Organic Chemistry of Nitrogen*, Oxford University Press, Oxford, England, 1937, p. 97.

(3) A. Lüttringhaus and H. Wulff, *Angew. Chem.*, **67**, 274 (1955).

(4) C. C. Irving and H. R. Gutmann, *J. Biol. Chem.*, **234**, 2878 (1959).

made. Increasing the final *p*H to 8.3 in the buffered solvent system resulted in the slow hydrolysis of 1,2-naphthoquinone-1-benzimide (rate constant: 0.67×10^{-4} sec.$^{-1}$ at 25°). The rate of hydrolysis of 1,2-naphthoquinone-1-acetimide in the buffered aqueous dioxane at *p*H 8.3 was almost three times faster (rate constant: 1.80×10^{-4} sec.$^{-1}$ at 25°) than the rate of hydrolysis of 1,2-naphthoquinone-1-benzimide in the same solvent system. After a solution of 1,2-naphthoquinone-1-acetimide in buffered aqueous dioxane at *p*H 8.3 had stood for several hours, the visible spectrum of the solution was identical with that of a solution of 1,2-naphthoquinone.

EXPERIMENTAL

1,2-Naphthoquinone,[5] 1,2-naphthoquinone-1-imine,[3] 1,2-naphthoquinone-1-acetimide[4] and 1,2-naphthoquinone-1-benzimide[6] were prepared by published methods. Dioxane was purified according to Fieser.[7] The visible and ultraviolet spectra were recorded on a Beckman Model DR Spectrophotometer.

1,2-Naphthoquinone-1-imine in aqueous ethanol. A comparison of the ultraviolet absorption spectra of 1,2-naphthoquinone and 1,2-naphthoquinone-1-imine is shown in Fig. 1. The rate of decrease in absorbance at 259 mμ was used to measure the rate of hydrolysis of 1,2-naphthoquinone-1-imine in aqueous ethanolic solutions. The concentration of 1,2-naphthoquinone-1-imine was calculated from the equation:

$$[QI]_t = \frac{E_t - [QI]_0 \epsilon_Q}{\epsilon_{QI} - \epsilon_Q}$$

where

$[QI]_t$ = concentration (mol. per l.) of 1,2-naphthoquinone-1-imine at time, t
E_t = absorbance at time, t
$[QI]_0$ = initial concentration (mol. per l.) of 1,2-naphthoquinone-1-imine
ϵ_{QI} = molar extinction coefficient of 1,2-naphthoquinone-1-imine at 259 mμ (log ϵ = 4.30)
ϵ_Q = molar extinction coefficient of 1,2-naphthoquinone at 259 mμ (log ϵ = 4.17).

The first order rate constants were calculated from the data obtained from the plot of the log of the concentration of 1,2-naphthoquinone-1-imine versus time in minutes. The rate plots were linear for the time intervals observed: 60 min. for 95–40% ethanol, 30 min. for 25% ethanol and 10 min. for 10% ethanol.

1,2-Naphthoquinone-1-acetimide and 1,2-naphthoquinone-1-benzimide in aqueous dioxane. 1,2-Naphthoquinone-1-acetimide and 1,2-naphthoquinone-1-benzimide have absorption maxima at 360 mμ in aqueous dioxane (20% dioxane by volume). The position of the maxima did not shift as the *p*H of the solution was changed from 6.1 to 8.3. The concentrations of solutions of 1,2-naphthoquinone-1-acetimide (log ϵ_{360} = 3.58) and of 1,2-naphthoquinone-1-benzimide (log ϵ_{360} = 3.68) were determined from their absorbancies at 360 mμ. Since the rate of hydrolysis of these quinone imides was only slight, absorption at 360 mμ due to the hydrolysis product, 1,2-naphthoquinone, was negligible during the initial time periods.[8]

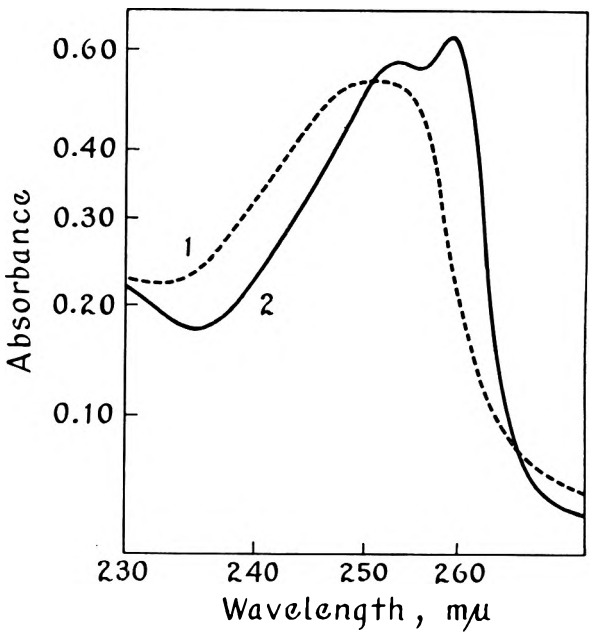

Fig. 1. Ultraviolet absorption spectra of 1,2-naphthoquinone (1) and 1,2-naphthoquinone-1-imine (2) in 95% ethanol

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VETERANS ADMINISTRATION HOSPITAL AND
DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY
UNIVERSITY OF MINNESOTA
MINNEAPOLIS

(5) L. F. Fieser, *Org. Syntheses*, **Coll. Vol. II**, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 430.

(6) R. Adams and J. M. Stewart, *J. Am. Chem. Soc.*, **74**, 5876 (1952).

(7) L. F. Fieser, *Experiments in Organic Chemistry*, 3rd Ed., D. C. Heath and Company, New York, N. Y., 1955, p. 285, procedure (a).

(8) Present address: Radioisotope Service, VA Medical Teaching Hospital, Memphis 15, Tennessee.

2-Imino-4-oxo-5-thiazolidineacetic Acid and Its Derivatives

A. N. ARAKELIAN, H. DUNN, JR., L. L. GRIESHAMMER, AND L. E. COLEMAN

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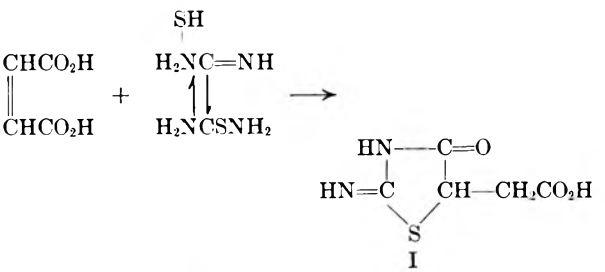
Tambach[1] and Andreash[2] in 1894–1895 reported that thiourea reacts in the enol form with maleic acid or fumaric acid to yield the 2-imino-4-oxo-5-thiazolidineacetic acid, I. Structure was proved



(1) R. Tambach, *Lieb. Ann.*, **280**, 233 (1894).
(2) R. Andreash, *Monatsch.*, **16**, 789 (1895).

TABLE I

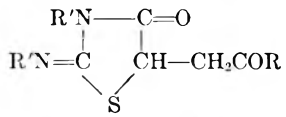
2-IMINO-4-OXO-5-THIAZOLIDINEACETIC ACID AND DERIVATIVES

Item	Reactant	Solvent	Yield, %	M.P.	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
1	Maleic acid	Alcohol	22	246 dec.[a]	16.05	16.00	18.43	18.32
2	Fumaric acid	Alcohol	74	244 dec.	16.05	15.80	18.43	18.25
3	Maleic anhydride	Methyl ethyl ketone	94	246 dec.	16.05	16.10	18.43	18.39
4	Diethyl maleate	Alcohol	51	159–160.5[b]	13.80	14.00	15.80	16.20
5	*N*-Butylmaleimide	Alcohol	66	184–185	18.30	18.30	13.90	14.20
6	*N*-Octylmaleimide	Alcohol	73	193–195	14.20	14.70	11.20	11.20
7	*N*-Decylmaleimide	Alcohol	72	197–198.5	13.58	13.30	10.35	9.87
8	*N*-Dodecylmaleimide	Alcohol	84	197	11.80	12.20	8.98	9.08
			1,3-Dibutylthiourea					
9	Maleic anhydride	Methyl ethyl ketone	66	82–83	9.79	9.82	11.18	11.20

[a] 210° dec., ref. 1. [b] 164–166°, ref. 3.

TABLE II

Ultraviolet Absorption Spectra of

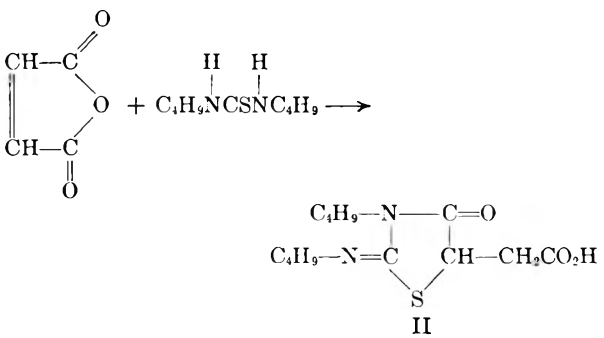


Item	R	R′	λ_{max}, Å	e × 10^{-3}	λ'_{max}, Å	e′ × 10^{-3}
1	—OH	—H	2213	21.9	2503	9.6
2	—OH	—H	2217	21.2	2507	9.4
3	—OH	—H	2218	20.9	2510	8.9
4	$-OC_2H_5$	—H	2218	20.5	2500	9.7
5	$-NHC_4H_9$	—H	2215	23.4	2504	9.9
6	$-NHC_8H_{17}$	—H	2216	20.5	2511	8.7
7	$-NHC_{10}H_{21}$	—H	2218	21.2	2508	9.2
8	$-NHC_{12}H_{25}$	—H	2211	22.2	2503	9.7
9	—OH	$-C_4H_9$	2200	16.6	—	—

by ring degradation. Recently, Japanese workers[3] reported that diethyl maleate reacts with thiourea to give the ethyl ester of I. Benzoyl peroxide was used as catalyst and a low yield of product was obtained. The *N*-ethylacetamide derivative of I was reported by Marrian,[4] who treated *N*-ethyl maleimide with thiourea.

In the course of study in our laboratory, we have made a more complete investigation of the reactions of thiourea with maleic acid, fumaric acid, maleic anhydride, diethyl maleate, and a series of *N*-alkylmaleimides. The resultant compounds were characterized by melting point, chemical analysis, and the infrared and ultraviolet absorption spectra.

Table I describes the various 2-imino-4-oxo-5-thiazolidineacetic acids and derivatives prepared from thiourea. Fumaric acid, maleic acid, diethyl maleate, and the four *N*-alkylmaleimides reacted readily in an alcohol solvent (ethanol-methanol $(8:19)_{wt.}$) to give the desired products. Reaction was slow or incomplete in methyl ethyl ketone. Maleic anhydride, on the other hand, reacted well in methyl ethyl ketone but gave very little reaction in the alcohol solution. Reaction of 1,3-dibutylthiourea with maleic anhydride in methyl ethyl ketone gave the product, II, which is also described in Table I.

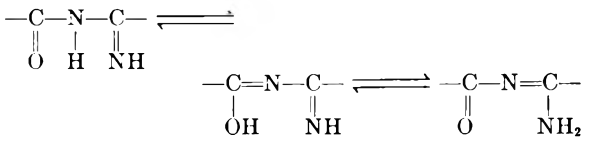


II

The ultraviolet absorption data of these compounds are shown in Table II. Compounds prepared from thiourea absorbed at 2211–2218Å and 2500–2511Å while the parent compound from 1,3-dibutylthiourea and maleic anhydride absorbed only at 2200Å. The absence of the 2500Å absorption in II indicates that this peak is probably due to the tautomerism in the cyclic structure, I,

(3) A. Nagasaka, R. Oda, and S. Nukina, *J. Chem. Soc. Japan*, **57**, 169 (1954).

(4) D. H. Marrian, *J. Chem. Soc.*, 1797 (1949).



which would be prevented by replacement of the *N*-hydrogen atoms by butyl groups.

EXPERIMENTAL

The compounds were prepared by heating equimolar amounts of reactants to reflux in either methyl ethyl ketone or the ethanol-methanol solvent for 3–38 hr. Analytical samples were purified by recrystallization from ethanol. All melting points are uncorrected. The ultraviolet absorption spectra were determined in ethanol using a Beckman DK-2 recording spectrophotometer.

Acknowledgment. The authors wish to thank Mr. H. Ferber for the chemical analysis of the compounds reported in this paper.

CHEMICAL RESEARCH LABORATORY
THE LUBRIZOL CORPORATION
CLEVELAND 17, OHIO

Organic Sulfur Compounds. II.[1] Synthesis of Indanyl Aryl Sulfides, Sulfoxides, and Sulfones

ALEXIS A. OSWALD

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Cracked petroleum distillates contain indene and aromatic thiols[2,3] and it is possible that an addition reaction between these compounds can occur. Therefore, a study of these compounds was undertaken with emphasis on the ease with which addition is accomplished and to determine the properties of the resulting indanyl aryl sulfides.

It was found that aromatic thiols readily add to indene even in the absence of any added peroxide catalyst. The addition yielded the same sulfides in the presence or absence of peroxide catalyst. It is assumed, therefore, that thiol-indene addition reactions normally proceed by a radical mechanism. The addition products are formulated as 2-indanyl derivatives, since the ionic addition of acids gives 1-indanyl derivatives.[4,5] The 2-indanyl aryl sulfides obtained are white crystalline compounds soluble in hydrocarbons. An aliphatic thiol, *n*-butanethiol, reacted with indene at a much slower rate than aromatic thiols. The reaction product, 2-indanyl butyl sulfide, is a colorless liquid.

As expected, these sulfides can be oxidized by hydrogen peroxide to the corresponding sulfoxides and sulfones which are less soluble in hydrocarbons in the order mentioned. 2-Indanyl-4-tolyl sulfoxide was also prepared by adding equivalent amounts of 4-toluenethiol and cumene hydroperoxide to an *n*-heptane solution of indene. In this case, the hydroperoxide at first acted as a catalyst for addition, and then as an oxidizing agent for the sulfide formed. Some physical properties and analytical data of the compounds synthesized are shown in Table I.

1-Indanyl aryl sulfides were also synthesized by treating 1-chloroindane[6] with sodium thiophenolates in benzene–isopropyl alcohol. The 1-indanyl, phenyl, and tolyl sulfides prepared were colorless liquids. They had slightly lower boiling points at 2 mm. pressure than the corresponding 2-indanyl aryl sulfides. The main absorption peaks in the spectra of I–II and III–IV, shown in Table I, were the same. However, triplets between 5.2 and 5.6 μ had peaks at slightly different wave length. To get a more convincing proof of the difference between the 1- and 2-indanyl derivatives, the 1-indanyl sulfides were oxidized to the corresponding sulfones. The latter were white crystalline compounds melting at slightly lower temperatures than their 2-indanyl isomers. Mixed melting-point determinations of the isomers gave a definite depression.

EXPERIMENTAL

Materials. The indene and mercaptans used in the experiments were vacuum distilled under nitrogen before use. The hydrogen peroxide was a Merck reagent (Superoxol) in the form of a 30% aqueous solution. The solvents were C.P. reagents.

Synthesis of 2-indanyl aryl sulfides. A 15–100% solution of 0.1 mole of aromatic mercaptan in n-heptane was added to 11.6 g. (0.1 mole) of freshly distilled indene. Although the initial reaction was exothermic, it was necessary, after a few hours, to heat the mixture on a water bath to complete the addition. The products were recrystallized from *n*-heptane or alcohol. The yields and some physical and analytical data are listed in Table I.

The experimental procedure described above was repeated with 4-chlorothiophenol and indene in the presence of 0.76 g. (0.05 mole) of cumene hydroperoxide (added to the indene before the thiophenol). The same sulfide was obtained in a yield similar to the experiment without the hydroperoxide. This latter experiment supports a radical mechanism of the mercaptan addition to indene.[7]

Synthesis of 2-indanyl aryl sulfoxides. The 2-indanyl aryl sulfide (0.1 mole) was dissolved in a mixture of 40 ml. acetic anhydride and 20 ml. acetic acid. To the solution, 0.1 mole

(1) For the preceding communication of this series, see *J. Org. Chem.*, **24**, 443 (1959).

(2) A. N. Sachanen, *The Chemical Constituents of Petroleum*, Reinhold Publishing Corp., New York, N. Y., 1945, p. 265.

(3) G. S. Windle, *Petroleum Refiner*, **23**, No. 2, 83 (1944).

(4) W. J. Pope and J. Read, *J. Chem. Soc.*, **101**, 758 (1912).

(5) R. Weissgerber, *Ber.*, **44**, 1436 (1911).

(6) 1-Chloroindane was synthesized according to Weissgerber[5] by the introduction of hydrogen chloride into cool indene. It was observed that at the low temperature, 1 mole of indene adsorbed about 2 moles of hydrogen chloride while the mixture turned red. (Details in Experimental.)

(7) E. Müller, *Methoden der organischen Chemie* (Houben-Weyl), G. Thieme Verlag, Stuttgart, W. Germany, 1955, Vol. 9, p. 120.

TABLE I

INDANYL SULFIDES, SULFOXIDES, AND SULFONES
'Indanyl-SO_x—R'

No.	-Indanyl	X	R	Formula	Yield,[a] %	M.P.[b]	B.P.[b] (2 mm.)	Calc. C	Calc. H	Calc. S
I	2	0	Phenyl	$C_{15}H_{14}S$	86	46–47	135–137	79.65	6.20	14.1
II[c]	1	0	Phenyl	$C_{15}H_{14}S$	67	...	127–128	79.65	6.20	14.1
III	2	0	4-Tolyl	$C_{16}H_{16}S$	90	86–86.5	140–142	80.00	6.67	13.3
IV[d]	1	0	4-Tolyl	$C_{16}H_{16}S$	69	...	135–136	80.00	6.67	13.3
V[e]	2	0	4-Chlorophenyl	$C_{15}H_{13}ClS$	89	90–91	...	69.08	5.02	12.3
VI	2	0	2-Naphthyl	$C_{19}H_{16}S$	91	99–100	...	82.61	5.79	11.6
VII[f]	2	0	*n*-Butyl	$C_{13}H_{18}S$	93	...	118–119	75.67	8.79	15.5
VIII	2	1	4-Tolyl	$C_{16}H_{16}OS$	89	107–108	...	75.00	6.25	12.5
IX[g]	2	1	4-Chlorophenyl	$C_{15}H_{13}OClS$	87	97–98	...	65.08	4.73	11.6
X	2	2	Phenyl	$C_{15}H_{14}O_2S$	91	107–108	...	68.77	5.46	12.4
XI	1	2	Phenyl	$C_{15}H_{14}O_2S$	84	105–106	...	68.77	5.46	12.4
XII	2	2	4-Tolyl	$C_{16}H_{16}O_2S$	94	134.5–135.5	...	70.59	5.88	11.8
XIII	1	2	4-Tolyl	$C_{16}H_{16}O_2S$	98	132–133	...	70.59	5.88	11.8
XIV[h]	2	2	4-Chlorophenyl	$C_{15}H_{13}O_2ClS$	95	137.5–138.5	...	61.53	4.47	10.9
XV	2	2	2-Naphthyl	$C_{19}H_{16}O_2S$	97	140–141	...	73.99	5.23	10.4
XVI	2	2	*n*-Butyl	$C_{13}H_{18}O_2S$	89	61–62	...	65.51	7.61	13.4

[a] Without the use of any catalyst. [b] Uncorrected. [c] n_D^{20} 1.6306. [d] n_D^{20} 1.6193. [e] Calcd.: Cl, 13.6. Found: Cl, 13.8. [f] n_D^{20} 1.5475. [g] Calcd.: Cl, 12.8. Found: Cl, 12.7. [h] Calcd.: Cl, 12.1. Found: Cl, 12.3.

of hydrogen peroxide was added in the form of an aqueous 30% solution. The reaction mixture was allowed to stand for 3 days at room temperature. After the oxidation was complete, the solution was diluted with water which precipitated the crude sulfoxide. The 2-indanyl sulfoxides obtained in this manner were purified by recrystallization from alcohol. The yields, physical and analytical properties of the compounds so obtained, are shown in Table I.

In another experiment, the addition of 2.4 g. (0.1 mole) of 4-toluenethiol to 11.6 g. (0.1 mole) of indene was followed by a mixture of *t*-butyl hydroperoxide (about 18 g., 0.2 mole) and di-*t*-butylperoxide (about 6 g.) prepared according to Milas and Surgenor.[8] After the addition of the peroxide, the reaction mixture was heated on a steam bath for 3 min., which caused gas evolution and color change. The heating was, therefore, discontinued, and the mixture was cooled to room temperature, where it was allowed to stand. After 3 days, the low boiling compounds (di-*t*-butylperoxide, *t*-butyl alcohol) were removed by distillation on a steam bath at 10 mm. Then the residue crystallized to a red mass, which after repeated recrystallizations from benzene–*n*-heptane and alcohol gave 12 g. (49.5%) colorless 2-indanyl-4-tolyl sulfoxide (m.p. 106.5–107.5°).

Synthesis of 2-indanyl aryl sulfones. An acetic anhydride–acetic acid solution of 0.1 mole of indanyl aryl sulfide and 0.2 mole of hydrogen peroxide, was heated on a water bath for 15 min. The reaction mixture was then diluted with water to precipitate the raw 2-indanyl aryl sulfone, which was purified by recrystallization from alcohol. The yields, physical and analytical properties of the compounds are tabulated.

The addition of n-butanethiol to indene. (a) *In the absence of peroxide catalyst.* A mixture of 11.6 g. (0.1 mole) of indene and 9 g. (0.1 mole) of *n*-butanethiol in a round-bottom flask was purged with nitrogen. Then the flask was closed, and the reaction mixture allowed to stand for 10 days. A mercaptan determination of the mixture, after 3 and 10 days, showed 75.7 and 68.1% of the original mercaptan concentration. After 10 days, the reaction mixture was fractionated *in vacuo*. After the removal of the unchanged *n*-butanethiol and indene, 6.1 g. (93% based on the amount of converted butanethiol) of indanyl butyl sulfide, b.p. 218–219° (2 mm.), n_D^{20} 1.5475, was obtained. Some further analytical data of the product are shown in Table I.

(8) N. A. Milas and D. M. Surgenor, *J. Am. Chem. Soc.*, **68**, 205 (1946).

(b) *In the presence of peroxide catalyst.* To the mixture of indene and *n*-butanethiol described in (a), 0.7 g. (0.005 mole) of cumene hydroperoxide was added. The resulting mixture became warm after 2 hr. standing. A mercaptan determination of the reaction mixture after 3 days showed 26.7% of the original mercaptan still present. A subsequent vacuum distillation yielded 13.5 g. (89% based on the amount of converted butanethiol) of indanyl butyl sulfide, b.p. 216–218° (1.9 mm.), n_D^{20} 1.5474. The infrared spectrum of this product was identical with the product obtained without any added peroxide catalyst under (a).

The peracetic acid oxidation of both sulfide products resulted in 2-indanyl *n*-butyl sulfone, m.p. 61–62°, in 89 and 87% yield, respectively. A mixed melting-point determination of the two products gave no depression. Their infrared spectra were identical. Some of the analytical data obtained are shown in Table I.

Synthesis of 1-chloroindane. Gaseous hydrogen chloride was introduced into 58 g. (0.5 mole) of cool indene; a method used by Weissgerber,[5] except that a Dry Ice–acetone mixture instead of salt-ice was used for cooling. The indene was cooled as low as possible without freezing it. During the introduction of the hydrogen chloride, the freezing point of the mixture decreased and finally a viscous red liquid resulted at −60° which had adsorbed about 36.5 g. (1 mole) of hydrogen chloride. This liquid, on coming to room temperature, released about 18.2 g. (0.5 mole) of hydrogen chloride and became almost colorless. On vacuum distillation, it yielded 68.7 g. (90%) 1-chloroindane, b.p. 103° (20 mm.). About 7.5 g. of viscous, orange liquid remained as a distillation residue.

Anal. Calcd. for C_9H_9Cl: Cl, 23.1. Found: Cl, 22.8.

Synthesis of 1-indanyl aryl sulfides. An aromatic thiol (0.1 mole), was dissolved in 1:1 benzene–isopropyl alcohol and allowed to react with 2.3 g. (0.1 mole) of sodium. To the resulting sodium thiophenolate was added 15.3 g. (0.1 mole) of 1-chloroindane in 50 ml. of benzene. The precipitation of sodium chloride from the reaction mixture started at room temperature. To complete the reaction, the mixture was refluxed for 6 hr. Then it was washed with water, 5% aqueous sodium hydroxide and water, dried, and distilled in vacuo. After the removal of benzene, the 1-indanyl aryl sulfides were obtained as colorless liquids. Some of the physical and analytical data of the products are shown in Table I.

Synthesis of 1-indanyl aryl sulfones. 1-Indanyl aryl sulfide (0.05 mole) was dissolved in a mixture of 30 ml. of acetic

TABLE I (*Continued*)

INDANYL SULFIDES, SULFOXIDES, AND SULFONES
'Indanyl-SO_x—R'

No.	Found C	Found H	Found S	Infrared Absorption Peaks (Microns)							
I	80.11	6.25	13.9	5.27	5.44	6.3	5.58			9.2	9.38	9.78
II[c]	79.18	6.24	14.0	5.22	5.33	6.3	5.53			9.2	9.38	9.78
III	80.72	6.67	13.3	5.27	5.46	6.25	5.69			9.18		9.84
IV[d]	79.56	7.02	13.4	5.25	5.55	6.25				9.18		9.84
V[e]	68.79	5.17	11.9	5.26	5.43	6.35				9.15		9.9
VI	83.23	5.89	11.2	5.24	5.43	6.15, 6.3	5.57			9.15		9.8
VII[f]	75.47	8.97	15.4	5.24	5.42	6.21, 6.27	5.57			9.13		9.76
VIII	74.89	6.34	12.8			6.25	7.68	7.87		9.25	9.75	9.9
IX[g]	64.64	4.83	11.4			6.3	7.6	7.85		9.2	9.7	9.9
X	69.01	5.83	11.8			6.3	7.65	7.8	8.75	9.23		9.8
XI	68.94	5.53	12.9			6.21, 6.28	7.65	7.75	8.85	9.25	9.79	10.01
XII	70.41	5.91	11.3			6.25	7.7		8.8	9.25		9.9
XIII	70.01	5.95	11.4									
XIV[h]	61.73	4.75	10.9			6.3	7.6	7.85	8.75	9.25		9.9
XV	74.08	5.51	9.7			6.15, 6.3	7.65	7.8	8.75	9.35		
XVI	65.73	7.69	12.8			6.21, 6.3	7.69	7.78	8.85	8.95		

anhydride and 10 ml. of acetic acid. Aqueous 30% hydrogen peroxide (11.4 g., 0.01 mole) was added to the sulfide solution at 5°. Then the reaction mixture was kept at that temperature for 24 hr., and at room temperature for an additional 48 hr. After the completion of the reaction, the crystalline 1-indanyl aryl sulfone was precipitated by careful addition of crushed ice. The crude crystalline product was filtered and twice recrystallized from 90% aqueous ethanol. The yields obtained and some of the physical and analytical data of the products obtained are shown in Table I.

When 1-indanyl aryl sulfides were oxidized with the same reagents on a water bath, a smaller yield of the sulfones was realized due to some decomposition.

Acknowledgments. The author wishes to thank J. L. Tiedje and C. B. Rupar for many helpful discussions, F. Noël for the technical assistance, A. J. Stephenson for the infrared analyses, J. Eagen and the late C. H. Stein for the elemental analyses.

RESEARCH DEPARTMENT
IMPERIAL OIL LIMITED
SARNIA, ONTARIO
CANADA

Carcinogenic Amine Derivatives Containing Nitrogen-15[1,2]

MURIEL DAHLGARD

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Several carcinogens have been found to bind to the protein of tissues in which they cause cancer. Since some chemically related noncarcinogens have also been found to bind to protein, this interaction may well be a necessary but not sufficient requirement for the production of tumors.[3]

In order to study this further, the synthesis of three carcinogens labeled with nitrogen-15 was undertaken. These were 4-acetylaminobiphenyl-N^{15}, 4'-fluoro-4-acetylaminobiphenyl-N^{15}, and N-(7-hydroxy-2-fluorenyl)acetamide-N^{15}, a weakly carcinogenic metabolite of the strong carcinogen, N-2-fluorenylacetamide.

2-Nitrofluorene-N^{15} had been prepared previously in this laboratory[4] by nitrating fluorene with aqueous nitric acid-N^{15} using acetic anhydride to remove the excess water. No reaction occurred when this method was used with biphenyl. When the reaction was carried out in sulfuric acid solvent or when potassium nitrate-N^{15} and sulfuric acid were used as the source of nitric acid, the material either failed to react or was sulfonated. The only effective nitrating agent proved to be 100% nitric acid-N^{15}. The procedure used for nitrating the biphenyl derivatives was based on the method of Maki and Obayashi.[5] The desired *para* isomers were separated from the *ortho* isomers and unchanged hydrocarbon by trituration with hexane, in which the *para* isomers are not soluble. 2-Acetoxyfluorene was nitrated by a modification of the procedure described by Bryant and Sawicki.[6] The nitro compounds were reduced and acetylated by the usual methods as described in the Experimental section.

(1) This investigation was supported by Research Grant C-1066 from the National Cancer Institute, National Institutes of Health, Public Health Service.

(2) Presented before the Meeting-in-Miniature, Florida Section, American Chemical Society, St. Petersburg, Fla., May 8–9, 1959.

(3) For detailed discussion see E. K. Weisburger and J. H. Weisburger, *Advances in Cancer Research*, Vol. 5, J. P. Greenstein and A. Haddow, editors, Academic Press, Inc., New York, 1958, p. 382.

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Biological testing of these compounds will be carried out by Drs. H. P. Morris and Helen Dyer at the National Cancer Institute. The results will be published elsewhere.

EXPERIMENTAL

Preparation of 100% nitric acid. (a) Isotopic nitric acid,[7] (6.79 g.; 0.108 mole as 52.72 g. of a 12.88% solution containing 62.8 atom % nitrogen-15) was carefully neutralized, with cooling, by addition of 4.32 g. (0.108 mole) of sodium hydroxide dissolved in the minimum amount of water. The water was removed by distillation and the dry salt was treated with concentrated sulfuric acid (18 ml., 0.32 mole). Distillation at atmospheric pressure gave 5.6 g. (0.089 mole) of 100% nitric acid-N^{15} b.p. 80–83° (82% recovery).

(b) Potassium nitrate (14.2 g.; 0.07 mole) containing 97.0 atom % nitrogen-15[7] and 31.1 ml. (0.56 mole) of concentrated sulfuric acid gave, upon distillation, 7.1 g. of 100% nitric acid-N^{15} b.p. 78–82° (81% recovery).

4'-Fluoro-4-nitrobiphenyl-N^{15}. A solution of 100% nitric acid-N^{15} (5.6 g.; 0.09 mole containing 62.8 atom % nitrogen-15) in 5.6 g. of glacial acetic acid was added dropwise with stirring to molten 4-fluorobiphenyl (18.4 g.; 0.107 mole, 20% excess), keeping the temperature between 75–82°. Acetic anhydride (12 ml., 0.13 mole) was then added slowly to remove water of reaction. The mixture was kept at 80° for 4 hr., then poured into ice water. After standing overnight the solid was removed by filtration, washed several times with water and then three times with 100-ml. portions of hexane. Crude yield of 4'-fluoro-4-nitrobiphenyl-N^{15} was 9.8 g. (50% based on the nitric acid used). Recrystallization from 175 ml. of ethanol gave 5.5 g. (28%) m.p. 125–126° (lit.,[8] m.p. 123°).

4'-Fluoro-4-acetylaminobiphenyl-N^{15}. 4'-Fluoro-4-nitrobiphenyl-N^{15} (5.5 g.; 0.025 mole) in 150 ml. of warm ethanol was hydrogenated at low pressure using 0.05 g. Adams' platinum oxide catalyst. The yellow solution was filtered free of catalyst into 20 ml. of concentrated hydrochloric acid. The ethanol was removed by distillation, the residue was taken up in hot water containing a little hydrochloric acid, and the solution filtered through a thin mat of charcoal. Potassium acetate was added to the solution just to turbidity, then acetic anhydride (25 ml.) was added, followed by potassium acetate to *p*H 5–6. Stirring was continued for 2 hr. and after standing overnight the 4'-fluoro-4-acetylaminobiphenyl-N^{15} which had precipitated amounted to 2.65 g. (46.5%) m.p. 206° (lit.[9], m.p. 205–206°).

4-Nitrobiphenyl-N^{15}. To molten biphenyl (15.9 g.; 0.103 mole) at 75° was added dropwise with stirring a solution of 5.4 g. (0.086 mole) of 100% nitric acid containing 97.0 atom % nitrogen-15 in 5.4 g. of glacial acetic acid, keeping the temperature below 80°. When the addition had been completed acetic anhydride (12 ml., 0.13 mole) was slowly added to remove water of reaction, then the mixture was kept at 75–80° for 4 hr. After pouring into ice water and leaving overnight, the water was decanted from the semisolid yellow residue, the residue was triturated three times with 50-ml. portions of hexane to remove unchanged biphenyl and 2-nitrobiphenyl and recrystallized from ethanol, giving 6.0 g. of 4-nitrobiphenyl-N^{15} (35.3% based on the nitric acid consumed), m.p. 113–114° (lit.,[10] m.p. 114°).

4-Aminobiphenyl-N^{15}. A mixture of 4-nitrobiphenyl-N^{15} (6.0 g., 0.03 mole), 175 ml. of ethanol, 2.1 g. of calcium chloride dissolved in 41 ml. of water, 63.6 g. of zinc dust, and 2.0 g. of Norit were refluxed for 3 hr., 1.0 ml. of 85% hydrazine hydrate was added and the mixture filtered to remove the zinc, the residue being washed twice with 25-ml. portions of hot ethanol. The alcoholic filtrates were poured into 2 l. of water and allowed to stand overnight. The white precipitate of 4-aminobiphenyl-N^{15} was filtered off and washed well with water, then air-dried. Yield was 4.6 g. (90%) m.p. 53–54° (lit.,[11] m.p. 50–52°).

4-Acetylaminobiphenyl-N^{15}. 4-Aminobiphenyl-N^{15} (4.6 g.; 0.027 mole) was dissolved with heating in 60 ml. of benzene, decanted from a little insoluble material and treated with 5 ml. of acetic anhydride. A precipitate began to form immediately. After refluxing for 15 min. the clear solution was allowed to cool slowly to room temperature. The white crystals which formed were filtered and washed several times with water, giving 5.2 g. (91%) of 4-acetylaminobiphenyl-N^{15} m.p. 171° (lit.[12], m.p. 171–172°) and containing 97.0 atom % nitrogen-15.

2-Nitro-7-acetoxyfluorene-N^{15}. The literature procedure[6] was modified as follows: A mixture of 5.6 g. (0.025 mole) of 2-acetoxyfluorene and 22.5 g. (0.375 mole) of glacial acetic acid was heated to 80° to effect solution, then allowed to cool to 50°. A solution prepared by adding 1.6 g. (0.025 mole) of 100% nitric acid containing 97.0 atom % nitrogen-15 to 12.8 g. (0.125 mole) acetic anhydride in an ice bath (exothermic reaction) was then added to the 2-acetoxyfluorene solution and an exothermic reaction set in. When the temperature reached 75° the mixture was cooled in an ice bath. After the initial exothermic reaction had subsided the mixture was kept at 70–75° for 5 min., then allowed to stand overnight. The yellow solid was filtered, washed with water until the filtrate was no longer acidic and dried, giving 5.4 g. (80.6%) of 2-nitro-7-acetoxyfluorene-N^{15} m.p. 192–193° (lit.[6], 191–192°).

N-(7-Hydroxy-2-fluorenyl)acetamide-N^{15}. To a boiling solution of 2-nitro-7-acetoxyfluorene-N^{15} (5.4 g.; 0.02 mole) in 1 l. of ethanol was added slowly over a period of 1 hr. a solution of 41.7 g. (0.22 mole) of stannous chloride dissolved in 350 ml. of concentrated hydrochloric acid. The solution was concentrated to one-third its volume, then brought up to one-half its original volume with concentrated hydrochloric acid and allowed to stand overnight. The precipitate was filtered and dissolved in 200 ml. of hot water containing a few drops of stannous chloride–hydrochloric acid solution. The solution was filtered through a mat of charcoal and then brought to *p*H 5–6 with potassium acetate. After addition of 40 ml. of acetic anhydride the mixture was allowed to stand overnight. The precipitate of *N*-(7-hydroxy-2-fluorenyl)acetamide-N^{15} containing 97.0 atom % nitrogen-15 amounted to 2.8 g. (48%) m.p. 229–231° (lit.,[13] m.p. 230–232°).

CANCER RESEARCH LABORATORY
UNIVERSITY OF FLORIDA
GAINESVILLE, FLA.

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A Preparation of 10-Hydroxydecanoic Acid

F. L. BENTON[1] AND A. A. KIESS

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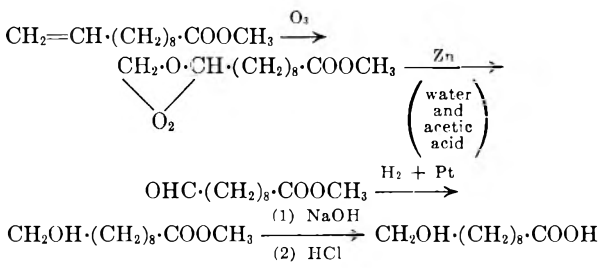
The synthesis of 10-hydroxydecanoic acid has been accomplished by three methods.[2–4] The one

reported by Lycan and Adams is the most direct but requires four steps:



The method reported herein eliminates two of these steps, conversion of methyl undecenoate ozonide to the aldehydo ester, and catalytic hydrogenation of the hydroxy ester. Instead, the ozonide is reduced directly to methyl 10-hydroxydecanoate with sodium borohydride. 10-Hydroxydecanoic acid is then obtained in an overall yield of nearly sixty per cent by saponification of the ester. Although reduction of ozonides has been accomplished with lithium aluminum hydride,[5] sodium borohydride was employed to avoid concomitant reduction of the ester moiety.[6]

EXPERIMENTAL

10-Hydroxydecanoic acid. A solution of 20.0 g. of methyl 10-undecenoate in 60 ml. of ethyl acetate, maintained at a temperature of −50 to −60°, was treated approximately for 1 1/4 hr. with a slow stream of ozone in oxygen until ozone was detected in the exit gases. The solution of ozonide[7] was then added rapidly (within 2 min.) to a vigorously stirred ice cold mixture of 6.0 g. of sodium borohydride and 120 g. of tetraethylene glycol dimethyl ether. The mixture was stirred for 2 hr. at ice-bath temperature and an additional hour at room temperature after which it was poured into 1 l. of water containing 30 ml. of concentrated hydrochloric acid. The hydrolysis mixture was saturated with salt; the oil which formed was separated and the aqueous fraction extracted with three 100-ml. portions of diethyl ether. The combined oil and ether extracts was washed successively with water, aqueous sodium carbonate, and water and dried over anhydrous magnesium sulfate. After removal of ether by evaporation under reduced pressure, the residual oil was heated at reflux temperature for 30 min. with 50 ml. of 20% aqueous sodium hydroxide. The saponification mixture was then steam distilled until turbidity and odor were no longer detected in the distillate, after which it was cooled in an ice bath and acidified with 1:1 aqueous hydrochloric acid. The resulting precipitate was filtered, washed with water until free from mineral acid, and dried. It was dissolved in hot ethylene dichloride, filtered to remove a small amount of insoluble material, and allowed to recrystallize. In this manner, 12.0 g. (59%) of a colorless crystalline product, m.p. 75–76°, was obtained.

Anal.[8] Neut. equiv. Calcd.: 188.2. Found: 189.2. Hydroxyl value. Calcd.: 9.02. Found: 9.15.

CENTRAL RESEARCH LABORATORIES
ARMOUR AND CO.
CHICAGO 9, ILL.

(1) Present address: Department of Chemistry, St. Mary's College, Notre Dame, Indiana.

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(7) The ozonide solutions were kept cold at all times and no difficulty was experienced in handling them under these conditions. As an added safety precaution, however, operations may be carried out behind an explosion-proof shield.

(8) The authors are indebted to Mr. L. D. Metcalfe for these analyses.

Conformational Analysis of the Prins Reaction

EDWARD E. SMISSMAN AND DONALD T. WITIAK[1]

Received September 8, 1959

It has been shown that the Prins reaction gives stereospecifically *trans*-2-hydroxymethylcyclohexanol when cyclohexene is employed as the olefin.[2,3] In an effort to elucidate the initial conformation of the products of this reaction we have employed the rigid *trans*-Δ^2-octalin[4] system (I).

It is generally agreed[3,5,6] that the first step in a Prins reaction involves the addition of a proton to a neutral formaldehyde molecule. The stereospecific *trans* addition of the hydroxy and the hydroxymethylene groups to the double bond of a cyclic olefin argues against a free carbonium ion but can be rationalized on the basis of a solvated cyclic intermediate. By comparison with other addition reactions involving cyclic intermediates, *i.e.* bromination, the product would be predicted to exhibit a diaxial conformation[7] of the hydroxy and hydroxymethylene groups. Our results confirm the above postulation.

Under the conditions of the Prins reaction, *trans*-Δ^2-octalin, I, gave *trans*-2-hydroxymethyl-3-hydroxy-*trans*-decalin, II. The conformation of this compound was proved in the following manner: The *mono*-tosylate, III, was prepared and subsequently displaced by cyanide ion. The latter re-

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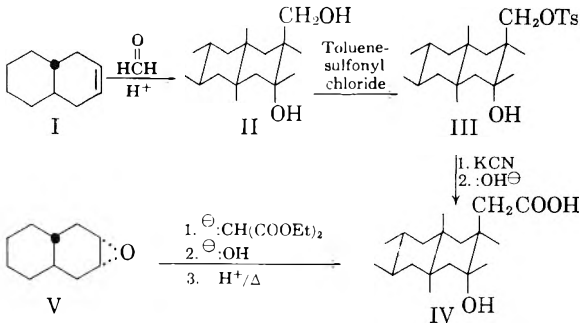
action was performed in dimethyl sulfoxide solution[8] and gave an uncrystallizable nitrile (4.43 μ). The nitrile was subjected to alkaline hydrolysis and yielded a hydroxy acid, IV.

The acid, IV, was identical in all properties with one prepared by Johnson and Bauer[9] through the opening of 2,3-epoxy-*trans*-decalin, V, with the anion of malonic ester, followed by hydrolysis and monodecarboxylation. This method could only give rise to a diaxial product, IV, hence the Prins product, II, must have the diaxial conformation.



EXPERIMENTAL

trans-2(a)-Hydroxymethyl-3(a)-hydroxy-trans-decalin, II. A mixture of 12 g. (0.4 mole) paraformaldehyde, 90 ml. glacial acetic acid, and 2 ml. sulfuric acid was heated to 85° while stirring. After solution was effected the temperature was lowered to 65° and 19 g. (0.14 mole) *trans*-Δ^2-octalin was allowed to drop into the stirred reaction mixture over a period of 0.5 hr. The mixture was then stirred at room temperature for 10 hr. and subsequently diluted with 150 ml. of water and extracted with three 150-ml. portions of ether. The combined ether extracts were then washed with 200 ml. water and with saturated sodium carbonate solution until the ethereal solution was neutral. The ethereal solution was then washed with 200 ml. of water and dried over anhydrous magnesium sulfate. The ether was removed and the residual oil was dissolved in a solution of 12 g. sodium hydroxide in 150 ml. ethanol and refluxed for 2 hr. The reaction mixture was diluted with 300 ml. water and extracted with three 200-ml. portions of ether. The solution was dried, the ether removed, and the residual oil crystallized on standing. Recrystallization from benzene yielded 8 g. (25%) of the product, m.p. 159–160°.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.93; H, 10.35.

trans-2(a)-Tosyloxymethyl-3(a)-hydroxy-trans-decalin, III. A solution of 20 ml. pyridine, 1 g. (0.006 mole) *p*-toluene sulfonyl chloride, and 1 g. (0.005 mole) *trans*-2(*a*)-hydroxymethyl-3(*a*)-hydroxy-*trans*-decalin was allowed to react at room temperature for 1 hr. The solution was then poured into an ice slurry of dilute hydrochloric acid. The resulting precipitate was filtered and recrystallized from Skellysolve B. White needles, m.p. 103.5–104° were obtained in a yield of 1.10 g. (55%).

Anal. Calcd. for $C_{18}H_{26}O_4S$: C, 62.93; H, 7.46; S, 9.88. Found: C, 63.40; H, 7.43; S, 9.47.

trans-2(a)-Cyanomethyl-3(a)-hydroxy-trans-decalin. A stirred mixture of 1.0 g. (0.003 mole) of the monotosylate, III, 1.2 g. (0.18 mole) potassium cyanide, and 20 ml. dimethylsulfoxide was heated at 210° for 5.5 hr. The reaction mixture was diluted with 150 ml. of water and extracted with three 100-ml. portions of ether. The ethereal extracts were then washed with two 75-ml. portions of water and dried over anhydrous magnesium sulfate. The ether was removed and the residual oil would not crystallize. Attempts to purify the oil by distillation failed. The infrared spectrum was in good agreement with the expected product and a sharp nitrile band at 4.43 μ was observed.

trans-2(a)-Carboxymethyl-3(a)-hydroxy-trans-decalin, IV. The crude nitrile was dissolved in 20 ml. of a solution of 10% sodium hydroxide in diethylene glycol and heated at 170° for 3 hr. The reaction mixture was diluted with 100 ml. water and extracted with two 150-ml. portions of ether. The aqueous layer was made acidic with 5*N* HCl and extracted with three 100-ml. portions of ether. The ether solution was then washed with water and dried. The ether was removed and the residual oil was chromatographed on a silicic acid–chloroform column using chloroform as the eluant. The acid was removed from the column as a distinct yellow band with 50% ethanol in chloroform. The solvent was removed and the residue crystallized on standing. Recrystallization from ethyl acetate gave 0.3 g. (50% based on the tosyl compound) of white crystalline material, m.p. 115–116°. There was no depression of melting point on admixture of this acid with that prepared by Johnson and Bauer. The infrared spectra were superimposable.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.26; H, 9.40.

Acknowledgment. We are grateful to Dr. W. S. Johnson and Dr. V. Bauer for a sample of *trans*-2-(*a*)-carboxymethyl-3(*a*)-hydroxy-*trans*-decalin.

DEPARTMENT OF PHARMACEUTICAL CHEMISTRY
UNIVERSITY OF WISCONSIN
MADISON, WIS.

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Some Reactions of 1,1,1-Trichloro-2-propanol[1]

O. R. PIERCE, E. E. FRISCH, AND D. D. SMITH[2]

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The dehydration of 1,1,1-trichloro-2-propanol has been studied by various researchers who have assigned to the product either the structure 3,3,3-trichloro-1-propene[3–5] or 1,1,2-trichloro-1-propene.[6] In this laboratory it was found that dehydration of the alcohol with phosphorus pentoxide did produce 1,1,2-trichloro-1-propene in confirmation of the work of Kirrmann.[6] Reaction of 1,1,1-trichloro-2-propanol with alumina at elevated temperatures or with zinc chloride in hydrochloric acid solution

(1) Presented before the Organic Division, 132nd Meeting of the American Chemical Society, New York, September, 1957.

(2) Present address: Aerojet-General Corporation, Azusa, Calif.

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gave 1,1-dichloroacetone in low yield resulting from dehydrochlorination rather than dehydration.

EXPERIMENTAL

Preparation of 1,1,1-trichloro-2-propanol. Methylmagnesium bromide (2*M* solution in ether) was added to a cold ethereal solution of chloral. The hydrolyzed mixture was dried and distilled, b.p. 69–71°/25 mm., m.p. (from ligroin) 46–48°. The average yield of several preparations was 75%. The structure of this material was confirmed by nuclear magnetic resonance spectroscopy.

A. *Reaction with alumina.* The alcohol was heated and swept by means of a stream of nitrogen into a one-inch diameter glass tube packed with 8 mesh alumina. The tube was heated over the length of its packing by a tube furnace, one foot in length. The temperature of the reacting surfaces was maintained between 200–250°. The exit end of the tube was connected to a Dry Ice-cooled trap. At the conclusion of the reaction, the product in the trap was washed with water, dried, and distilled. The product thus obtained had the properties: b.p. 115°, n_D^{25} 1.4440. It was shown by infrared analysis to contain a carbonyl group, and a qualitative test for chloride ion following sodium fusion was positive.

Anal. Calcd. for $C_4H_4Cl_2O$: Cl, 55.8; C, 28.3. Found: Cl, 55.8; C, 28.8.

The 2,4-dinitrophenylhydrazone was prepared: m.p. (from ethanol) 110–112°.

Anal. Calcd. for $C_9H_8Cl_2N_4O_4$: N, 18.2. Found: N, 17.9.

The semicarbazone was prepared, and found to behave as follows on heating: sintering at 163°, melting with decomposition between 173–175°.

Anal. Calcd. for $C_4H_7Cl_2N_3O$: Cl, 36.5. Found: Cl, 35.8.

The yield of 1,1-dichloroacetone was poor, only 18 g. (0.14 mole, 28%) being obtained from 79 g. of the alcohol.

B. *Reaction with zinc chloride–hydrochloric acid.* A solution of zinc chloride (136 g., 1 mole) in concentrated hydrochloric acid (100 ml.) was prepared and a few grams of the alcohol was added. The mixture was heated to reflux and the remainder of the alcohol (82 g., 0.5 mole) was added slowly. After 5 hr. the mixture was distilled with steam. The organic layer was separated, dried, and distilled to yield 13.5 g. (21% yield) of 1,1-dichloroacetone, b.p. 115°, n_D^{25} 1.4440. The infrared spectrum of this material was superimposable on that obtained from the material from A above; a mixture of semicarbazone derivative with that from A melted without depression.

C. *Reaction with phosphorus pentoxide.* An intimate mixture of the alcohol (92 g., 0.56 mole) with excess phosphorus pentoxide was heated until no more distillation occurred. The resulting distillate was redistilled from phosphorus pentoxide then fractionally distilled. Three fractions were obtained: Fraction A (17 g.), b.p. 105–112°; Fraction B (13 g.), b.p. 112–115°; and Fraction C (34 g.), b.p. 115–116°, n_D^{25} 1.4790.

Fraction C was identified as 1,1,2-trichloro-1-propene by its physical properties and by comparison of its infrared spectrum with that from an authentic sample of 1,1,2-trichloro-1-propene.[6]

Fractions A and B were shown to contain, respectively, 69% and 80% 1,1,2-trichloro-1-propene by infrared analysis. The remainder of the material appeared to be a mixture of an acid chloride and anhydride.

The yield of 1,1,2-trichloro-1-propene was 69% based on the pure material in all fractions and 41% based on Fraction C alone.

DOW CORNING CORPORATION
FLUORINE RESEARCH LABORATORY
MIDLAND, MICH.

Cyclic Analogs of DDT-like Compounds

A. KALUSZYNER

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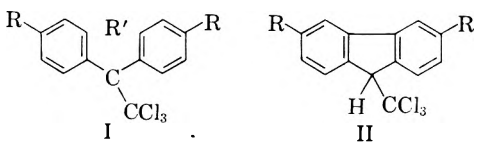
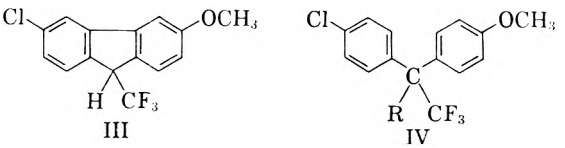
In view of the current theories on the correlation between geometrical structure and biological activity of the insecticides of the DDT group,[1] it seemed of interest to compare the insecticidal properties of 1,1-diaryl-2,2,2-trichloroethanes (I) and of the corresponding fluorenes (II). Unlike I, compounds of type II have a completely rigid molecular structure.





Attempts to prepare 9-trichloromethylfluorene (II, R = H) by chlorination of 9-methylfluorene, by addition of hydrogen chloride to 9-dichloromethylenefluorene or by reaction between 9-fluorenyl sodium and carbon tetrachloride, failed.[2] Another route we explored and which is analogous to the well known conversion of benzilic acid into 9-fluorene-carboxylic acid under the influence of aluminum chloride, is the reaction of the recently[3] described diphenyltrichloromethylcarbinol (I, R = H; R′ = OH) with aluminum chloride. While in benzene mainly tarry material was formed, the reaction in carbon disulfide as solvent gave, in addition to much polymeric material, a compound of m.p. 164–166°, which was identified as $\alpha,\alpha,\alpha',\alpha'$-tetrachlorobibenzyl. Analogous rearrangements are known.[4]

Eventually, 3 - chloro - 6 - methoxy - 9 - trifluoromethylfluorene (III) and 1-(*p*-chlorophenyl)-1-(*p*-methoxyphenyl)-2,2,2-trifluoroethane (IV, X = H) were used for the comparative experiments. The choice of (III) and (IV, R = H) seemed reasonable since replacement of the *para*-chlorine atoms in DDT by methoxyl groups does not destroy the insecticidal activity.[5]

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Compound (III) has been prepared before;[6,7] compound IV, R = H was obtained by the reduction of 1-(*p*-chlorophenyl)-1-(*p*-methoxyphenyl) 2,2,2-trifluoroethanol (IV, R = OH), which in turn was synthesized by the reaction between *p*-chloro-ω,ω,ω-trifluoroacetophenone and *p*-methoxyphenylmagnesium bromide.

Attempts to prepare (IV. R = H) by the reaction between 1 - (*p* - methoxyphenyl) - 2,2,2 - trifluoroethanol and chlorobenzene or between 1-(*p*-chlorophenyl)-2,2,2-trifluoroethanol and anisole in the presence of concentrated sulphuric acid, failed.

The biological tests carried out by Dr. A. S. Tahori (Israel Institute of Biological Research) showed that for a housefly strain of moderate resistance to DDT, compound IV was six to seven times more active (LD_{50} = 10–12γ per fly) than compound III (LD_{50} = 75γ per fly). Cyclization and the ensuing greater rigidity of the molecule thus reduce the insecticidal activity.

EXPERIMENTAL

Reaction of diphenyltrichloromethylcarbinol and aluminum chloride. To diphenyltrichloromethylcarbinol[3] (7.6 g.; 0.025 mol.) in carbon disulphide (90 ml.), anhydrous aluminum chloride (10 g.; 0.075 mol.) was added with stirring. The mixture was refluxed for 3 hr., cooled, and decomposed with ice, followed by cold water (100 ml.) and concentrated hydrochloric acid (50 ml.). The organic solution yielded on evaporation a brown solid (1.2 g.), which was treated with ethyl acetate, leaving 0.25 g. undissolved. The insoluble material did not melt at 300° and was not further investigated. The ethyl acetate solution was concentrated and the residue purified by sublimation. Colorless crystals melting at 164–166° were obtained; the compound was identified as α,α,α′,α′-tetrachlorobibenzyl[8] by mixed melting point.

p-Chloro-ω,ω,ω-trifluoroacetophenone. To the Grignard reagent prepared from *p*-bromochlorobenzene (144 g.; 0.75 mol.) and magnesium turnings (18.2 g.; 0.75 mol.) in ether (300 ml.), trifluoroacetic acid (28.5 g.; 0.25 mol.) in ether (70 ml.) was added at 5–10°. After decomposition with 5% hydrochloric acid, separation of the organic layer and distillation in a Todd column, the desired *ketone* (30.5 g.; 58%) was obtained, b.p. 182–184° (lit.[9]: b.p. 180–183°).

1-(p-Chlorophenyl)-1-(p-methoxyphenyl)-2,2,2-trifluoroethanol (IV, R = OH). To a solution of *p*-methoxyphenylmagnesium bromide, prepared from *p*-bromoanisole (28 g.; 0.15 mol.) in ether (70 ml.), toluene (35 ml.) was added, the ether removed and a solution of *p*-chloro-ω,ω,ω-trifluoroacetophenone (15.6 g.; 0.075 mol.) in toluene (35 ml.) added slowly. After the usual treatment, the *carbinol* (IV. R = OH) (15.6 g.; 66%) boiled at 170–173° (4 mm). The product was purified by chromatography on alumina (solvent: petroleum ether; eluent: ether-petroleum ether) and distilled again.

Anal. Calcd. for $C_{15}H_{12}ClF_3O_2$: C, 57.0; H, 3.8. Found: C, 56.9; H, 4.0.

1-(p-Chlorophenyl)-1-(p-methoxyphenyl)-2,2,2-trifluoroethane (IV, R = H). (a) A mixture of the *foregoing compound*, (IV, R = OH) (9.5 g.), glacial acetic acid (20 ml.), water (0.3 ml.), red phosphorus (3.0) and iodine (1.3 g.) was refluxed for 250 hr. The mixture was cooled, filtered, poured into water, neutralized with sodium bicarbonate solution, extracted with ether, and distilled. A slightly yellowish viscous oil (6.9 g.; 77%), b.p. 150–155° (2 mm.), was obtained. n_D^{25} 1.5440, d_{25}^{25} 1.324; MR, calcd. 71.87; MR, found, 71.64. The compound slowly crystallized from petroleum ether and melted at 50–51°.

Anal. Calcd. for $C_{15}H_{12}ClF_3O$: C, 60.0; H, 4.0. Found: C, 59.6; H, 3.9.

(b) *p*-Methoxy-ω,ω,ω-trifluoroacetophenone was prepared in 70% yield by the same procedure as the *p*-chloro compound; b.p. 115–120° (25 mm.) (lit.[10]): 70–70.5° (2 mm.)). Reduction of this compound with lithium aluminum hydride in ether gave a 79% yield of 1-(*p*-methoxyphenyl)-2,2,-2-trifluoroethanol, b.p. 102–103° (3 mm.); n_D^{30} 1.4740; (lit.[10]: b.p. 87–88° (1 mm.); n_D^{30} 1.4743). From the reaction of this product (5.2 g.) with concentrated sulfuric acid (50 ml.) and chlorobenzene (8 ml.), no defined products could be isolated.

(c) In the analogous condensation of 1-(*p*-chlorophenyl)-2,2,2-trifluoroethanol[9] with anisole (with or without acetic acid as diluent), only the starting materials were recovered.

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Dehalogenation in the Elbs Reaction

ERNST D. BERGMANN AND JOCHANAN BLUM

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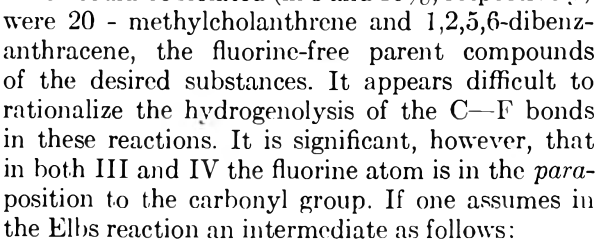
In the course of a study of fluoro-derivatives of carcinogenic polycyclic hydrocarbons[1], attempts were made to prepare 6-fluoro-20-methylcholanthrene (I) and 3-fluoro-1,2,5,6-dibenzanthracene (II) by pyrolysis (Elbs reaction) from 4-methyl-7-(4-fluoro-1-naphthoyl)hydrindene (III) and 4-fluoro - 2 - methyl - 1 - (2 - naphthoyl)naphthalene (IV), respectively. The only defined products which could be isolated (in 5 and 10%, respectively) were 20 - methylcholanthrene and 1,2,5,6-dibenzanthracene, the fluorine-free parent compounds of the desired substances. It appears difficult to rationalize the hydrogenolysis of the C—F bonds in these reactions. It is significant, however, that in both III and IV the fluorine atom is in the *para*-position to the carbonyl group. If one assumes in the Elbs reaction an intermediate as follows:



in accordance with Cook[2] and Fieser and Dietz,[3] the intermediate could tautomerize

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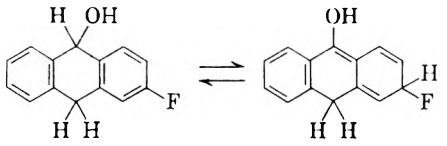
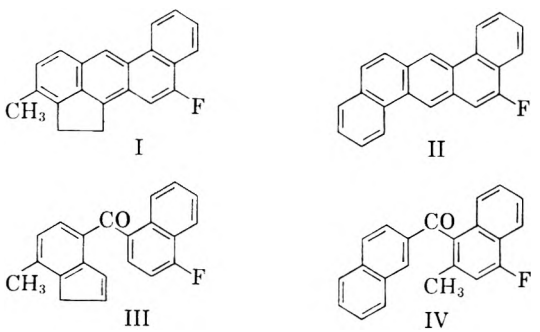


creating a nonaromatic fluorine atom and thus facilitating its elimination.[4] Similar schemes have been suggested in other abnormal reactions.[5]

It is recalled that the synthesis of the chloro- and methoxy-analogs of I also resulted at least very largely in the elimination of the substituents,[6] while 2- and 3-methoxy-[6-8] and 3-chloro-20-methyl-cholanthrene[8] could be obtained without difficulties.



EXPERIMENTAL

4-Methyl-7-(4-fluoro-1-naphthoyl)hydrindene (III). Following Fieser and Seligmann's work[9] for the synthesis of methylcholanthrene, 50 ml. of dry benzene and 17 g. of 4-methyl-7-cyanohydrindene[9] in 80 ml. of benzene were added to a Grignard solution prepared from 4 g. of magnesium and 27 g. of 4-fluoro-1-bromonaphthalene in 100 ml. of ether. The reaction mixture was refluxed and stirred for 12 hr. and decomposed with cold 18% hydrochloric acid. The organic solvents were then removed by steam distillation and the remaining imine hydrochloride of III was filtered and hydrolyzed by refluxing it for 3 hr. with a mixture of 100 ml. of hydrochloric acid, 200 ml. of water, 100 ml. of glacial acetic acid, and 120 ml. of toluene. The aqueous layer was extracted with toluene and the combined toluene solutions were treated with steam in the presence of 10% sodium hydroxide solution. A dark oil was obtained which was dissolved in benzene, dried, and distilled. The fraction boiling at 205° (0.5 mm.) was a viscous oil which crystallized quickly upon trituration with ether. From methanol, beautiful crystals of m.p. 123° were obtained. Yield, 22 g. (95%).

Anal. Calcd. for $C_{21}H_{17}FO$: C, 82.9; H, 5.6; F, 6.2. Found: C, 82.8; H, 5.7; F 6.0.

Pyrolysis. The foregoing ketone (18 g.) was pyrolyzed for 40 min. at 410°. The product was dissolved in benzene and flash-distilled under 2 mm. pressure after drying. Thus, 1.3 g. of a product was obtained which upon addition of ether to its benzene solution deposited yellow crystals (0.85 g.) of m.p. 180–181° (lit.[9] m.p. 179.5–180°). The analysis and properties showed that 20-methylcholanthrene had been isolated; yield, 5%.

Anal. Calcd. for $C_{21}H_{16}$: C, 94.0; H, 6.0. Found: C, 93.6; H, 6.0.

By working at somewhat lower temperatures (365°) one can raise the yield to about 15%, but even under these conditions no fluorine-containing substance could be isolated.

1-Fluoro-3-methylnaphthalene. The diazotization of 9 g. of 1-amino-3-methylnaphthalene hydrochloride, prepared by the reduction of the nitro-compound,[10] was carried out with 15 ml. of concentrated hydrochloric acid, 20 ml. of water, and 3.5 g. of sodium nitrite at 0°. To the clear solution, 10 ml. of 50% fluoboric acid was added and the precipitate filtered after 30 min. Thermal decomposition of the salt gave a dark oil which was dissolved in benzene, washed with alkali, dried, and distilled. B.p. 123° (20 mm.); yield, 5 g. (62%).

Anal. Calcd. for $C_{11}H_9F$: C, 82.5; H, 5.6; F, 11.8. Found: C, 82.3; H, 5.7; F, 11.7.

4-Fluoro-2-methyl-1-(2-naphthoyl)-naphthalene (IV). To a mixture of 4.5 g. of 1-fluoro-3-methylnaphthalene, 4.5 g. of 2-naphthoyl chloride, and 50 ml. of carbon disulfide, 4.5 g. of aluminum chloride was added. The mixture was stirred at 0° for 5 hr. and decomposed by addition of 20 ml. of cold 18% hydrochloric acid. Upon distillation with steam, a brown oil remained which crystallized after trituration with petroleum ether. The solid was treated with hot 10% sodium carbonate solution, dried, and recrystallized successively from glacial acetic acid and ethanol. Thus 7.2 g. (91%) of almost colorless crystals of m.p. 136° was obtained.

Anal. Calcd. for $C_{22}H_{15}FO$: C, 84.1; H, 4.8; F, 6.0. Found: C, 83.8; H, 5.0; F, 6.5.

Pyrolysis. The pyrolysis of 4 g. of the foregoing ketone was carried out at 420° for 1 hr. and the product flash-distilled at 2 mm. pressure. The distillate was dissolved in hot benzene and separated upon cooling as glistening, yellowish platelets of m.p. 260–262°. They were identified by analysis as 1,2,5,6-dibenzanthracene (lit.[7], m.p. 266°). Yield, 0.35 g. (10%).

Anal. Calcd. for $C_{22}H_{14}$: C, 95.0; H, 5.0. Found: C, 94.7; H, 5.4.

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JERUSALEM, ISRAEL

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Preparation of L-Xylose

E. DIMANT AND M. BANAY[1]

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L-Xylose has been prepared from D-glucose by Reichstein *et al.*[2] The preparation involved oxi-

(1) Part of a thesis to be submitted to the Senate of the Hebrew University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

dation of D-glucose to D-glucosaccharic acid, with subsequent reduction of D-glucosaccharic acid γ-lactone to L-gulonic acid γ-lactone, and degradation of the calcium salt of the latter acid with hydrogen peroxide to L-xylose.

Vargha[3] very markedly simplified the preparation of L-xylose by oxidizing 2,4-benzal-D-sorbitol with lead tetraacetate to 2,4-benzal L-xylose which was extracted from the oxidizing mixture with ethyl acetate and crystallized. Subsequent hydrolysis of the benzal moiety with 15% acetic acid resulted in the formation of the free sugar.

L-Xylose is a starting material in a chemical synthesis of L-ascorbic acid.[2] New interest in this sugar arose when it was found that the L-aldopentose sugar is an intermediate in the normal metabolic breakdown of L-ascorbic acid in the guinea pig.[4]

This note describes a simplified preparation of L-xylose from 2,4-benzal-D-sorbitol.

EXPERIMENTAL[5]

Benzal sorbitol. Benzal sorbitol was prepared according to the directions of Vargha.[3] One recrystallization from ethanol gave needles of m.p. 172–173°, yield 50–60% of theory.

L-Xylose. A 13.5-g. sample of 2,4-benzal-D-sorbitol (0.05*M*) was suspended in 50 ml. hot dioxane. Water, 50 ml., was added to the hot suspension with stirring, and warming was continued until all the solid had dissolved. After cooling to 35–45°, 100 ml. of 0.5*M* periodic acid solution was added, mixed well, and the solution kept in the refrigerator for 30 min. The excess periodate and iodate formed were reduced to iodide by bubbling a slow stream of hydrogen sulfide through the solution for approximately 45 min. The solution turned brown (iodine) and then colorless again with the appearance of a cake of sulfur and sometimes a drop or emulsion of benzaldehyde. The solution was decanted from the sulfur cake into an Erlenmeyer flask and the sulfur treated with a little hot water and hydrogen sulfide gas to extract the sugar derivative and reduce the iodine which adhered to the sulfur. This extraction was repeated twice.

Hydrolysis of 2,4-benzal-L-xylose was performed by immersing the combined water extracts in a boiling water bath for 1 hr. The cloudy solution obtained was decanted from a drop of oil (benzaldehyde) which settled to the bottom of the flask. Silver carbonate, 20 g., was added to the cooled solution to precipitate iodide ion. The suspension was swirled occasionally and usually left overnight. A filtered aliquot of the supernatant solution usually contained soluble silver ion and the *p*H of the solution rose to 5.0–6.0. The solution was boiled with carbon (Norit A) filtered by suction and the filtrate freed of silver ion with hydrogen sulfide. Vacuum filtration with carbon (Norit A) gave a clear, colorless solution, which was concentrated *in vacuo* to approximately 150 ml. The concentrate was sometimes cloudy and was extracted in liquid-liquid Soxhlet extraction apparatus for 24–48 hr. with freshly distilled ether. A slight white precipitate containing sulfur sometimes deposited during the ether extraction.

The extracted solution was treated with carbon (Norit A) and concentrated *in vacuo* (50°) to a sirup, which was dried in a desiccator over phosphorus pentoxide. After recrystallization from absolute ethanol and standing in the refrigerator, white prisms were obtained within 24 hr. Yield 6.2 g., 80% of the theoretical, m.p. 142°.

L-Xylose-2,4-dinitrophenylhydrazone. A suspension of 0.01*M* 2,4-dinitrophenylhydrazine (1.98 g.) in 200 ml. ethanol was added to 0.01*M* L-xylose (1.5 g.), dissolved in 5 ml. of water and refluxed for 12 hr. The solution was filtered when warm, kept at room temperature overnight and the clear solution was concentrated *in vacuo* to dryness. The residue thus obtained, a mixture of red plates and yellow needles, was extracted with 50 ml. of hot ethyl acetate and filtered. Upon recrystallization of the undissolved fraction from ethanol-water (1:1) red plates and yellow needles were formed. By fractional crystallization from ethanol-water (1:1) pure yellow needles, m.p. 165°, were obtained. The melting point of the D-isomer as recorded by Lloyd *et al.*[6] is 162–163°.

Anal. Calcd. for $C_{11}H_{14}O_8N_4$: C, 40.00; H, 4.24; N, 16.96. Found: C, 39.51; H, 4.01; N, 16.85. C, 39.81; H, 4.08, N, 16.80.

L-Xylose p-nitrophenylhydrazone. A 1.5-g. sample of *p*-nitrophenylhydrazine (0.01*M*) was dissolved in 100 ml. ethanol. To the clear solution 1.5 g. L-xylose (0.01*M*) was added and the solution was heated to boiling. The solution was kept at room temperature for 1 hr. and concentrated under reduced pressure to a crystalline mass. The crystals were washed with cold water, then with cold ethanol and recrystallized from ethyl acetate as prismatic needles, m.p. 152°.

Anal. Calcd. for $C_{11}H_{15}O_6N_3$: C, 46.31; H, 5.26; N, 14.73. Found: C, 46.46; H, 5.48; N, 14.70.

(L-xylo)-1,2,3,4-tetrahydroxybutylbenzimidazole hydrochloride (L-xylose benzimidazole hydrochloride). Barium L-xylonate was prepared according to the directions of Moore and Link.[7] A 1.7-g. sample of L-xylose yielded a white hygroscopic barium salt which was washed by three centrifugations in methanol. The salt was suspended in 20 ml. of water and a slight excess of 1*N* sulfuric acid was added. Precipitated barium sulfate was removed by centrifugation and the supernatant liquid was concentrated under reduced pressure. The sirup obtained was dissolved in ethanol (5 ml.). To the cloudy solution, 55 ml. *n*-butanol, 0.9 g. *o*-phenylenediamine dihydrochloride and 0.6 g. *o*-phenylenediamine were added, and the mixture was then refluxed for 8 hr.

The solution obtained after filtration was concentrated under reduced pressure to about 30 ml. The crystallization of L-xylo-benzimidazole hydrochloride was spontaneous; the crystals were twice crystallized from *n*-butanol as long prisms, m.p. 180°. $[n]^{20}_D$, −15.5° (*c*, 2; H_2O). Huebner *et al.*[8] report m.p. 181–182°, $[n]^{20}_D$, +17.3 (*c*, 2; H_2O), for the D-isomer.

Anal. Calcd. for $C_{11}H_{15}O_4N_2Cl$: C, 48.1; H, 5.5; N, 10.2. Found: C, 48.3; H, 5.5; N, 9.8.

DEPARTMENT OF BIOLOGICAL CHEMISTRY
THE HEBREW UNIVERSITY
JERUSALEM, ISRAEL AND
INSTITUTE FOR BIOLOGICAL RESEARCH
NES-ZIONIA, ISRAEL

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Instability of the Butenylcadmium Reagent

JAMES CASON AND RALPH FESSENDEN[1]

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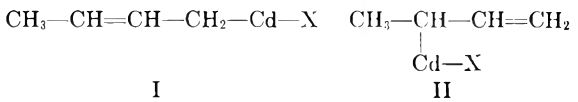
Although organocadmium reagents have found wide application for synthesis of ketones,[2] the only alkyl radicals which may be utilized satisfactorily are primary ones. Secondary or tertiary alkylcadmium reagents are too unstable,[3] even at 0°, to allow their effective use in synthesis. It seems probable that the principal route[4] of decomposition of the cadmium reagent involves dissociation to free radicals which disproportionate to a mixture of alkane and alkene. Although it would be predicted that the crotylcadmium reagent would be more prone to dissociate than an *n*-alkylcadmium reagent, because of resonance stabilization of the radical containing an allylic structure, the allyl type of reagent might still prove sufficiently stable for use in synthesis provided its structure involves only the primary radical (I or the dialkenylcadmium structure) and no equilibration with the secondary structure (II). The nuclear magnetic



I II

resonance spectrum of allylmagnesium bromide[5] has been interpreted as indicating an equilibrium between forms with either terminal carbon attached to magnesium; however, the ultraviolet spectrum of the Grignard reagent from cinnamyl bromide[6] has a form suggesting the primary structure analogous to I.

Since work in this laboratory has been concerned with utilization of the cadmium reagents in synthesis,[7] the stability of the butenylcadmium reagent has been examined. When the butenyl Grignard reagent was treated in the normal manner for conversion to a cadmium reagent,[2] and the reaction product was then treated with decanoyl chloride, the only higher-boiling products of the reaction appeared to be condensation products from the acid chloride. A preparation was then examined immediately after reaction of the Grignard reagent with cadmium chloride. Treatment of the solution with water at this point yielded only coupling products of the butenyl radicals, and no butene; therefore, it must be concluded that the butenylcadmium reagent, if it is formed as such, rapidly dissociates at the temperature of boiling ether. Since the butenyl radical is relatively stable to disproportionation, coupling results.

Preparation of the butenyl Grignard reagent at high dilution[8] gave about 75% yield of reagent, as judged by titration, and about 25% yield of coupling products. The mixture of isomeric octadienes (III, IV, V) obtained as coupling products in

$CH_2{=}CHCH(CH_3)CH(CH_3)CH{=}CH_2$ III
$CH_3CH{=}CHCH_2CH(CH_3)CH{=}CH_2$ IV
$CH_3CH{=}CHCH_2CH_2CH{=}CHCH_3$ V

this preparation has been separated by distillation and characterized in work by Young, Roberts, and Wax.[9] Gas chromatographic analysis was used in the present work to obtain the ratio between isomers which is recorded in Table I. Although the ratio of isomers differs somewhat from that obtained previously by distillation, the order of abundance of isomers is the same (IV>V>III). After the Grignard reagent had been treated with cadmium chloride, there was obtained 78% yield of octadienes, and it is of interest that the ratio of

TABLE I

ISOMER DISTRIBUTION IN MIXTURES OF OCTADIENES[a]

	Distribution of Isomers,[b] %		
	III	IV	V
Coupling product after preparation of Grignard reagent	11	55	34
Coupling product after reaction with cadmium chloride[c]	10 14.5	50 49	40 36.5
Previously reported[d] from Grignard reagent	2	88	10

[a] Undistilled samples or unfractionated distillates were used for injection into an 8 mm. o.d. × 2 m. gas chromatography column containing as partitioning agent about 5% di-2-ethylhexyl phthalate on 30–60 mesh Celite firebrick. At a temperature of 53°, with helium flow of about 50 ml./min., retention times (from time of injection to maximum in peak) for isomers III, IV, and V were respectively 2:33 (min., sec.), 3:00 and 4:26. [b] Per cent of an isomer reported is the per cent of the area under all bands represented by the area under the band for that isomer. Bands were assigned on the basis of the boiling points previously reported,[9] i.e. the lowest-boiling isomer was assigned to the band of shortest retention time. In addition, one run was partially separated by fractional distillation (*cf.* Experimental). [c] Results given first are from the slow reaction with cadmium chloride in a dilute solution in ether, while those given second are in more concentrated solution (*cf.* Experimental). [d] See ref. 9.

(1) Present address: Department of Chemistry, San Jose State College, San Jose, Calif.

(2) J. Cason, *Chem. Revs.*, **40**, 15 (1947); D. A. Shirley, *Org. Reactions*, Vol. 8, John Wiley and Sons, Inc., New York, 1954, p. 28.

(3) J. Cason and F. S. Prout, *J. Am. Chem. Soc.*, **66**, 46 (1944).

(4) J. Cason, G. Sumrell, and R. S. Mitchell, *J. Org. Chem.*, **15**, 850 (1950).

(5) J. E. Nordlander and J. D. Roberts, *J. Am. Chem. Soc.*, **81**, 1769 (1959).

(6) R. H. DeWolfe, D. L. Hagmann, and W. G. Young, *J. Am. Chem. Soc.*, **79**, 4795 (1957).

(7) For the preceding report in this field, *cf.* J. Cason and R. J. Fessenden, *J. Org. Chem.*, **22**, 1326 (1957).

(8) W. G. Young, A. N. Prater, and S. Winstein, *J. Am. Chem. Soc.*, **55**, 4908 (1933).

(9) W. G. Young, J. D. Roberts, and H. Wax, *J. Am. Chem. Soc.*, **67**, 841 (1945).

isomers (*cf.* Table I) is in essential agreement with that obtained during preparation of the Grignard reagent. Thus, whatever mechanism is involved in the reaction of butenylmagnesium bromide with butenyl bromide, the factors controlling isomer distribution give results quite similar to those resulting from coupling of the butenyl radical.

EXPERIMENTAL[10]

Butenyl Grignard reagent was prepared according to the procedure of Young, Prater, and Winstein[8] from 1.5 moles of magnesium turnings and 0.5 mole of crotyl bromide.[11] There was used a total of 1 l. of anhydrous ether, and the bromide was added during about 4 hr.

Titration[12] of the solution of Grignard reagent indicated yields, in several runs, between 70 and 80%. In one run, the solution of Grignard reagent was concentrated by distillation of about 75% of the ether. Within the limits of experimental error (±10%), the assay by titration remained unchanged.

In a run in which the Grignard reagent was decomposed with water soon after it had been prepared, there was a violent reaction and evolution of large quantities of gas (not trapped). Work-up of the ether solution and distillation yielded 8.1 g. (25%) of a mixture of octadienes, b.p. 99–124°. This mixture was subjected to analysis by gas chromatography, with the results reported in Table I; no crotyl bromide was present. The infrared spectrum of the octadiene mixture exhibited absorption bands at the following wave lengths (μ): 3.32, 3.41 (doublet), 6.05, 6.82, 7.00, 7.25, 10.04, 10.32, 10.95.

Reaction of the butenyl Grignard reagent with cadmium chloride. A solution of Grignard reagent prepared as described above was transferred under nitrogen pressure to another flask in order to remove the large excess of magnesium. Assay of the transferred solution by titration was the same within experimental error (±3%) as before transfer. After there had been added over a 3-min. period 0.43 mole of anhydrous cadmium chloride, the mixture was stirred and heated under reflux until the Gilman test for Grignard reagent had become negative.[13] Titration[12] of the mixture after this period showed the presence of no material-consuming acid.

To the mixture was added 100 ml. of water, then the ether layer was separated, washed with water, and dried with magnesium sulfate. The bulk of the ether was removed by fractional distillation and the residue was subjected to analysis by gas chromatography (*cf.* Table I). Distillation[10] yielded a total of 21.7 g. (78%) of octadienes, b.p. 99–124°. This material was distributed in three main fractions: (1) b.p. 99–109°, n_D^{25} 1.4154–1.4209; (2) b.p. 110–114°, n_D^{25} 1.4233–1.4259; (3) b.p. 118–124°, n_D^{25} 1.4302–1.4309. For the isomeric octadienes (*cf.* formulas in text) there have been reported:[9] (III) b.p. 102°, n_D^{20} 1.4211; (IV) b.p. 111°, n_D^{20} 1.4240; (V) b.p. 124°, n_D^{20} 1.4336. Gas chromatography of the three fractions showed incomplete separation, as would be judged from the boiling point range; however, bands for only three components were observed, and the major band in each fraction was that expected from a correlation of retention time with boiling point.

The infrared spectrum of this mixture of octadienes was nearly identical with that exhibited by the mixture obtained directly from the preparation of Grignard reagent.

In one run, before cadmium chloride was added, a gas absorption line was arranged so that any exit gases would pass through two tubes of bromine thermostatted at 30° and then through a trap cooled in Dry Ice. Periodically, the flask and train were flushed with nitrogen. After the negative test for Grignard reagent had been obtained, the bromine was decomposed with sodium bisulfite; no water insoluble material was obtained. Also, no liquid was retained by the cold trap. A new absorbing train was put in place before water was added to the mixture. Again, no volatile gases were recovered.

In the run in which reaction with cadmium chloride was accelerated by concentration of the ether solution, results were essentially the same as when the dilute solution was utilized. Analysis of the octadiene mixture is included in Table I.

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BERKELEY, CALIF.

(10) Boiling points are uncorrected; distillations were through a 65 cm. column of the simple Podbielniak design (*cf.* J. Cason and H. Rapoport, *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., Englewood Cliffs, 1950, p. 237). Infrared spectra were recorded on a Baird spectrophotometer, using thin films.

(11) Gas chromatography of the "crotyl" bromide on silicone grease as partitioning agent indicated a composition of 11% methylallyl bromide and 89% crotyl bromide. Since the Grignard reagents from these two bromides have been found to be indistinguishable [*cf.* R. H. DeWolfe and W. G. Young, *Chem. Revs.*, **56**, 735 (1956)], it was deemed not worthwhile to separate the minor content of methylallyl bromide.

(12) H. Gilman, P. D. Wilkinson, W. P. Fishel, and C. H. Meyers, *J. Am. Chem. Soc.*, **45**, 150 (1923).

(13) The cadmium reagent gives a negative result in this test [*cf.* H. Gilman and J. F. Nelson, *Rec. trav. chim.*, **55**, 518 (1936)]. In the dilute solution in which the Grignard reagent was prepared, about 12 hr. elapsed before the test was negative, but in a run in which the solution was concentrated to one-fourth volume the test became negative after about 30 min. under reflux. The slow reaction with cadmium chloride in dilute ether solution has been noted on several previous occasions in this laboratory.

Preparation and Spectra of Some Dinitroparaffins

J. K. STILLE AND EUGENE D. VESSEL[1]

Received November 4, 1959

The only method reported in the literature for preparing α,ω-dinitroparaffins has been the classical Victor Meyer reaction in which the appropriate diiodoalkane was treated with silver nitrite in an ethereal solution.[2] A recent study has demonstrated, however, that this reaction is really useful only for the synthesis of primary nitroparaffins.[3] This note describes the preparation and spectra of a series of α,ω-dinitroparaffins and a comparable secondary dinitro compound.

The α,ω-dinitroparaffins can be successfully prepared by treating the appropriate dibromoalkane with sodium nitrite in *N,N*-dimethylformamide:

(1) This investigation was supported in part by a Research Grant from Socony Mobil Oil Company, Inc., Paulsboro, New Jersey.

(2) H. Feuer and G. Leston, *Org. Syntheses*, **34**, 37 (1954).

(3) N. Kornblum, B. Taub, and H. Ungnade, *J. Am. Chem. Soc.*, **76**, 3209 (1954); N. Kornblum, R. Smiley, H. Ungnade, A. White, and S. Herbert, *J. Am. Chem. Soc.*, **77**, 5528 (1955).

TABLE I

Dinitroparaffin	Yield,[a] %	M.P.	B.P.	n_D^{20}	Infrared (NO_2)	Cm.$^{-1}$
1,6-Dinitrohexane	42	36–37°[b]	100–103°/0.3 mm.		1550	1385
1,5-Dinitropentane	29		113–115°/0.2 mm.[c]	1.4597[c]	1550	1383
1,4-Dinitrobutane	33	33.5–34.5°[d]			1550	1379
1,3-Dinitropropane	6		100–101°/0.5 mm.[e]	1.4635[e] (25°)	1550	1385
2,5-Dinitrohexane[f]	7	51–52°			1538	1389 1357 1317

[a] Pure compound. [b] Lit.[2] m.p. 36.5–37.5°. [c] Lit.[2] b.p. 134°/1.2 mm., n_D^{20} 1.4610. [d] Lit.[2] m.p. 33–34°. [e] Lit.[12] b.p. 103°/1.0 mm., n_D^{25} 1.4638. [f] *Anal.* Calcd. for $C_6H_{12}N_2O_4$: C, 40.90; H, 6.87; N, 15.90. Found: C, 41.02; H, 6.96; N, 15.61.

$$R\text{--}CH(CH_2)_nCH\text{--}R \xrightarrow[D.M.F.]{NaNO_2} R\text{--}CH(CH_2)_nCH\text{--}R$$

(Br, Br → NO_2, NO_2)

R = H, CH_3 n = 1 – 4

The yields of pure products decrease with decreasing size of the alkyl portion of the molecule and a low yield is observed in the preparation of the secondary dinitroparaffin, 2,5-dinitrohexane. Apparently steric hindrance plays an important role in this reaction and thus reduces the applicability of the procedure for the lower members of the series.[4] (Table I). The preparation of 1,6-diiodo-1,6-dinitrohexane is also described.

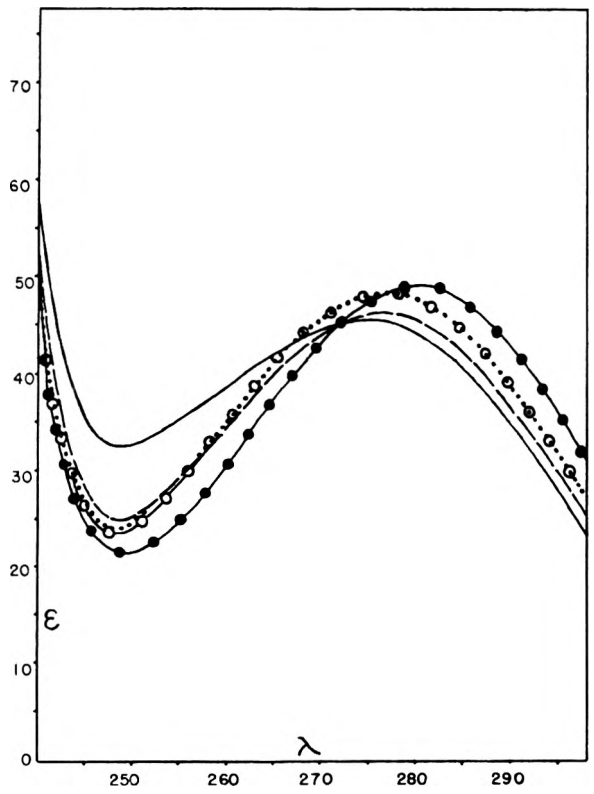

Fig. 1. Ultraviolet spectra of dinitroparaffins in 95% ethanol

—— 1,3-Dinitropropane —○— 1,6-Dinitrohexane
— — 1,4-Dinitrobutane —●— 2,5-Dinitrohexane
..... 1,5-Dinitropentane

(4) D. Mooberry, Ph.D. Thesis, Purdue University (1954).

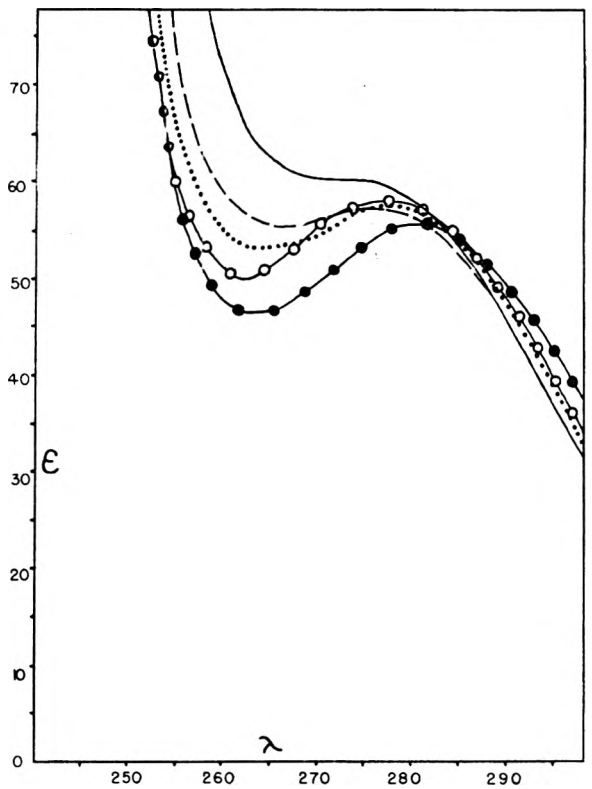

Fig. 2. Ultraviolet spectra of dinitroparaffins in dioxane

—— 1,3-Dinitropropane —○— 1,6-Dinitrohexane
— — 1,4-Dinitrobutane —●— 2,5-Dinitrohexane
..... 1,5-Dinitropentane

Aliphatic nitroparaffins are characterized by a low intensity, broad absorption band in the ultraviolet region at 270–280 mμ and a second high intensity band which lies below 200 mμ.[5,6] No fine structure is observed in the 280 mμ band. Solvent effects on the ultraviolet spectra of nitroparaffins and for nitromethane.[6,7] In those studies benzene, toluene, and dioxane were "active" solvents and increased the intensity of absorption as compared with a series of nonactive solvents. This perturbation has been considered to arise

(5) R. Hazeldine, *J. Chem. Soc.*, 2525 (1953).
(6) N. Bayliss and C. Brackenridge, *J. Am. Chem. Soc.*, **77**, 3959 (1955).
(7) H. Ungnade and L. Kissinger, *J. Org. Chem.*, **22**, 1088 (1957).
(8) G. Kortum, *Z. Electrochem.*, **47**, 55 (1941).

either from a 1:1 complex formation with the solvent or from a direct physical perturbation.

In this investigation the ultraviolet spectra of the series of dinitroparaffins prepared were observed in both 95% ethanol (Fig. 1) and in dioxane (Fig. 2). The molar absorbtivities of these compounds were approximately twice as great as those reported for similar mononitroparaffins, indicating that the nitro groups absorb independently with little or no interaction in the molecule. Both bathochromic and hyperchromic shifts were observed with increasing chain length in the series. Less solvent perturbation occurs with secondary nitroparaffins than with similar primary compounds. No absorption band was observed near 380 mμ when ethanol was used as solvent and therefore it appears that no ionization of these compounds in the solvents studied occurs.[8] Thus the α,ω-dinitroalkanes are considerably weaker acids than either nitromethane or the *gem*-dinitro compounds.

In the case of *gem*-dinitroparaffins, the molar absorptivity is increased by the active solvents to the extent that the 280 mμ band was completely submerged.[7] With this series of α,ω-dinitroparaffins, the molar absorptivities were increased only slightly (9–10 absorptivity units) when dioxane was employed as solvent. Of those compounds examined, 1,3-dinitropropane appears to be the strongest acid in the series. This would indicate that solvent perturbation in the case of *gem*-dinitro compounds (stronger acids) involves a considerable amount of 1:1 complex formation. However, the small amount of solvent perturbation of α,ω-dinitroparaffins is probably the result of active solvent molecules forming a cage in close proximity to and surrounding the solute (a physical perturbation).

Electrolyses of aqueous solutions of the *aci*-salt of 1,6-dinitrohexane using a procedure described by Bahner were unsuccessful in an attempt to prepare 1,2-dinitrocyclohexane via oxidative ring closure.[9]

EXPERIMENTAL

The dinitroalkanes (Table I) were prepared essentially by the modified Victor Meyer procedure.[10] A representative procedure is described for the preparation of 1,6-dinitrohexane.

1,6-Dinitrohexane. To 1.5 l. of freshly distilled dimethylformamide at 0° were added, with stirring, 180 g. (3.0 mol.) of dry urea, 180 g. (2.61 mol.) of dry sodium nitrite, and 146.4 g. (0.6 mol.) of redistilled 1,6-dibromohexane. The mixture was allowed to stir at 0° for 90 min. after which time 160 g. (1.27 mol.) of anhydrous phloroglucinol was added to scavenge the nitrite esters formed. The reaction mixture was allowed to warm to room temperature over a period of 24 hrs. The mixture was then poured into 1 l. of crushed ice and extracted with methylene chloride. The extracts were washed with water and a saturated salt solution, and then dried. The solvent was removed under reduced pressure and the residual liquid was fractionally distilled, b.p. 100–103°/0.3 mm. The distillate recrystallized from absolute methanol at −78°.

1,6-Diiodo-1,6-dinitrohexane. To a cold solution of 8.4 g. (0.38 mol.) of the disodium salt of 1,6-dinitrohexane, (prepared from the reaction of 1,6-dinitrohexane with sodium methoxide in methanol) in 75 ml. distilled water was added a cold solution of 11.4 g. (0.07 mol.) sodium iodide and 19.2 g. (0.07 mol.) iodine in 100 ml. water.[11] Decolorization of the iodine solution was instantaneous and was accompanied by the formation of a light yellow finely divided precipitate. The precipitate was removed by filtration and washed with a cold solution of sodium iodide and several portions of water to yield 10.4 g. (64%) of impure 1,6-diiodo-1,6-dinitrohexane. The product was recrystallized from petroleum ether (30–60°), from ethanol-water and from carbon tetrachloride to yield pure product, m.p. 68.5–69.5°. The compound gave a positive qualitative test for iodine.

Anal. Calcd. for $C_6H_{10}N_2O_4I_2$: C, 16.83; H, 2.36. Found: C, 16.70; H, 2.21.

Ultraviolet absorption spectra. The ultraviolet absorption spectra were determined for freshly prepared 2–3 × 10^{-2} molar solutions in purified solvents with a Cary Model 11 recording spectrophotometer. Cell corrections, determined with pure solvent, were subtracted from the absorbancy values.

STATE UNIVERSITY OF IOWA
IOWA CITY, IOWA

(9) C. Bahner, U. S. patent **2,485,803**, Oct. 25, 1949; *Chem. Abstr.*, **44**, 2876 (1950).

(10) N. Kornblum, H. Larson, R. Blackwood, D. Mooberry, E. Eliveto, and G. Graham, *J. Am. Chem. Soc.*, **78**, 1497 (1956).

(11) L. Seigle, Ph.D. Thesis, Purdue University (1939).

(12) J. Kispersky, H. Hass, and D. Holcomb, *J. Am. Chem. Soc.*, **71**, 516 (1949).

Structure and Spectra. I. Ultraviolet Absorption Spectra of 2,4-Dinitrophenylhydrazones of Aliphatic Dienones and Styryl Ketones

SAMUEL YAROSLAVSKY

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The ultraviolet absorption spectrum of 2,4-dinitrophenylhydrazones of saturated and α,β-unsaturated carbonyl compounds is characterized by two distinct bands at 250–260 mμ and 350–400 mμ. The absorption of the 2,4-dinitrophenylhydrazones of styryl ketones, where the α,β-olefinic bond is conjugated to an aryl moiety, has now been examined. In every case a third maximum was observed at 300–310 mμ, not as a shoulder on the two other bands, but as a separate band, usually having an absorption intensity lower than the other two.

The spectra of some 2,4-dinitrophenylhydrazones of styryl ketones are reported in Table I, and some examples are described in Fig. 1. It is seen that the K-bands fall in the region 390–400 mμ, which is beyond that found by Braude and Jones[1] for

(1) E. A. Braude and E. R. H. Jones, *J. Chem. Soc.*, 498 (1945).

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF 2,4-DINITROPHENYLHYDRAZONES OF STYRYL KETONES mμ[a]

2,4-Dinitrophenylhydrazone of	Formula	First Band		K-Band		Third Band	
		λ_{max}	ϵ	λ_{max}	ϵ	λ_{max}	ϵ
Benzalacetone[b]	I	258	15,600	395	40,100	307	14,800
Benzalacetophenone[c]	II	257	28,000	397	40,000	307	22,300
5-Carbethoxy-3-phenyl-2-cyclopentenone-2-acetic acid[d]	III	263	30,000	390	32,500	301	15,300
Ethyl 3-phenyl-2-cyclopentenone-2-acetate[d]	IV	268	23,000	395	34,000	300	15,800
Ethyl 3-β-naphthyl-2-cyclopentenone-2-acetate[e]	V	263	25,000	400	36,000	314	12,500

[a] All measurements were made in chloroform, using a Beckman DU spectrophotometer. [b] N. L. Drake and P. Allen Jr., *Org. Syntheses*, Coll. Vol. I, 77 (1951). [c] E. P. Kohler and H. M. Chadwell, *Org. Syntheses*, Coll. Vol. I, 78 (1951). [d] E. D. Bergmann, S. Yaroslavsky, and H. Weiler-Feilchenfeld, *J. Am. Chem. Soc.*, 81, 2775 (1959). [e] E. D. Bergmann and S. Yaroslavsky, unpublished results.

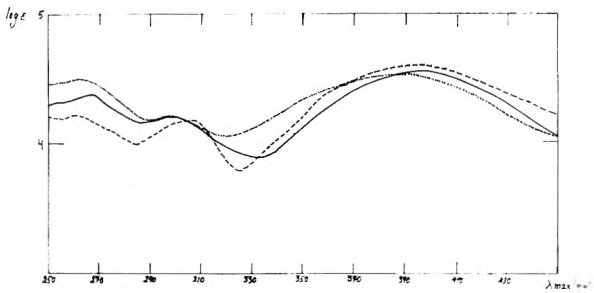


Fig. 1. Ultraviolet absorption spectra of 2,4-dinitrophenylhydrazones of styryl ketones: I ----. III ····. IV ——.

2,4 - dinitrophenylhydrazones of α,β - unsaturated carbonyl compounds. The characteristic shift to longer wave lengths and the appearance of a third ultraviolet absorption band constitute two criteria which may help identify the 2,4-dinitrophenylhydrazones of styryl ketones.

The spectra of the 2,4-dinitrophenylhydrazones of the aliphatic dienone system have been examined by Braude and Jones.[1] The K-bands fall in the region 390–400 mμ, found by us characteristic for the 2,4-dinitrophenylhydrazones of styryl ketones. As for the appearance of a third band, the results are summarized in Table II. In some cases there appears a third ultraviolet band, while in others not. A careful examination of the latter cases will reveal the rule in the dienone system.

TABLE II

A THIRD BAND IN THE ULTRAVIOLET SPECTRA OF THE 2,4-DINITROPHENYLHYDRAZONES OF ALIPHATIC DIENONES (mμ)

2,4-Dinitrophenylhydrazone of	Formula	Third Band
$CH_3CH{=}C(CH_3)CH{=}CHCHO$	VI	308
Furfural	VII	302
ψ-Ionone	VIII	309
β-Ionone	IX	—
$C(CH_3)_2{=}CHCOCH{=}C(CH_3)_2$	X	—
Benzophenone	XI	—

Compound X is not a 2,4-dinitrophenylhydrazone of a normal (long-chained) dienone, but of a cross-conjugated one. According to Woodward[2] and Ruzicka[3] cross-conjugated dienones absorb approximately as α,β-unsaturated ketones, that is about 50 mμ lower than the normal dienones.[4] Therefore 2,4-dinitrophenylhydrazones of cross-conjugated dienones should show the same spectral properties as those of α,β-unsaturated ketones.

Benzophenone, carrying a phenyl group on each side of a carbonyl radical, has the properties of a cross-conjugated dienone. Indeed, its absorption maximum (252 mμ[5]) falls in the region of α,β-unsaturated ketones.

We may therefore conclude that every 2,4-dinitrophenylhydrazone of a normal dienone system (in contrast with 2,4-dinitrophenylhydrazones of a cross-conjugated one) shows a third band in the ultraviolet absorption spectrum. The only exception is the absorption of the 2,4-dinitrophenylhydrazone of β-ionone. But as this ketone shows many other abnormal properties (*e.g.*, the K-band of its 2,4-dinitrophenylhydrazone is about 20 mμ lower than that of ψ-ionone,[1] and the K-band of its semicarbazone is about 25 mμ lower than that of ψ-ionone[6]) it cannot upset the rule.

One would expect longer conjugated 2,4-dinitrophenylhydrazones to contain the third band, too. Indeed the 2,4-dinitrophenylhydrazones of the two trienones furfurylidene diethyl ketone and 2,4,6-octatrienal cited by Braude and Jones,[1] do show this band.

DEPARTMENT OF ORGANIC CHEMISTRY
THE HEBREW UNIVERSITY
JERUSALEM, ISRAEL

(2) R. B. Woodward, *J. Am. Chem. Soc.*, **62**, 1208 (1940); **63**, 1123 (1941).
(3) L. Ruzicka *et al.*, *Helv. Chim. Acta*, **21**, 1735 (1937).
(4) *Cf.* E. A. Braude and F. C. Nachod, *Determination of Organic Structures by Physical Methods*, Academic Press, N. Y., 1955, p. 155, Table 10.
(5) H. Ley and H. Wingchen, *Ber.*, **67**, 501 (1934).
(6) A. Burawoy, *J. Chem. Soc.*, 20 (1941).

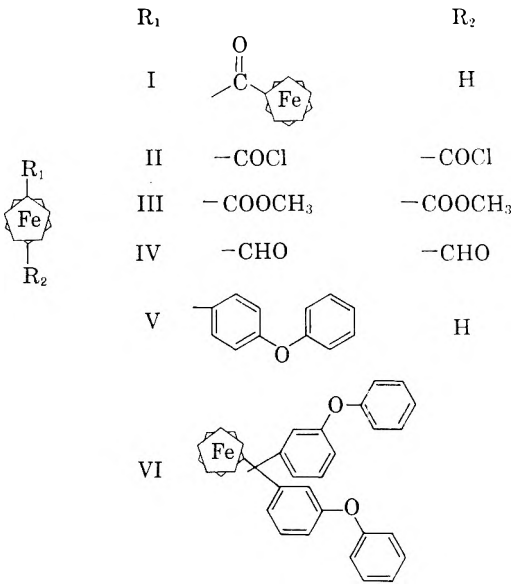
Some Oxygen-Containing Ferrocenes

STANLEY I. GOLDBERG[1]

Received June 18, 1959

In connection with this Laboratory's research program, the oxygen-containing ferrocene derivatives, I–VI, were prepared. Of these only IV, V and VI have not been previously described.

Present interest in the known compounds, I, II and III, lies in the methods used to prepare them. Thus, I[2] was obtained from treatment of ferrocene with oxalyl chloride in the presence of aluminum chloride. Preparation of I by this reaction[3] is analo-



gous to the similar reaction of benzene which yielded diphenylketone.[4]

The diacid chloride, II, was obtained from treatment of ferrocenedicarboxylic acid with PCl_3. Use of this reagent instead of the more conventional reagents, PCl_5 or $SOCl_2$, gave II in almost quantitative yield with no sign of decomposition.[5] Successful preparation of II was shown by treatment of the crude product with methanol followed by isolation and characterization of the known diester, III. The yield, therefore, is reported for the pure diester derivative.

While several accounts of the preparation of formylferrocene have appeared in the literature[6,7,8,9], preparation of 1,1′-diformylferrocene (IV) has not been reported. In the present work, II was treated with lithium tri-*tert*-butoxyaluminohydride, a reagent known to effect conversion of acid chlorides to the corresponding aldehydes.[10] Although it was not possible to obtain a pure sample of IV, its existence was strongly indicated by the infrared spectrum prepared from the crude material. No absorption was present in the O—H stretching region, while a strong band at 6.00 μ was observed. Infrared absorption of the carboxyl-carbonyl in 1,1′-ferrocenedicarboxylic acid, the starting material, occurs at 6.12 μ,[11] while that of the aldehyde-carbonyl in formylferrocene is reported as occurring at 5.91 μ,[6] 5.95 μ,[7] 5.9–6.0 μ[8] and 6.02 μ.[9] Additional evidence which showed the product not to be the starting diacid was its total insolubility in aqueous base.

Compound V, obtained *via* treatment of ferrocene with diphenyl ether-4-diazonium chloride, was of interest because it gave rise to an infrared spectrum (KBr disc) which possessed a band near 9 μ but not near 10 μ (9–10 Rule[12]). When the spectrum was obtained from a carbon disulfide solution of V, however, both the 9-band and the 10-band were present; so that the absence of the 10-band in the former case was attributed to a solid state effect, and not to an inconsistency with the 9–10 Rule.

Compound VI was prepared by the same technique as was V. In this case the diazonium salt of 3-phenoxyaniline was used, and the product obtained, VI, contained two phenoxyphenyl substituents. Presence of absorption at 9 and 10 microns in the infrared spectrum of the liquid compound showed it to possess an unsubstituted cyclopentadienyl ring.[12]

EXPERIMENTAL[13]

Reaction of Oxalyl Chloride and Ferrocene. Diferrocenylketone (I). To a vigorously stirred solution of ferrocene (5.58 g.; 30 m.moles) and 50 ml. of pure dry methylene dichloride, cooled to 0°, was added anhydrous aluminum chloride (2.67 g.; 20 m.moles) in small portions over a 1 hr. period. A cold (0°) solution of oxalyl chloride (1.27 g.; 10 m.moles) and 50 ml. of methylene chloride was slowly added (1 hr.) to the above described suspension. The dark violet colored reaction mixture was stirred while it gradually reached room temperature (approx. 2 hr.). After the mixture was rapidly poured onto 100 ml. of crushed ice and water, it was phase

(1) Present Address: Department of Chemistry, University of Illinois, Urbana, Illinois.

(2) E. Csendes in M. Rosenblum's Doctoral Dissertation, Harvard University, 1953.

(3) R. Riemschneider and D. Helm, *Chem. Ber.*, **89**, 155 (1956), reported that no reaction occurred between ferrocene and oxalyl chloride in the presence of aluminum chloride.

(4) H. Staudinger, *Chem. Ber.*, **41**, 3558 (1908).

(5) After the completion of this work, A. N. Nesmeyanov and O. A. Reuton, *Doklady Akad. Nauk S. S. S. R.*, **120**, 1267 (1958), described a very similar procedure for the preparation of II.

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(7) M. Rosenblum, *Chem. and Ind. (London)*, 72 (1957).

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separated. The organic phase (deep red) was dried and evaporated to a mass of orange-red colored crystalline material from which unchanged ferrocene was separated by means of vacuum sublimation. The red-colored residue, after chromatography on alumina followed by several recrystallizations from benzene, gave rise to pure I (200 mg., 0.5%), m.p. 206.5–207.0° (liter, 206–208°[2]). This product, when melted in admixture with a sample of I, prepared *via* the Friedel-Crafts Reaction of ferrocene and ferrocenoyl chloride,[14] exhibited no melting point depression; and, both materials gave rise to identical infrared spectra.

Anal. Calcd. for $C_{21}H_{18}Fe_2O$: C, 63.39; H, 4.56; Fe, 28.1. Found: C, 63.34; H, 4.47; Fe, 28.9.

1,1'-Bis(chlorocarbonyl)-ferrocene (II). 1,1'-Ferrocenedicarboxylic acid (276 mg.; 1.0 m.moles) was added to an excess of PCl_3 (approx. 10 ml.), and heated in an atmosphere of dry nitrogen under reflux during 24 hr. At the end of that time—the diacid was dissolved and the reaction mixture assumed a deep red-coloration—the excess PCl_3 was evaporated *in vacuo*, and the red solid residue obtained was cooled to 0°. The crude II was carefully treated with methanol—a procedure which gave rise to a vigorous reaction, including evolvement of HCl gas. The reaction mixture was evaporated to dryness *in vacuo*, and the solid residue obtained was found to be completely insoluble in aqueous base. It did, however, dissolve in ether, and no trace of the ether-insoluble ferrocene diacid was observed. The ethereal solution was evaporated to a red-colored residue which, when chromatographed on alumina, yielded, from the benzene-methanol (50:1) eluant, II (265 mg.; 88%). The product was recrystallized from cyclohexane and gave orange-red colored needles, m.p. 114.0–114.6° (lit., 116.5–117.5°,[15] 114–115°[16,17,18]).

Anal. Calcd. for $C_{14}H_{14}FeO_4$: C, 55.66; H, 4.67. Found: C, 55.67, 55.56; H, 4.81, 4.69.

1,1'-Diformylferrocene (IV). 1,1'-Ferrocenedicarboxylic acid (2.76 g.; 10.0 m.moles) was converted to II as described above. The crude product, free of PCl_3 and dissolved in 50 ml. of pure dry diglyme,[19] was cooled to −78° by means of a Dry Ice–acetone bath, and slowly treated with a cold (−78°) solution of lithium tri-*tert*-butoxyaluminohydride[10] (30 m.moles) and 15 ml. of diglyme during 1 hr. The mixture, vigorously agitated by means of a magnetically operated stirrer, was allowed to warm to room temperature and remain overnight. Addition of 200 ml. of a mixture of crushed ice and water produced a mass of red crystalline precipitate which was collected and triturated with several portions of dilute sodium hydroxide solution to remove any unreacted ferrocene diacid. After the residue was washed with water to free it of residual base, it was treated with portions of hot ethanol (total volume, approx. 300 ml.) which eventually dissolved all but a trace of the material. The ethanolic solution was evaporated to a red crystalline residue, presumed to be crude IV (1.75 g., 73%). This product decomposed when heated above 200°. Its infrared spectrum (KBr disc) was found to be different from that of the starting diacid. The material was so difficultly soluble in the variety of solvents tried, that a large volume of solvent (methanol or ethanol were best) was necessary to dissolve a small sample. Crystallization under these conditions could not be induced. Attempts to purify the product by means of vacuum sublimation only resulted in its decomposition. Preparation of a pure sample for combustion analysis was not possible, and analysis of the crude material gave equivocal results.

4-Ferrocenyldiphenyl Ether (V). A solution of 4-aminodiphenyl ether[20] (2.97 g.; 16 m.moles) and 175 ml. of water containing 10 ml. of conc. HCl, cooled to −5°, was treated with sodium nitrite (1.28 g.; 17.5 m.moles) to form the diazonium salt from the amine. The temperature of the reaction mixture was not allowed to rise above 0°, excess nitrous acid was destroyed by addition of urea and the mixture finally neutralized with sodium acetate solution. This solution of diazonium salt was then rapidly added to a cold (0°) ethereal solution of ferrocene (3.36 g.; 16 m.moles) and vigorously stirred during 30 min. After the blue-black colored reaction mixture was allowed to warm to room temperature (40 min.), it was phase-separated. The deep blue colored aqueous phase was treated with zinc and conc. HCl until the blue coloration, characteristic of the presence of ferricium ion,[21] was discharged. Ether extraction of the *leuco*-aqueous mixture yielded 1.89 g. of a soft dark-colored substance which was combined with similar material (2.32 g.) obtained by evaporation of the original ether phase. This crude product was then submitted to continuous extraction by petroleum ether (40–50°) in a Soxhlet Apparatus during 5 days.

Evaporation of the petroleum ether extract yielded a residue of orange-colored crystalline material (3.19 g.) from which unchanged ferrocene (1.39 g.) was sublimed. Several recrystallizations of the sublimation-residue from *n*-propanol raised its melting point from 125–127° to 129.5–130.5°, and afforded pure V (1.74 g.; 31%).

Anal. Calcd. for $C_{22}H_{18}FeO$: C, 74.60; H, 5.12. Found: C, 74.68, 74.61; H, 5.08, 5.00.

Bis(3-phenoxyphenyl)-ferrocene (VI). A solution of 3-phenoxyaniline[22] (3.70 g.; 20 m.moles) in 15 ml. of water containing 50 m.moles of conc. HCl was diazotized as described above. The solution of diazonium salt was rapidly added to a cold (0°) solution of ferrocene (3.72 g.; 20 m. moles) in 70 ml. of ether. The reaction mixture was worked up as in the previous case, and the partially purified product, VI, was obtained from a column-chromatogram of the crude reaction product. Pure VI (883 mg.; 8.5%) was collected after two molecular distillations in a Späth Bulb. The red-colored fluid slowly vaporized at 150° under a pressure of 0.05 mm.

Anal. Calcd. for $C_{34}H_{26}FeO_2$: C, 78.17; H, 5.02; Fe, 10.7. Found: C, 77.82; H, 5.21; Fe, 11.0.

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WRIGHT AIR DEVELOPMENT CENTER
WRIGHT-PATTERSON AIR FORCE BASE, OHIO

(14) Unpublished data of M. Rausch, Monsanto Chemical Co., Dayton, Ohio.

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(20) Prepared by means of the reduction of 4-nitrodiphenyl ether according to the procedure reported by Hazlet and Dornfeld, *J. Chem. Soc.*, 1781 (1944).

(21) The oxidized form of ferrocene, or the dicyclopentadienyl iron (III) cation.

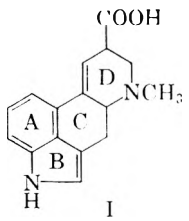
(22) Obtained from The Merck Chemical Co., Rahway, N. J.; m.p. 37.8–38.2°.

Communications TO THE EDITOR

New Synthetic Approach to Benzo[f]quinolines and Dihydrolysergic Acid

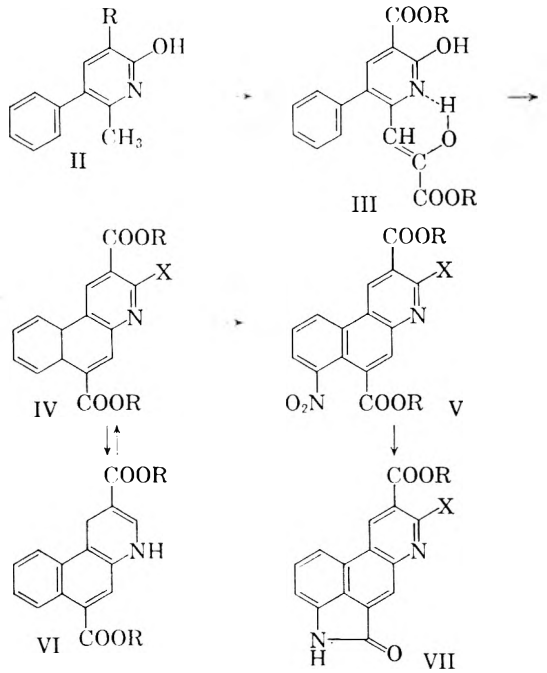
Sir:

The elegant total synthesis[1] of lysergic acid (I) and syntheses of the corresponding dihydro compound[2] and unsaturated ergolines[3-5] have been accomplished by various schemes which, with one recent exception,[6] were based upon the general concept of ring D closure after construction of a suitable ABC tricyclic compound[1-4] or substituted AC (naphthalene) system.[4,5]



I

We wish to report now a series of reactions, differing in principle from these methods, in which ring C and then finally ring B of a dihydrolysergic acid precursor are formed after establishing rings A and D. The present approach involves some methods which although not unprecedented, are novel inasmuch as they have not been applied until now to elaboration of this or any other type of complex polycyclic compound. These methods include: (1) preparation of 5-phenyl-6-methyl-2-pyridones, (2) means for conversion of the methyl group in such pyridones (II) to the pyruvic acid side chain (III) required for cyclization to a benzo[f]quinoline (IV), and (3) reduction of α-chlorobenzoquinolines (IV. X = Cl) to 1,4-dihydro compounds (VI) which may be rearomatized to the dechlorinated compounds (IV. X = H).



Compound II (R = CN) (m.p. 296° dec. *Anal.* Found: C, 74.25; H, 4.93; N, 12.9) was obtained by condensation of 1-hydroxymethylene-1phenylpropanone[7] with cyanoacetamide, and was hydrolyzed to the acid II (R = COOH) (m.p. 265° dec. *Anal.* Found: C, 68.17; H, 4.89; N, 6.3). Treatment of this acid with oxalyl chloride in the presence of phosphorus oxychloride gave, after treatment with water, a partly-complexed product consisting essentially of the chelated enolic acid III (R = H) (dec. from 190°; green ferric chloride test), which was identified by the corresponding ethyl ester, III (R = C_2H_5) (m.p. 170°. *Anal.* Found: C, 63.88; H. 5.44; N, 4.05; deep green ferric chloride test; infrared in Nujol, 5.79, 5.94, 6.12, and 6.21 μ). Cyclization of III (R = H) with concd. sulfuric acid gave IV (R = H; X = OH) (m.p. > 360°. *Anal.* Found: N, 5.04), again better characterized as the ethyl ester, IV (R = C_2H_5; X = OH) (m.p. 211°; *Anal.* Found: C, 67.03; H, 5.04; N, 4.17; infrared in Nujol: 5.80, 5.88, 6.01, and 6.16 μ). The tricyclic structure for IV was confirmed by absence of both the ferric chloride test and the infrared monosubstituted benzene peak (700 cm.$^{-1}$) shown by III, and by the enhanced ultraviolet absorption at long wave lengths. Compound IV (R = H; X = OH) was converted to the corresponding chloro-acid chloride (X = Cl) with phosphorus pentachloride in phosphorus oxychloride, and thence by treatment with methanol to IV (R = CH_3; X = Cl) (m.p.

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(7) G. N. Walker, *J. Org. Chem.*, **23**, 34 (1958).

188°; *Anal.* Found: C, 61.99; H, 3.69; N, 4.44; Cl, 1.09; λ_{max}^{Nujol} 5.79 μ). Although nitration of this chloroester gave V (R = CH_3; X = Cl) (m.p. 231° dec. *Anal.* Found: C, 54.9; H, 3.2; N, 7.4; Cl, 9.6) which could be converted *via* palladium-catalyzed reduction to VII (R = CH_3; X = Cl) (m.p. 306° dec. *Anal.* Found: C, 61.47; H, 3.03; N, 9.15; Cl, 11.6), dechlorination of these compounds was impracticable and it was therefore necessary to proceed as follows. Reduction of IV (R = CH_3; X = Cl) with sodium borohydride removed the chlorine and reduced the benzo[f]-quinoline to corresponding 1,4-dihydroderivate, VI (R = CH_3) (m.p. 218° dec. *Anal.* Found: 68.9; H, 5.08; N, 4.74; infrared in Nujol, 3.05, 5.83 and 6.03 μ) which was aromatized with palladium-charcoal in xylene to IV (R = CH_3; X = H) (m.p. 150°. *Anal.* Found: C, 69.17; H, 4.50; N, 4.89; infrared, 5.75 and 5.80 μ). Nitration of the latter compound in analogy with Jacobs' experiments[5] on similarly constituted compounds, led almost exclusively to V (R = CH_3; X = H) (m.p. 204°. *Anal.* Found: C, 59.86; H, 3.66; N, 8.5), and subsequent reduction and lactam ring closure, using palladium-charcoal in acetic acid,[8] afforded compound VII (R = CH_3; X = H) (*Anal.* Found: C, 69.04; H, 3.68; N, 10.06), identical, in respect to melting point (302°), mixed melting point (undepressed), infrared spectrum (identical, with ester and lactam peaks at 5.80 and 5.84 μ, respectively), and ultraviolet spectrum with an authentic specimen[2,9] of that compound. Hydrolysis gave the corresponding acid,[2] VII (R = X = H) (m.p. > 360°. *Anal.* Found: C, 68.0; H, 3.2; N, 10.6) which has been converted[2] to dihydrolysergic acid.

A full account of this work and related studies will appear in the future. We wish to express our sincere appreciation to Mr. Louis Dorfmann and his entire staff for microanalytical and spectral data, and to Dr. E. Schlittler for unfailing encouragement.

CHEMICAL RESEARCH DIVISION GORDON N. WALKER
CIBA PHARMACEUTICAL PRODUCTS, INC.
SUMMIT, N. J. BARBARA N. WEAVER

Received February 4, 1960

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(9) We are greatly indebted to Dr. Frederick C. Uhle of Harvard Medical School for a generous sample of this compound. The ultraviolet spectrum has been published (*cf.* ref. 6).

Substitution Reactions of Derivatives of 2-Anthrol at the 1- and 3-Positions[1]

Sir:

Discrepancies contained in recent work[2,3] on the Fries rearrangement of 2-anthryl acetate (I) prompt us to publish briefly the preliminary results obtained in our independent study[4] of this reaction and of the formylation of 2-methoxyanthracene (II). Thus, both the hydroxyketone (III), m.p. 218–219° dec., obtained[3] in 83% yield from the high-temperature rearrangement of I, and the hydroxyketone (IV), m.p. 112–113°, obtained[2] in unspecified low yield from rearrangement in nitrobenzene at room temperature, are reported to be methyl 2-hydroxy-1-anthryl ketone, an apparently rigorous proof of structure having been offered in each case.

Both III and IV have been obtained independently in this Laboratory[4] under roughly similar conditions but in greatly different yields. Thus, the Fries rearrangement of I in nitrobenzene (0.5 hr. at room temperature) produced IV, m.p. 115–116.5°, in yields of about 60%, whereas the high temperature reaction (1.5 hr. at 140°, no solvent) produced III, m.p. 226–227° dec., in yields of 3–13%. Mixture melting points of the methyl ethers and acetates of III and IV have shown that they are different isomers, and repeated attempts to obtain III in higher yield have failed.

The proof of structure described by Shah and Sethna[2] was independently employed by us,[4] and their assignment of the 2,1 orientation to IV is confirmed. The 2,3 orientation is assigned to III, since infrared spectra[5] revealed strong intramolecular hydrogen bonding. The Dakin oxidation of III to 1,2-anthradiol, which Jain and Seshadri[3] advanced as proof of structure, conceivably could be explained by contamination with IV, which also is formed in low yield from the high-temperature Fries rearrangement.

Formylation of II with *N*-methylformanilide and phosphorus oxychloride has afforded a mixture (about 70% yield) of approximately equal amounts of two difficultly separable methoxyaldehydes, m.p. 192–194.5° and 116–117°. Separate demethylations produced, respectively, the known 2-hydroxy-1-anthraldehyde[3] (V), m.p. and mixed m.p. 166.5–167°, and a new hydroxyaldehyde (VI), m.p. 228–231° dec., most probably the 3,2 isomer since infrared spectra[5] revealed strong intramolecular hydrogen bonding. The 1,2 orientation of both IV and V was confirmed by proton magnetic resonance spectra.[6]

The above work apparently represents the first two examples of the formation of comparable

(1) This study was supported, in part, by Grant G-7640 from the National Science Foundation and by a grant from the Research Corp.

(2) N. H. Shah and S. Sethna, *J. Org. Chem.*, **24**, 1783 (1959).

(3) A. C. Jain and T. R. Seshadri, *J. Sci. Industr. Res.*, **15B**, 61 (1956).

(4) J. L. Ferrari and I. M. Hunsberger, Abstracts of Papers, 136th Meeting of the American Chemical Society, Sept. 1959, p. 21 P.

(5) Determined at the University of Illinois through the courtesy of Dr. H. S. Gutowsky.

(6) Determined at the University of Illinois through the courtesy of Dr. H. S. Gutowsky and Dr. A. L. Porte.

amounts of 2,3- and 2,1- isomers by substitution into a 2-substituted anthracene. A rigorous chemical proof of structure of III and IV is in progress and will be reported later, along with details of the above reactions and evidence (derived from infrared and proton magnetic resonance spectra) concerning the bond structure of anthracene.

DEPARTMENT OF CHEMISTRY
FORDHAM UNIVERSITY
NEW YORK 58, N. Y.

JOHN L. FERRARI
I. MOYER HUNSBERGER

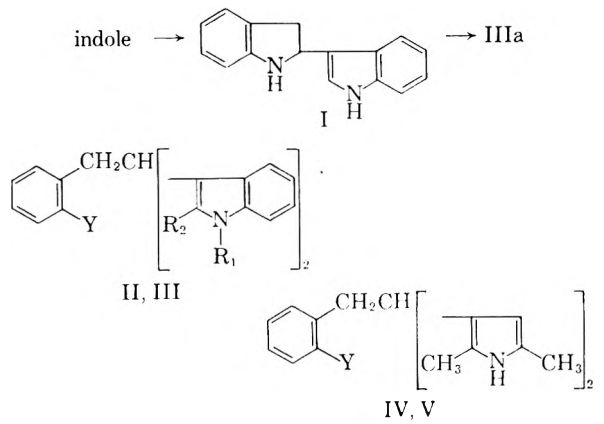
Received February 3, 1960

The Synthesis of Triindole, and Mixed Indole and Indole:Pyrrole Trimers

Sir:

The structure of triindole, the stable terminal product from the acid-catalyzed polymerization of indole, remained an enigma from the time of its discovery in 1913[1] until 1954, when a structure was proposed which could be derived through a plausible electronic mechanism.[2] Based on the discovery that it forms a Schiff base with benzaldehyde, and, therefore, must contain a primary amino group, Smith proposed the bisindole structure IIIa for triindole. The mechanism proposed for the formation of triindole[3] involves diindole as an intermediate. The correct structure for diindole (I), first proposed in 1954,[2] was confirmed by degradation in 1957.[4] We have now confirmed structure IIIa for triindole by an independent synthesis.

In the manner common for formation of bisindoles, by condensation of indoles with aldehydes,[5] an excess of indole condensed with *o*-nitrophenylacetaldehyde[6] in warm acetic acid solution (100°, 2 hr.) to give 3,3′-[2-(2-nitrophenyl)ethylidene]-bisindole (IIa) in 85% yield, light yellow crystals from ethanol water, m.p. (softens above 205°) 208–209°; *Anal.* Calcd. for $C_{24}H_{19}N_3O_2$ (381.42): C, 75.57; H, 5.02: N, 11.02. Found: C, 75.64; H, 5.20; N, 11.10; ν_{NH} 3450, ν_{NO_2} 1522, 1347 cm.$^{-1}$ in Nujol; λ_{max} in 95% C_2H_5OH: 223 mμ (log ϵ 4.84), 275 (4.12), 282 (4.13), 291 (4.08). Hydrogenation of IIa at 2 atm. in methanol over Raney nickel catalyst gave triindole (IIIa) in 77% yield, m.p. and mixed m.p. with an authentic sample,[7] 169–170.5°. The infrared spectra of the two samples in Nujol were identical in every respect.



II, IV. Y = NO_2
III, V. Y = NH_2
IIa, IIIa. R_1 = R_2 = H
IIb, IIIb. R_1 = H, R_2 = CH_3
IIc, IIIc R_1 = R_2 = CH_3

In a similar manner (except at 50°, 17 hr.) were prepared 2,2′-dimethyl-3,3′-[2-(2-nitrophenyl)-ethylidene]bisindole (IIb) in 87% yield, pale yellow crystals from 95% ethanol, m.p. 231–232.5°; *Anal.* Calcd. for $C_{26}H_{23}N_3O_2$ (409.47): C, 76.26; H, 5.66; N, 10.26; Found: C, 75.98; H, 5.89; N, 10.49; ν_{NH} 3380, ν_{NO_2} 1530, 1365 cm.$^{-1}$ in Nujol; λ_{max} in 95% C_2H_5OH: 228 mμ (4.80), 283 (4.18), 292 (4.14); 1,1′,2,2′-tetramethyl-3,3′-[2-(2-nitrophenyl)ethylidene]bisindole (IIc) in 99% yield, yellow crystals from 95% ethanol, m.p. 180–181.5°; *Anal.* Calcd. for $C_{28}H_{27}N_3O_2$ (437.52): C, 76.86; H, 6.22; N, 9.61; Found: C, 76.94; H, 6.31; N, 9.83; ν_{NO_2} 1523, 1357 (also strong bands at 1381 and 1371) cm.$^{-1}$ in Nujol; λ_{max} in 95% C_2H_5OH: 230 mμ (4.81), 287 (4.16), 294 (4.16); and 2,2′,5,5′-tetramethyl-3,3′-[2-(2-nitrophenyl)ethylidene]bispyrrole (IV) in 90% yield, golden yellow crystals from 95% ethanol, m.p. (darkens above 185°) 217–218°; *Anal.* Calcd. for $C_{20}H_{23}N_3O_2$ (337.41): C, 71.19; H, 6.87; N, 12.45; Found: C, 70.89; H, 7.06; N, 12.69; ν_{NH} 3330, ν_{NO_2} 1518, 1340 cm.$^{-1}$ in Nujol; ultraviolet spectrum in 95% ethanol contains only rising end absorption.

Hydrogenation as with triindole gave the corresponding amines: IIIb in 79% yield, colorless crystals from methanol water, m.p. (softens at 175°) 245–246°; *Anal.* Calcd. for $C_{26}H_{25}N_3$ (379.48): C, 82.29; H, 6.64; N, 11.07; Found: C, 82.28; H, 6.72; N, 10.99; ν_{NH} 3420 (strongest), 3350, 3190 cm.$^{-1}$ in Nujol; λ_{max} in 95% C_2H_5OH: 229 mμ (4.82), 285 (4.18), 292 (4.15); IIIc in 79% yield, colorless crystals from methanol water, m.p. 182–183°; *Anal.* Calcd. for $C_{28}H_{29}N_3$ (407.54): C, 82.51; H, 7.17; N, 10.31; Found: C, 82.57; H, 7.24; N, 10.06; ν_{NH} 3480, 3390 cm.$^{-1}$ in Nujol;

(1) K. Keller, *Ber.*, **46**, 726 (1913).
(2) G. F. Smith, *Chem. and Ind. (London)*, 1451 (1954).
(3) For a further discussion of the mechanism of formation of triindole and mixed indole and indole:pyrrole trimers, see W. E. Noland and C. F. Hammer, *J. Org. Chem.*, **25**, forthcoming (1960).
(4) H. F. Hodson and G. F. Smith, *J. Chem. Soc.*, 3544 (1957).
(5) E. Fischer, *Ann.*, **242**, 372 (1887).
(6) R. A. Weerman, *Ann.*, **401**, 1 (1913).
(7) O. Schmitz-Dumont, B. Nicolojannis, E. Schnorrenberg, and H. H. Saenger, *J. prakt. Chem.*, **131**, 146 (1931).

λ_{max} in 95% C_2H_5OH: 231 mμ (4.83), 289 (4.16), 294 (4.15); V in 65% yield, colorless crystals (which darken rapidly) from methanol, m.p. (softens and darkens at 183°) 197–199°; *Anal.* Calcd. for $C_{20}H_{25}N_3$ (307.42): C, 78.13; H, 8.20; N, 13.67; Found: C, 77.98; H, 8.29; N, 13.70 ν_{NH} 3380 (strongest), 3320, 3240 cm.$^{-1}$ in Nujol. The melting point and infrared spectrum of the latter showed it to be identical with indole:di-2,5-dimethylpyrrole trimer,[3] thus confirming structure V for the mixed trimer by an independent synthesis.

SCHOOL OF CHEMISTRY
UNIVERSITY OF MINNESOTA
MINNEAPOLIS 14, MINN.

WAYLAND E. NOLAND
WILLIAM C. KURYLA[8]

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