THE JOURNAL OF Organic Chemistry®

Volume 24, Number 4

~~May~~ April 4, 1959

[CONTRIBUTION FROM THE LABORATORY OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF KANSAS SCHOOL OF PHARMACY]

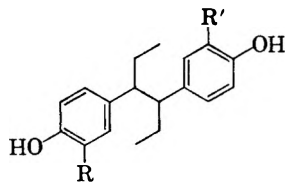
Steroidal Hormone Relatives. V. The Conversion of Hexestrol to Promethestrol *via* the Mannich Reaction[1]

J. H. BURCKHALTER AND ROBERT J. SEIWALD[2]

Received October 13, 1958

A *bis* Mannich base of *meso*-hexestrol has been prepared and converted through hydrogenolysis to promethestrol, thus affording an alternate synthesis and establishing the configuration of the latter as *meso*.

During a continuation of the synthesis of compounds related to the steroid hormones,[3] it was observed that three substances, melting at 145°,[4] 180°,[5] and 167°,[6] have been described as 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)hexane (I). Inasmuch as the methods of synthesis of I were not stereospecific it was considered desirable to prepare I from *meso*-hexestrol (II) and thereby to establish unequivocally the identity of the *meso* form of I.



	R	R'
I	CH_3	CH_3
II	H	H
III	$CH_2N(C_2H_5)_2$	$CH_2N(C_2H_5)_2$
IV	$CH_2N(C_2H_5)_2$	H

Also, in view of the fact that the configuration of the dipropionate of I, which is the important estrogen promethestrol (Meprane) dipropionate, has not definitely been established, there is a further reason for the suggested synthesis.

Starting with *meso*-hexestrol (II), paraformaldehyde and diethylamine, we proposed to prepare III under the conditions of the Mannich reaction[7] and to subject III, which is a bis-benzylamine, to hydrogenolysis in order to obtain the desired *meso* isomer of I. In attempting the synthesis of Mannich base III, we found that the identity and yield of the product depended upon such variables as the temperature and the proportions of reactants. For a maximum yield of 78% of diamine III, a mixture of two moles of paraformaldehyde and eight moles of diethylamine for each mole of hexestrol was heated at reflux temperature for three hours. No solvent other than the diethylamine was employed. Isolation of III as the dihydrochloride salt gave apparently greater yields but its high melting point did not allow an indication of purity.

The monoamine IV hydrochloride was prepared in 47% yield using molar equivalents of hexestrol and paraformaldehyde and eight molar equivalents of diethylamine and no solvent, or four equivalents of diethylamine with alcohol as solvent. All attempts to introduce four basic groups into hexestrol failed and only diamine III was isolated.

The hydrogenolysis of *meso*-3,4-bis(*m*-diethylaminomethyl-*p*-hydroxyphenyl)hexane (III) was

(1) This study was supported by Grant H-1756 from the National Heart Institute of the National Institutes of Health and by the General Research Fund, University of Kansas.

(2) Present address: Department of Chemistry, University of San Francisco, San Francisco 17, Calif.

(3) J. H. Burckhalter and P. Kurath, *J. Am. Chem. Soc.*, **81**, 395 (1959).

(4) V. Niederl, C. A. Siconolfi, A. Bloom, and C. T. Van Meter, *J. Am. Chem. Soc.*, **70**, 508 (1948); V. Niederl and A. Bloom, U. S. Patents **2,500,855** and **2,520,052** [*Chem. Abstr.*, **44**, 5912 (1950) and **45**, 3421 (1951)].

(5) A. Bloom and V. Niederl, U. S. Patent **2,419,516** [*Chem. Abstr.*, **41**, 5150 (1947)].

(6) S. Tanabe and S. Onishi, *J. Pharm. Soc. Japan*, **70**, 618 (1950) [*Chem. Abstr.*, **45**, 6174 (1951)].

(7) F. F. Blicke, *Org. Reactions*, **1**, 303 (1942).

accomplished using Adkins' copper chromite catalyst at elevated temperature and pressure, according to the method of Caldwell and Thompson.[8] The reduction took place in excellent yield, providing the starting material (III) was pure. Impure base resulted in decreased yields of the bicresol (I) together with increased amounts of oily by-products. It was also necessary to use a glass liner in the high pressure bomb, as contact between the metal and the catalyst promoted reduction of the latter to copper accompanied by decomposition and discoloration of the product.

The bicresol I, obtained from the hydrogenolysis of diamine III, has been assigned the *meso* configuration since it was prepared from *meso*-hexestrol. It melts at 164–165° which compares favorably with the 166–167° given by Tanabe and Onishi.[6] Their material must be identical with I and be assigned the *meso* configuration, while the 145°-melting compound of Niederl *et al.*[4] may be either the racemic modification or a polymorphic form of the *meso*. It would also appear that the melting point of 180° mentioned in Niederl's earliest patent[4] was in error or it represents a higher melting modification of I.

In order to determine the configuration of the commercial promethestrol dipropionate (Meprane Dipropionate) which is the diester of the bicresol I, the diester[9] was saponified to yield a product melting at 162–164°, which did not depress the melting point of the bicresol obtained from the hydrogenolysis of the Mannich diamine (II). The dipropionates of the two bicresols were also found to be identical. Thus, promethestrol has been synthesized from *meso*-hexestrol and its configuration has been established as *meso*.

EXPERIMENTAL

Meso-3,4-bis(m-diethylaminomethyl-p-hydroxyphenyl)hexane (III). A mixture of 5.4 g. (0.02 mole) of *meso*-hexestrol, 1.32 g. (0.044 mole) of paraformaldehyde and 12 g. (0.16 mole) of diethylamine was heated at reflux temperature for 3 hr. The excess diethylamine was removed under reduced pressure and the residue dissolved in 25 ml. of hot methyl alcohol. After the solution was cooled overnight in the refrigerator, 6.9 g. (78% yield) of a white crystalline product was collected, m.p. 107–110°. After recrystallization from methyl alcohol, it melted at 113–114°.

Anal. Calcd. for $C_{28}H_{44}N_2O_2$: C, 76.32; H, 10.06. Found: C, 76.38; H, 10.27.

Dry hydrogen chloride gas was passed into an alcoholic solution of the diamine (III) to precipitate the *hydrochloride of* III, m.p. >300° dec. For analysis, it was recrystallized from alcohol containing a small amount of methyl alcohol.

Anal. Calcd. for $C_{28}H_{44}N_2O_2.HCl$: C, 65.48; H, 9.03; Cl, 13.81. Found: C, 65.08; H, 9.30; Cl, 13.62.

The methyl alcoholic filtrate remaining after base III had been separated was evaporated to dryness, and the residue was dissolved in anhydrous ether. Dry hydrogen chloride, when passed into the solution, precipitated 1.8 g. of white solid which melted over a wide range. When triturated with hot water, 0.4 g. (5% yield) of IV hydrochloride (*vide infra*) was obtained, m.p. 220–222°.

3-(m-Diethylaminomethyl-p-hydroxyphenyl)-4-(p-hydroxyphenyl)hexane (IV) *hydrochloride*. A mixture of 5.4 g. (0.02 mole) of *meso*-hexestrol, 0.6 g. (0.02 mole) of paraformaldehyde and 12 g. (0.16 mole) of diethylamine was heated at reflux temperature for 3 hr. The excess diethylamine was removed under reduced pressure and the residue dissolved in 25 ml. of hot methyl alcohol. After cooling the solution overnight in the refrigerator, the diamine III separated. It was recrystallized from petroleum ether (86–100°) to give 1.2 g. (14% yield) of by-product III, m.p. 113–114°.

The solvent was removed from the methyl alcohol filtrate, the residual oil was dissolved in ether, and dry hydrogen chloride was passed into the solution to precipitate a white solid. After trituration of the substance with acetone and drying 3.3 g. (47% yield) of IV hydrochloride was obtained, m.p. 222–223°. After recrystallization from alcohol, it melted at 226–226.5°.[10]

Anal. Calcd. for $C_{23}H_{33}NO_2.HCl$: C, 70.47; H, 8.74; Cl, 9.05. Found: C, 70.12; H, 8.79; Cl, 9.07.

A total of 1.3 g. (24%) of unreacted hexestrol was recovered from the ether and petroleum ether filtrates.

The *free base* (IV) was liberated from an aqueous solution of the salt by means of sodium carbonate. The solid was recrystallized from benzene and petroleum ether (86–100°), m.p. 130–131°.

Anal. Calcd. for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36. Found: C, 77.71; H, 9.41.

Meso-3,4-bis-(m-methyl-p-hydroxyphenyl)-hexane (I). *From* III. The general method of Caldwell and Thompson[8] was followed. A solution of 2.2 g. (0.005 mole) of *meso*-3,4-bis-(*m*-diethylaminomethyl-*p*-hydroxyphenyl)hexane (III) in 25 ml. of absolute alcohol contained in a glass liner was subjected to hydrogenolysis in the presence of copper chromite catalyst at 170° and at about 200 atmospheres of pressure for 4 hr. The mixture was then cooled, filtered, and evaporated to dryness. The solid residue was dissolved in 300 ml. of ether, the solution washed successively with 5% hydrochloric acid and water, and dried over sodium carbonate. After filtration, the ethereal solution was distilled to leave a solid residue. Recrystallized from alcohol, 1.42 g. (95% yield) of white powder was obtained, m.p. 164–165°.

From promethestrol dipropionate. A mixture of 1 g. of promethestrol dipropionate and 10 ml. of Claisen solution (100 g. of potassium hydroxide dissolved in 100 ml. of water, cooled, and then diluted with an equal volume of methyl alcohol) was heated on the steam bath for 10 min. After the solution was allowed to stand overnight, it was diluted with 100 ml. of water, filtered, and then acidified with mineral acid. The white solid precipitate was recrystallized from dilute alcohol, m.p. 162–164°. When mixed with the product from the previous preparation, it gave no depression in melting point.

Meso-3,4-bis(m-methyl-p-propionoxyphenyl)hexane. From 1 g. of I, obtained from the diamine III, and propionic anhydride, the dipropionate of I was prepared in the usual manner. After three recrystallizations from dilute alcohol, it melted at 114–115°.[4,11] Mixed with promethestrol dipropionate,[9] it gave no depression in melting point.

LAWRENCE, KAN.

(8) W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, **61**, 765 (1939).

(9) Obtained through the courtesy of Dr. B. J. Brent, Reed and Carnick, Jersey City 6, N. J.

(10) First prepared by Dr. R. Meyer in this laboratory.

(11) Note that this agrees with that reported in ref. 4, although the melting point of the unesterified phenol (I) is given as 145° instead of 164°.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, GEORGIA INSTITUTE OF TECHNOLOGY]

Some Compounds Derived from Lanosterol

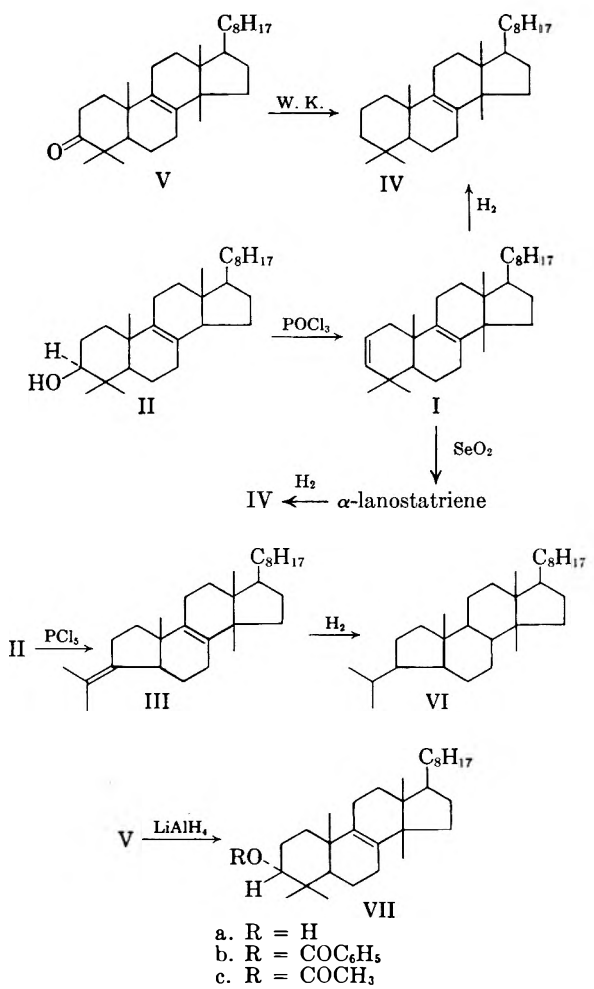
JOHN W. HUFFMAN

Received September 8, 1958

The selenium dioxide oxidation of $\Delta^{2,8}$-lanostadiene to α-lanostatriene has been reinvestigated, and α-lanostatriene has been shown to be an impure sample of $\Delta^{2,8}$-lanostadiene. Δ^{8}-Lanosten-3α-ol has been prepared and exists with the A ring in the boat form. This observation has been rationalized by conformational arguments.

During the course of the degradation of the tetracyclic triterpene lanosterol, it was reported that the hydrocarbon I, obtained by the dehydration of dihydrolanosterol, Δ^{8}-lanosten-3β-ol, (II) with phosphorus oxychloride in pyridine gave upon oxidation with alcoholic selenium dioxide a nonconjugated triene (α-lanostratriene) $C_{30}H_{48}$.[1]

In the time which has passed since the elucidation of the structure of the lanostane group of triterpenes,[2] and the confirmation of this degradative work by total synthesis,[3] the structure of α-lanostatriene has not been investigated.



a. R = H
b. R = COC_6H_5
c. R = $COCH_3$

In our hands, dehydration of dihydrolanosterol with phosphorus oxychloride in pyridine proceeded in 30% yield to give a hydrocarbon, $C_{30}H_{50}$, which after chromatography on alumina, and several recrystallizations, had m.p. 79–81°. The earlier workers reported that this material melted at 118°. It is known[4] that dehydration of lanostan-3β-ol with phosphorus oxychloride in pyridine affords Δ^{2}-lanostene which is contaminated with several per cent of the isomeric isolanostene. It is possible that our $\Delta^{2,8}$-lanostadiene is similarly contaminated with a small amount of isolanostadiene (III), accounting for our low melting point. Attempts to achieve a separation or purification of this substance, either by chromatography, crystallization, or by partial bromination[4] failed to give higher melting material. In order to confirm that our hydrocarbon was actually $\Delta^{2,8}$-lanostadiene, a portion of the lanostadiene was catalytically hydrogenated using platinum in acetic acid to Δ^{8}-lanostene, (IV) identical to an authentic sample prepared by the Wolff-Kishner reduction of Δ^{8}-lanosten-3-one(V).[5]

The hydrogenation of the diene proceeded smoothly with one mole of hydrogen being taken up. The product was somewhat difficult to crystallize and purify, lending more weight to the argument that our lanostadiene was not completely pure. Since the principal impurity in our diene was in all probability isolanostadiene[4] (III), a sample of isolanostadiene was hydrogenated under the same conditions as were used for $\Delta^{2,8}$-lanostadiene. Much to our surprise 1.8 moles of hydrogen were absorbed readily giving a saturated hydrocarbon, or more probably, a mixture of hydrocarbons, $C_{30}H_{54}$, m.p. 56–59°, VI. This is extremely unusual in view of the normal inertness to hydrogenation of the double bond in the 8:9 position in the lanostane ring system.[2]

This unusual reactivity can be explained as follows.

(1) C. Doree, J. F. McGhie, and F. Kurzer, *J. Chem. Soc.*, 1467 (1947).

(2) J. Simonsen and W. C. J. Ross, *The Terpenes*, Cambridge (1957), Vol. IV, pp. 39–116, give a complete account of the degradation of these compounds.

(3) D. H. R. Barton, D. A. J. Ives, R. B. Kelly, R. B. Woodward, and A. A. Patchett, *J. Am. Chem. Soc.*, 76, 2852 (1954); *J. Chem. Soc.*, 1131 (1957).

(4) D. H. R. Barton, D. A. Lewis, and J. F. McGhie, *J. Chem. Soc.*, 2907 (1957).

(5) J. F. McGhie, M. K. Pradhan, and J. F. Cavalla, *J. Chem. Soc.*, 3176 (1952).

The steric strain introduced into the B ring of the lanostane skeleton, by the *trans* fusion of the five-membered A ring to it, could permit the relatively facile hydrogenation of the 8:9 double bond, which is twisted somewhat from its normal bond angles. This same strain could also permit the migration of the double bond to some other position in the molecule, (*e.g.* the Δ^6 olefin) by the action of the platinum catalyst.[6]

Hydrogenation of the isopropylidene double bond could then proceed normally, either by direct hydrogenation, or by migration of the isopropylidene double bond into the five-membered ring. Both of these phenomena have been observed in the hydrogenation of β-amyrilene.[7-9] A combination of these possible alternatives indicates that there are sixteen possible stereoisomers for the hydrocarbon VI. For this reason we do not imply any stereochemical relationships in the hydrocarbon VI.

A possible alternative to the explanation that the strained 8:9 double bond migrates during hydrogenation, is that the isolanostadiene does not have the structure assigned to it by earlier workers, but is in fact a double-bond isomer. There is some precedent for the migration of the 8:9 double bond under acid conditions,[1,2] and the preparation of the diene is carried out in acid medium. The position of the isopropylidene double bond has been established adequately by chemical means.[2]

The infrared spectrum of isolanostadiene (CS_2) shows a medium intensity band at 12.33μ which could be due either to the C–H out-of-plane deformation of a trisubstituted olefin, or a hydrogen in an isopropyl group (C-24).[10] However, the proton magnetic resonance spectrum of this compound lacks the peak at 60 to 80c ycles per second above chloroform which is usually present in compounds containing vinyl hydrogens.[11] Inasmuch as the existence of any but tetrasubstituted double bonds in isolanostadiene is excluded, the structure of this compound is as originally formulated, and the possibility of bond migration during dehydration must be ruled out.

Oxidation of I with selenium dioxide in alcohol gave a white compound, m.p. 79–81°, compared with the reported m.p. 82–84° for α-lanostatriene.[1] This material did not depress the melting point of the starting material, and had an identical infrared spectrum. By increasing the reaction time the amount of solid material obtained could be reduced to virtually none, and only yellow oils could be obtained. The analytical figures reported by the English workers for α-lanostatriene, while fitting the formula $C_{30}H_{48}$ better than $C_{30}H_{50}$ (a lanostadiene), are still within the acceptable range for a compound $C_{30}H_{50}$.[12]

Catalytic hydrogenation of our "α-lanostatriene" afforded the same Δ^8-lanostene (IV) obtained by hydrogenation of $\Delta^{2,8}$-lanostadiene or reduction of Δ^8-lanosten-3-one. It would seem very unusual for selenium dioxide, which reacts smoothly with Δ^8-lanostene to yield the conjugated $\Delta^{7,9}$-lanostadiene,[1] and with Δ^8-lanosten-3-yl acetate to yield $\Delta^{7,9}$-lanosten-3-yl acetate,[1,2] to give a nonconjugated triene on reaction with $\Delta^{2,8}$-lanostadiene. The oxidation to a nonconjugated triene would require oxidation at an unactivated carbon atom, *under conditions milder than those used for the oxidations which were cited above.* Doree[1] reported that oxidation of lanostadiene with *N*-bromosuccinimide gave the same "triene," however, in our hands this reaction gave only intractable oils. It is now apparent that "α-lanostatriene" probably does not exist as such but is unoxidized $\Delta^{2,8}$-lanostadiene, recovered from the reaction with selenium dioxide.

In an effort to prepare a sample of $\Delta^{2,8}$-lanostadiene, uncontaminated with any isolanostadiene, a suitable preparation for the C-3 epimer of dihydrolanosterol was sought. It is well known that triterpenoid alcohols, bearing an equatorial hydroxyl group at C-3, dehydrate readily to give a Ring A contracted product,[13] (II→III) while those compounds bearing axial hydroxyl group in this position react with phosphorus pentachloride to give a normal dehydration product.[13,14] It was felt that the best hope for obtaining a reasonable amount of *epi*-dihydrolanosterol, Δ^8-lanosten-3α-ol, was by the lithium aluminum hydride reduction of Δ^8-lanosten-3-one(V). Barton[15] has stated that reduction of sterically hindered ketones with metal hydrides affords axially oriented hydroxyl groups. However, there appear to be relatively few examples in the literature of the reduction of moderately hindered alcohols with metal hydrides. Fieser[16] has reduced 3β-acetoxycholestan-7-one to a mixture of the 3β, 7α, and 3β, 7β diols, while Corey[17] has

(6) The direct hydrogenation would lead to a *cis* B—C ring fusion, while the bond migration would be expected to lead to the more stable *trans* ring fusion. It is difficult however to make similar generalizations regarding the stereochemistry about the isopropyl group, or the A—B ring fusion.

(7) L. Ruzicka, H. Silbermann, and M. Furter, *Helv. Chim. Acta*, **15**, 482 (1932).

(8) L. Ruzicka, H. Silbermann, and P. Pieth, *Helv. Chim. Acta*, **15**, 1285 (1932).

(9) F. S. Spring, *J. Chem. Soc.*, 1345 (1933).

(10) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen, London, 1954, pp. 24, 44.

(11) We would like to thank Prof. J. Goldstein and Dr. H. L. Clever of the Department of Chemistry, Emory University, for their kindness in carrying out and interpreting the proton magnetic resonance spectrum of isolanostadiene.

(12) Calcd. for $C_{30}H_{48}$: C, 88.23; H, 11.76. Calcd. for $C_{30}H_{50}$: C, 87.81; H, 12.19. Found: C, 88.12; H, 11.83.

(13) W. Klyne, *Progress in Stereochemistry*, Butterworth's, London, 1954, Vol. I, p. 70.

(14) R. Novak, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **32**, 323 (1949).

(15) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(16) L. F. Fieser, M. Fieser, and R. N. Chakarvarti, *J. Am. Chem. Soc.*, **71**, 2226 (1949).

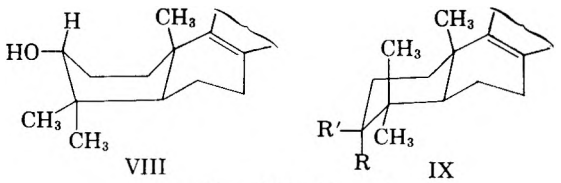
(17) E. J. Corey and J. J. Ursprung, *J. Am. Chem. Soc.*, **78**, 5041 (1956).

found that friedelin affords only the axial alcohol, *epi*-friedelanol, on reduction with lithium aluminum hydride. On the other hand, both β-amyranone[18] and 4,4-dimethylcholestan-3-one[3] afford the equatorial isomers on reduction with metal hydrides.

Reduction of Δ^8-lanosten-3-one with lithium aluminum hydride in ether gave 69% of an alcohol, (VIIa); m.p. 142–143. The melting point was not depressed on mixing with a sample of dihydrolanosterol, however the infrared spectrum (CS_2) showed a medium intensity peak at 12.28μ which was absent from the spectrum of dihydrolanosterol and there were also various other small differences in the spectra of these two materials. The benzoate of the alcohol (VIIb) was prepared and found to have m.p. and mixed m.p. of 193–194°. The acetate of the lithium aluminum hydride reduction product however has m.p. 133–135°, while several workers[2] have found dihydrolanosteryl acetate to melt at 121°. Marker[19] has reported that reduction of lanostenone by the Meerwein-Pondorff-Verley method yield a small amount of an *epi*-dihydrolanosterol, m.p. 139°, acetate m.p. 167.5°. Ruzicka's group,[20] however, found that the same conditions afforded only dihydrolanosterol. This observation coupled with the discrepancies in physical constants between our material and that of Marker make it appear rather doubtful that Marker actually obtained *epi*-dihydrolanosterol.

An interesting consequence of the great similarity of the infrared spectra of our *epi*-dihydrolanosterol and its acetate to that of dihydrolanosterol is the presence of the C—O stretching band at 9.76μ, in both compounds. Jones[21] has found that equatorial, steroidal hydroxyl groups have a C—O stretching band in the vicinity of 9.70μ, while axial substituents show absorption at 9.90μ. The acetates of the epimeric alcohols both have a single strong band at 8.06μ, which has been shown to be characteristic of equatorial acetoxyl groups.[21] Although these empirical rules have been set down for steroidal alcohols and their acetates, they have been applied in the decalin series,[22,23] and are certainly applicable to lanosterol derivatives.

The only explanation, compatible with this spectral evidence is that Δ^8-lanosten-3α-ol exists in the boat form VIII rather than the more conventional chair form IXa, as is also the case in some 2β-bromolanosterol derivatives.[4]



a. R = OH, R′ = H
b. R = H, R′ = OH

Additional evidence for this assignment of conformation can be found in the difference in the reaction of dihydrolanosterol and its epimer with phosphorus oxychloride in pyridine and with phosphorus pentachloride. Reaction of *epi*-dihydrolanosterol with phosphorus pentachloride under precisely the same conditions as used for the preparation of isolanostadiene (III) gave only a low yield of noncrystalline material, as contrasted to the dehydration of the axially substituted *epi*-lupanol to Δ^2-lupene.

The dehydration of the equatorially substituted Δ^8-lanosten-3β-ol with phosphorus oxychloride in pyridine on the steam bath gave a dark brown reaction mixture, from which could be easily isolated $\Delta^{2,8}$-lanostadiene. The same conditions applied to *epi*-dihydrolanosterol gave a colorless reaction mixture from which no organic material could be obtained in the usual manner. This is probably due to the formation of phosphate esters, a phenomenon recently observed in the attempted dehydration of some sterically hindered steroidal alcohols.[24]

If this reaction is carried out at the boiling point of pyridine, a low yield of solid material is obtained, which, while it is undoubtedly hydrocarbon in nature, (eluted readily from an alumina column by hexane) is certainly inhomogeneous, for even after chromatography and several recrystallizations it melts over a 17° range.

Since *epi*-lupanol can be inferred to exist in the normal chair conformation by virtue of its dehydration reactions, and the only significant difference in *epi*-lupanol and *epi*-dihydrolanosterol in the A and B rings is the presence of the 8:9 double bond, it is undoubtedly the presence of this double bond which forces *epi*-lanosterol into the boat form. It is well known that the presence of a 1:2 double bond in a *trans* fused decalin system is thermodynamically unstable.[25,26] The cause of this instability is the abnormal puckering of the saturated carbocyclic ring fused *trans* to the ring containing the double bond.[27]

In dihydrolanosterol (IXb) this puckering has the effect of increasing the distance between the axial

(18) T. R. Ames, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 450 (1951).
(19) A. F. Marker and E. L. Wittle, *J. Am. Chem. Soc.*, **59**, 2289 (1937).
(20) L. Ruzicka, R. Denss, and O. Jeger, *Helv. Chim. Acta*, **28**, 759 (1945).
(21) R. N. Jones, P. Humphries, and K. Dobriner, *J. Am. Chem. Soc.*, **73**, 3215 (1951).
(22) W. G. Dauben and E. Hoerger, *J. Am. Chem. Soc.*, **73**, 1504 (1951).
(23) W. G. Dauben, E. Hoerger, and N. K. Freeman, *J. Am. Chem. Soc.*, **74**, 5206 (1952).
(24) E. R. H. Jones, G. D. Meakins, and J. S. Stephenson, *J. Chem. Soc.*, 2158 (1958).
(25) R. B. Turner, W. R. Meador, and R. C. Winkler, *J. Am. Chem. Soc.*, **79**, 4122 (1957).
(26) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **77**, 2505 (1955).
(27) J. W. Huffman, Ph.D. thesis, Harvard University, 1957.

methyl groups at C-4 and C-10, and decreasing the distance between the axial hydrogens at C-1, C-3, and C-5. In the chair conformation of *epi*-dihydrolanosterol, the axial hydrogen at C-3 is replaced by the somewhat bulkier hydroxyl group, and in order to decrease the interaction between this hydroxyl group and the axial hydrogens, the A ring assumes the boat form. In the case of *epi*-lupanol, the A ring is not puckered by a double bond in the B ring and the axial-axial interactions are considerably less.

We have made several other attempts to prepare pure $\Delta^{2,8}$-lanostadiene both by pyrolysis of dihydrolanosteryl benzoate, and dehydration with alumina in xylene,[28] however both these methods failed to afford any crystalline material.

EXPERIMENTAL[29]

$\Delta^{2,8}$-Lanostadiene. To a slurry of 4.0 g. of Δ^{8}-lanosten-3-ol[20] in 75 ml. of dry pyridine was added slowly 6.0 ml. of phosphorus oxychloride. The resulting mixture was warmed on the steam bath for 1 hr., during which time the solution became homogeneous, and turned a deep brown color. The reaction mixture was cooled, poured into water, and extracted twice with ether. The ethereal extracts were combined, washed several times with water, and finally with 10% hydrochloric acid. The ether solution was dried, and the solvent removed at reduced pressure, affording a pale yellow oil which partially crystallized on standing. The impure hydrocarbon was dissolved in hexane and filtered through a column of Merck alumina. Removal of the solvent afforded a colorless oil which slowly crystallized. Two recrystallizations from chloroform-methanol gave 1.01 g. (29%) of fluffy white needles, m.p. 72–74°.

A solution of 0.222 g. of this material in hexane was chromatographed on 8.0 g. of neutral alumina, Brockmann activity I. The bulk of the material (0.214 g.) could be accounted for in the first fraction eluted with hexane. This fraction crystallized readily on removal of the solvent, and after recrystallization from chloroform-methanol had m.p. 79–81°. Repeated recrystallization from the same solvent pair did not alter the melting point. Doree and co-workers[1] report a melting point of 116–118° for this compound.

Anal. Calcd. for $C_{30}H_{50}$: C, 87.73; H, 12.27. Found: C, 87.98; H, 12.35.

"α-Lanostatriene." To a solution of 0.50 g. of $\Delta^{2,8}$-lanostadiene in 45 ml. of 95% ethanol was added 0.40 g. of selenium dioxide. The mixture was heated under reflux for 8 hr., cooled, and filtered through Filter-Cel. The resulting clear yellow solution was evaporated to dryness at reduced pressure, and the residual yellow oil taken up in hexane and chromatographed on Merck alumina. Elution with hexane afforded 0.069 g. of white solid, which on recrystallization from chloroform-methanol-acetone gave white crystals, m.p. 81–82°. Doree[1] reported that α-lanostatriene had m.p. 82–84°. Our material had an infrared spectrum (chloroform) identical to that of $\Delta^{2,8}$-lanostadiene, and the two materials on mixing showed no depression in melting point.

Elution of the column with benzene-pentane mixtures afforded only yellow oils from which no solid could be obtained.

Δ^{8}-Lanostene. (a) To a slurry of 0.01 g. of prehydrogenated platinum oxide in 10 ml. of glacial acetic acid was added a solution of 0.085 g. of $\Delta^{2,8}$-lanostadiene (m.p. 72–74°). The reaction mixture was hydrogenated at room temperature and atmospheric pressure, until the uptake of hydrogen ceased; 4.2 ml.[30] (87% for one mole) of hydrogen had been absorbed. The reaction mixture was filtered, water added, and the turbid mixture extracted twice with ether. The ethereal extracts were washed repeatedly with water, and finally with 10% sodium bicarbonate. On removal of the solvent at the water pump, a colorless oil was obtained which partially crystallized on standing. The semisolid was taken up in hexane and chromatographed on activity I alumina. Elution with hexane afforded 0.077 g. (85%) of colorless oil which slowly crystallized. Several recrystallizations from chloroform-methanol afforded white crystals, m.p. 67–69°, identical with an authentic sample of Δ^{8}-lanostene prepared by the Wolff-Kishner reduction of Δ^{8}-lanosten-3-one.[5]

(b) A 0.056 g. sample of α-lanostatriene was hydrogenated by the same method and found to absorb 3.7 ml. of hydrogen (115% for one mole).[30] The product was worked up as in part (a) and 0.034 g. of white crystals, m.p. 69–71° were obtained. This material was also identical to a sample of Δ^{8}-lanostene prepared from Δ^{8}-lanosten-3-one.

Hydrogenation of isolanostadiene. A 0.115 g. sample of isolanostadiene[4] in 10 ml. of glacial acetic acid was hydrogenated in the same manner as $\Delta^{2,8}$-lanostadiene. A total of 11.7 ml. (1.8 moles) of hydrogen was absorbed. On working up the reaction mixture a colorless oil was obtained, which was dissolved in hexane and chromatographed on activity I alumina. Elution with hexane gave 0.054 g. of colorless oil which partially crystallized on standing. Recrystallization from chloroform-methanol gave white crystals m.p. 51–55°. Several additional recrystallizations gave material m.p. 56–59°.

Anal. Calcd. for $C_{30}H_{54}$: C, 86.88; H, 13.12. Found: C, 86.98; H, 12.83.

Δ^{8}-Lanosten-3α-ol. To a stirred suspension of 0.20 g. of lithium aluminum hydride in 15 ml. of dry ether was added 0.35 g. of Δ^{8}-lanosten-3-one.[2] The reaction mixture was stirred at room temperature for 1 hr. The excess hydride was decomposed with a solution of ethyl acetate in dry ether. Water and 10% hydrochloric acid were added, and the aqueous layer drawn off. The ethereal solution was washed with successive portions of water, 5% sodium bicarbonate, and again with water, dried, and the solvent removed at reduced pressure, leaving a waxy solid. Recrystallization from ethyl acetate-methanol gave 0.24 g. (69%) of crystals, m.p. 141–143°. A mixed melting point with Δ^{8}-lanosten-3β-ol (dihydrolanosterol) gave no depression, although their infrared spectra differed. Additional recrystallizations from ethyl acetate-methanol gave material m.p. 142–143°.

Anal. Calcd. for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 84.05; H, 12.39.

The benzoate was prepared with benzoyl chloride in pyridine by the method of Wieland.[31] It formed silky needles from chloroform-ethyl acetate-methanol, m.p. 193–194°, undepressed on mixing with a sample of Δ^{8}-lanosten-3β-yl-benzoate.

Anal. Calcd. for $C_{37}H_{56}O_2$: C, 80.97; H, 10.28. Found: C, 81.08; H, 10.50.

The acetate was prepared by the method used for the preparation of Δ^{8}-lanosten-3β-yl acetate,[31] and formed small needles, m.p. 133–135°; from ethyl acetate-methanol, Δ^{8}-

(28) B. Riegel, G. P. Hager, and B. L. Zenitz, *J. Am. Chem. Soc.*, 68, 2562 (1946).

(29) All melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer model 137 spectrophotometer, using chloroform or carbon disulfide as a solvent for the sample. Analyses were carried out by Galbraith Analytical Laboratories, Knoxville, Tenn.

(30) The apparatus used was accurate to ±0.5 ml., precluding very precise measurements on a semimicro scale.

(31) H. Wieland, H. Pasedach, and A. Ballauf, *Ann.*, 529, 68 (1937).

lanosten-3β-yl acetate has been reported to melt at 120–121°.[2]

Anal. Calcd. for $C_{32}H_{54}O_2$: C, 81.63; H, 11.56. Found: C, 82.12; H, 11.76.

Reaction of Δ⁸-lanosten-3α-ol with phosphorus oxychloride. (a) To a solution of 0.10 g. of *epi*-dihydrolanosterol in 5.0 ml. of dry pyridine was added 0.20 ml. of phosphorus oxychloride. The homogeneous, colorless reaction mixture was warmed on the steam bath for 2 hr. After about 1 hr. the solution turned milky and deposited a colorless oil. (Compare dihydrolanosterol.) The reaction mixture was poured into water, and extracted twice with ether. The ethereal extracts were washed well with water, and finally 10% hydrochloric acid, and the solvent removed at the water pump. By this procedure approximately 1 mg. of organic material could be recovered. Additional extractions of the aqueous phases with chloroform afforded no organic material.

(b) To a solution of 0.05 g. of *epi*-dihydrolanosterol in 3 ml. of dry pyridine was added 0.10 ml. of phosphorus oxychloride and the mixture heated under reflux for 2 hr. The reaction was worked up as in (a) and a yellow oil obtained which was dissolved in hexane and filtered through an alumina column. On removal of the solvent, a colorless glass was obtained which was crystallized from chloroform methanol to afford 0.010 g. of semicrystalline solid, m.p. 87–94° with previous sintering. Several recrystallizations from the same solvents gave a minute amount of material. m.p. 95–112°.

Reaction of Δ⁸-lanosten-3α-ol with phosphorus pentachloride. To a suspension of 0.05 g. of *epi*-dihydrolanosterol in 5.0 ml. of hexane was added 0.05 g. of phosphorus pentachloride. The reaction was stirred 2 hr. at room temperature, and then heated under reflux for an additional hour. The reaction mixture was diluted with ether, washed with successive portions of water, 5% sodium bicarbonate, and again with water, dried, and the solvent removed at reduced pressure. The resulting yellow oil was taken up in hexane and filtered through an alumina column. Removal of the hexane afforded a small amount of colorless oil, which could not be induced to crystallize. Under identical conditions dihydrolanosterol in our hands yields isolanostadiene.

ATLANTA, GA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FORDHAM UNIVERSITY]

Studies on Some Oxidation and Reduction Products of Thiamine. II.[1] Thiamine Disulfide-Thioglycolic Acid Reaction.[2-4]

GUIDO E. BONVICINO[5] AND DOUGLAS J. HENNESSY

Received October 13, 1958

Thioglycolic acid in aqueous solution at *p*H 5 reduces thiamine disulfide (I) to thiamine (IIa). When the reaction conditions are more vigorous, thioglycolic acid displaces the thiazole moiety of thiamine and of oxythiamine (IIb) to give (4-amino-2-methyl-5-pyrimidinylmethylthio)acetic acid (IIIa) and (4-hydroxy-2-methyl-5-pyrimidinylmethylthio)acetic acid (IIIb) respectively and 5-(β-hydroxyethyl)-4-methylthiazole (IV). The structures of IIIa and IIIb were established by Raney-nickel desulfurization to give 4-amino-2,5-dimethylpyrimidine (Va) and 2,5-dimethyl-4-hydroxypyrimidine (Vb) respectively and acetic acid. IIIa was converted to IIIb and Va was converted to Vb by 6*N*-hydrochloric acid at reflux temperature. IIIa was synthesized from 4-amino-5-bromomethyl-2-methylpyrimidine hydrobromide (VI) and thioglycolic acid.

The possibility of vitamin B_1 activity in natural products being due, at least in part, to the biologically active oxidation product thiamine disulfide[6,7] and other reversibly oxidized forms of thiamine[8] led us to modify the thiochrome assay[9] by including a reduction step in the procedure. The reduction of thiamine disulfide to thiamine is necessary because thiamine disulfide is not oxidized to thiochrome by alkaline ferricyanide. We used thioglycolic acid for the reduction of thiamine disulfide[10] in the thiochrome procedure. While investigating this reduction, it was observed that the recovery of thiamine disulfide as thiamine decreased when the thioglycolic acid concentration was too high.[10] This low recovery was thought to be caused by a further reaction between thiamine and thioglycolic acid following the reduction. To test this hypothesis, an aqueous solution of thiamine and three molar equivalents of thioglycolic acid was adjusted to *p*H 5, and refluxed for one hour. The crystalline product, which separated in 70–75% yield on cooling the reaction mixture, analyzed for a compound of empirical formula $C_8H_{11}N_3O_2S$ (IIIa or IIIc). The ether extract of the basified aqueous filtrate yielded 5-(β-hydroxyethyl)-4-methylthiazole (IV) in 65–70% yield, identified as the picrate and picrolonate salts.

(1) Paper I: G. E. Bonvicino and D. J. Hennessy, *J. Am. Chem. Soc.*, **79**, 6325 (1957).

(2) This work was aided by a grant from the Williams-Waterman Fund.

(3) From the dissertation submitted by G. E. Bonvicino in partial fulfillment of the requirements for the degree of Doctor of Philosophy, the Graduate School, Fordham University, 1952.

(4) Presented before the Division of Biological Chemistry, American Chemical Society, (a) 116th Meeting, Atlantic City, N. J., September, 1949; see Abstracts, p. 63C, (b) 117th Meeting, Philadelphia, Pa., April, 1950; see Abstracts, p. 49C.

(5) Present address: Organic Chemical Research Section, Research Division, American Cyanamid Co., Lederle Laboratories, Pearl River, N. Y.

(6) O. Zima and R. R. Williams, *Ber.*, **73**, 941 (1940).

(7) O. Zima, K. Ritsert, and T. Moll, *Z. physiol. Chem.*, **267**, 210 (1941).

(8) M. Fujiwana, H. Watanabe, and K. Matsui, *J. Biochem. (Japan)*, **41**, 29 (1954).

(9) D. J. Hennessy, *Biol. Symposia*, **12**, 111 (1947).

(10) G. E. Bonvicino and D. J. Hennessy, in preparation.

When thiamine disulfide was reacted with thioglycolic acid, under the same conditions as thiamine, the insoluble product which was isolated had the same composition as IIIa or IIIc. From the aqueous solution, IV was again isolated in good yield. Oxythiamine[11] behaved like thiamine and thiamine disulfide in the reaction with thioglycolic acid. The thiazole (IV) was again isolated and identified as its picrate and picrolonate salts. The pyrimidine fraction analyzed for a compound of empirical formula $C_8H_{10}N_2O_3S$ (IIIb or IIId).

The nucleophilic displacement of IV by thioglycolic acid was expected because of the work of Snyder and Speck[12] and of Raison.[13] The 4-amino group of the pyrimidine moiety of thiamine (IIa) or the 4-hydroxy group of the pyrimidine moiety of oxythiamine (IIb), being in the ortho position, exerts an electromeric effect (+E); $H_2\overset{\frown}{N}-C^4=C^5(\overset{\frown}{\delta+})-CH_2-\overset{\frown}{N}+$, to facilitate the rupture of the methylene bridge carbon-thiazolium nitrogen bond during the attack of the nucleophilic thiol group. This is quite analogous to the sulfite cleavage reaction of thiamine.[14]

Recently Kupstas and Hennessy[15] have postulated a similar mechanism for the biosynthesis of icthiamine.

Setkina and Kursanov[16] have reported reactions of quaternary ammonium salts of the type $ROCH_2-\overset{\diagup\!\diagup}{N}+\ Y^-$, with carboxylic acids and their salts whereby a displacement reaction took place as follows:

$$ROCH_2-\overset{\diagup\!\diagup}{N}{}^+\ Y^- + R'COOM \longrightarrow ROCH_2OCOR' + |\overset{\diagup\!\diagup}{N} + MY$$

The tertiary amine is displaced by the carboxylate radical resulting in the formation of alkoxymethyl esters. If the reaction of thiamine or oxythiamine with thioglycolic acid took place in a similar manner, the structure of the pyrimidine reaction products would be IIIc and IIId respectively. However, when one considers that the reaction product, $C_8H_{11}N_3O_2S$, is amphoteric, insoluble in organic solvents and melts with decomposition at 290°, then the reaction product seems to have the structure IIIa rather than IIIc. That the 4-amino group of the pyrimidine moiety of the vitamin was unaltered in the reaction product $C_8H_{11}N_3O_2S$ (IIIa) was shown by its conversion to $C_8H_{10}N_2O_3S$ by refluxing IIIa with 6*N* hydrochloric acid for six hours. This product was identical with that obtained from the oxythiamine-thioglycolic acid reaction. Both decompose at 230° and have identical infrared spectra. The product of the oxythiamine-thioglycolic acid reaction must be represented as IIIb rather than IIId. Furthermore, the reaction conditions of Setkina and Kursanov were very much different from ours, *i.e.*, anhydrous medium at 150–170° for three or more hours.

The application of the Raney-nickel desulfurization reaction to the product $C_8H_{11}N_3O_2S$ (IIIa or IIIc) was especially satisfactory because it yielded 4-amino-2,5-dimethylpyrimidine (Va)[17] and acetic acid. Under the same conditions, $C_8H_{10}N_2O_3S$ (IIIb or IIId) afforded 2,5-dimethyl-4-hydroxypyrimidine (Vb)[17] and acetic acid. The acetic acid obtained in both cases was characterized as its *p*-bromophenacyl ester.[18] Compounds Va and Vb were identical with authentic samples of 4-amino-2,5-dimethylpyrimidine[17b,19] and 2,5-dimethyl-4-hydroxypyrimidine[16b] respectively. Had the reaction taken the path described by Setkina and Kursanov, the desulfurization reaction should have afforded the acetate esters of 4-amino-5-hydroxymethyl-2-methylpyrimidine (Vc) and of 4-hydroxy-5-hydroxymethyl-2-methylpyrimidine (Vd) respectively. To complete the structural proof of $C_8H_{11}N_3O_2S$ and of $C_8H_{10}N_2O_3S$, fragment Va was converted to Vb with boiling 6*N* hydrochloric acid for six hours.

Compound IIIa was synthesized from 4-amino-5-bromomethyl-2-methylpyrimidine hydrobromide (VI)[20] and thioglycolic acid in the presence of sodium bicarbonate in 50% aqueous ethanol. The elemental analysis and the infrared spectrum of the synthesized product were in agreement with those of IIIa, obtained by reaction of thiamine chloride with thioglycolic acid. The synthesized sample of IIIa gave Va with Raney-nickel, identical with an authentic sample,[17,19] and acetic acid, characterized as before.

(11) (a) M. Soodak and L. R. Cerecedo, *J. Am. Chem. Soc.*, **66**, 1988 (1944); (b) L. R. Cerecedo and A. J. Eusebi, *J. Am. Chem. Soc.*, **72**, 5749 (1950); (c) H. N. Rydon, *Biochem. J.*, **48**, 383 (1951).

(12) H. R. Snyder and J. C. Speck, *J. Am. Chem. Soc.*, **61**, 688, 2895 (1939).

(13) C. G. Raison, *J. Chem. Soc.*, 2074 (1949).

(14) R. R. Williams, R. E. Waterman, J. C. Keresztesy, and E. R. Buchman, *J. Am. Chem. Soc.*, **57**, 536 (1935).

(15) E. E. Kupstas and D. J. Hennessy, *J. Am. Chem. Soc.*, **79**, 5222 (1957).

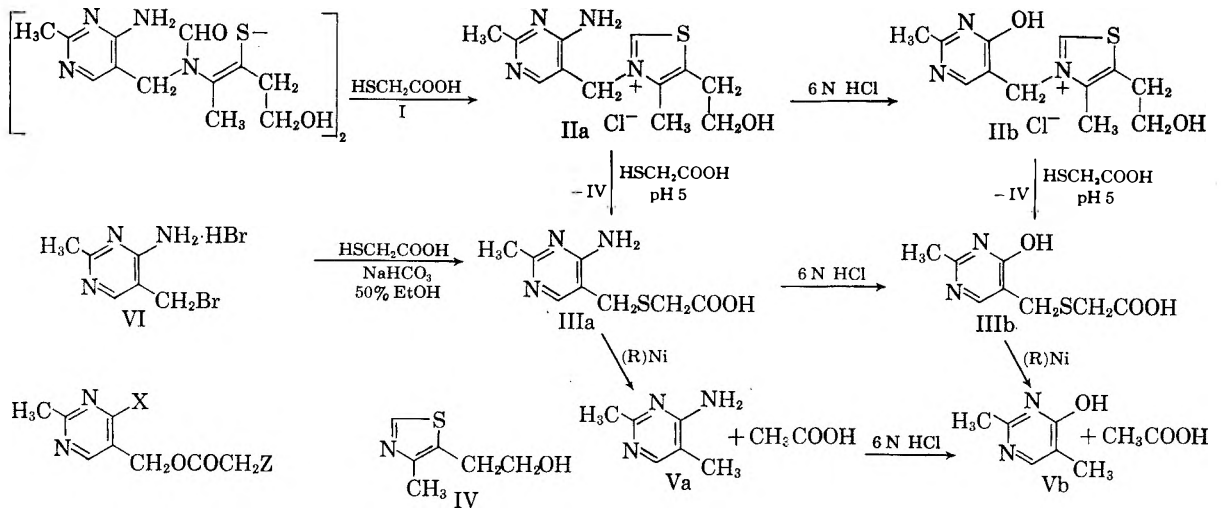
(16) V. N. Setkina and D. E. Kursanov, *Otdel. Khim. Nauk.*, 190 (1949); *Chem. Abstr.*, **43**, 6161 (1949).

(17) (a) J. C. Cline, R. R. Williams, A. E. Ruehle, and R. E. Waterman, *J. Am. Chem. Soc.*, **59**, 530 (1937); (b) R. R. Williams, A. E. Ruehle, and J. Finkelstein, *J. Am. Chem. Soc.*, **59**, 526 (1937).

(18) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, 3rd Ed., John Wiley and Sons, Inc., New York, 1948, p. 157.

(19) The authors are indebted to Dr. Ellis V. Brown of the Chemistry Department, Seton Hall University, for an authentic sample of this material.

(20) Kindly furnished by Merck and Co. Inc., Rahway, N. J.



IIIc, X = NH_2, Z = SH
IIId, X = OH, Z = SH
Vc, X = NH_2, Z = H
Vd, X = OH, Z = H

Fermenting yeast did not resynthesize thiamine from IIIa in the presence of added IV.[21]

EXPERIMENTAL[22]

(4-Amino-2-methyl-5-pyrimidinylmethylthio)acetic acid (IIIa). (*a*) *From thiamine and thioglycolic acid.* A solution of 13.8 g. (0.15 mole) of thioglycolic acid, 16.9 g. (0.05 mole) of thiamine in 50 ml. of water was adjusted to *p*H 5 with 20% sodium hydroxide and refluxed for 1 hr. After the reaction mixture was cooled in an ice bath for several hours, the precipitated product was collected by filtration and dried. The filtrate was saved for the isolation of IV. Recrystallization from hot water afforded 8.0 g. (73%) of product, m.p. 290° dec.

Anal. Calcd. for $C_8H_{11}N_3O_2S$: C, 45.06; H, 5.20; N, 19.71; S, 15.03. Found: C, 45.09; H, 5.20; N, 19.39; S, 14.86.

(*b*) *From thiamine disulfide and thioglycolic acid.* Thiamine disulfide, 2.81 g. (0.005 mole) and 2.76 g. (0.03 mole) of thioglycolic acid were dissolved in 10 ml. of water and the solution adjusted to *p*H 5 with 10% sodium hydroxide and heated under reflux for 1 hr. The reaction product was isolated as described in (*a*) above. Recrystallization from hot water afforded 2.0 g. (60%) of product, m.p. 289–291° dec.

Anal. Calcd. for $C_8H_{11}N_3O_2S$: C, 45.06; H, 5.20; N, 19.71; S, 15.03. Found: C, 45.30; H, 5.06; N, 19.91; S, 15.14.

(*c*) *From 4-amino-5-bromomethyl-2-methylpyrimidine hydrobromide*[20] *and thioglycolic acid.* To a solution of 5.5 g. (0.06 mole) of thioglycolic acid in 50 ml. of 50% ethanol was added 8.4 g. (0.02 mole) of 4-amino-5-bromomethyl-2-methylpyrimidine hydrobromide. The mixture was refluxed for 2 hr. and then cooled. The precipitated product was collected, washed with hot alcohol, and dissolved in hot water. The hot solution was treated with sodium carbonate to *p*H 8–8.5, Norite and filtered. The colorless filtrate was cooled in an ice bath and was acidified with acetic acid to *p*H 5. The crystalline product which slowly precipitated was collected and recrystallized from hot water. The product, 3.0 g. (70%), melted with decomposition at 291°.

Anal. Calcd. for $C_8H_{11}N_3O_2S$: C, 45.06; H, 5.20; N, 19.71; S, 15.03. Found. C, 44.85; H, 4.96; N, 19.83; S, 15.14.

The products obtained by procedures (*a*), (*b*), and (*c*) above all had identical infrared and ultraviolet spectra.

(4-Hydroxy-2-methyl-5-pyrimidinylmethylthio)acetic acid (IIIb). (*a*) *From* IIIa (*Thiamine-thioglycolic acid reaction product*). A solution of 4.3 g. (0.02 mole) of IIIa in 250 ml. of 6*N* hydrochloric acid was refluxed for 6 hr. The solution was evaporated to dryness on a steam bath at reduced pressure. The residue was dissolved in 25 ml. of water, adjusted to *p*H 4.5, and cooled in an ice bath. A crystalline solid separated, which on recrystallization from 25 ml. of hot water afforded 2.6 g. (60%) of product, m.p. 230° dec.

Anal. Calcd. for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.71; N, 13.07; S, 14.96. Found: C, 44.78; H, 4.86; N, 12.91; S, 14.76.

(This procedure is essentially that used by Rydon[11c] for the preparation of oxythiamine from thiamine.)

(*b*) *From oxythiamine* (IIb). A solution of 16.9 g. (0.05 mole) of oxythiamine[11c] in 50 ml. of water and 13.8 g. (0.15 mole) of thioglycolic acid was adjusted to *p*H 5 and refluxed for 2 hr. The clear solution was cooled in an ice bath for 1 hr. and then stored overnight in a refrigerator. The crystalline product which had separated was collected by filtration. (The filtrate was saved for the isolation of the thiazole moiety.) Recrystallization of the collected material from 15 ml. of hot water afforded 6.7 g. (63%) of product, m.p. 231° dec.

Anal. Calcd. for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.71; N, 13.07; S, 14.96. Found: C, 44.77; H, 4.36; N, 13.03; S, 15.07.

5-(β-Hydroxyethyl)-4-methylthiazole (IV). (*a*) *Isolation from the thiamine-thioglycolic acid reaction.* The aqueous filtrate (after separation of IIIa) was adjusted to *p*H 9 with potassium carbonate and extracted with four 50-ml. portions of ether. The combined ether extract was dried over anhydrous magnesium sulfate and evaporated to dryness to give 5.0 g. (70%) of an oil. A sample of this product was converted to the picrate salt in 73% yield, m.p. 163–164° (lit.,[23] 162–163°), and to the picrolonate salt in 80% yield, m.p. 185–186° (lit.,[24] 184°). Mixed melting points with the authentic salts showed no depression.

(*b*) *Isolation from the thiamine disulfide-thioglycolic acid reaction.* The isolation was the same as described in (*a*), above. The yield was 0.7 g. (50%), characterized as the picrate, m.p. 163° and the picrolonate, m.p. 184–185°. The picrate salt was analyzed.

(21) Thiamine regeneration studies were done by Dr. R. J. Moshy, Fordham University.

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

(23) H. T. Clarke and S. Gurin, *J. Am. Chem. Soc.*, **57**, 1876 (1935).

(24) E. R. Buchman, R. R. Williams, and J. C. Keresztesy, *J. Am. Chem. Soc.*, **57**, 1849 (1935).

Anal. Calcd. for $C_{12}H_{12}N_4O_8S$: C, 38.71; H, 3.25; N, 15.05; S, 8.61. Found: C, 38.88; H, 3.42; N, 15.20; S, 8.31.

(*c*) *Isolation from the oxythiamine-thioglycolic acid reaction.* The filtrate, obtained after the isolation of IIIb (see (*b*)), was basified with excess potassium carbonate and extracted with five 50-ml. portions of ether. The combined etherial extract was dried over anhydrous magnesium sulfate and evaporated to dryness. The residue, 4.3 g. (60%) was characterized as the picrate, m.p. 163–164° (lit.[22] 162–163°), and the picrolonate salt, m.p. 184–186° (lit.,[23] 184°). Mixed melting points with authentic samples were 163–165° and 184–186° respectively.

4-Amino-2,5-dimethylpyrimidine (Va). (*a*) *Raney-nickel desulfurization of* IIIa (*from the thiamine-thioglycolic acid reaction*). A suspension of 10.7 g. (0.05 mole) of IIIa, 100 g. of alcohol-free Raney-nickel (prepared according to the procedure of Mozingo *et al.*,[25] the weight was estimated as suggested by Adkins)[26] in 350 ml. of water was refluxed for 2.5 hr. The hot mixture was filtered and the filtrate adjusted to *p*H 10–11 with 20% sodium hydroxide and again filtered hot over a bed of filter-aid. The filtrate was evaporated to dryness, redissolved in 100 ml. of hot water, decolorized with charcoal, and filtered. The filtrate on cooling deposited 4.0 g. (65%) of product, m.p. 203–204° (lit.,[17b] 201–202°). The picrate salt from ethanol melted at 224–225° dec. (lit.,[17b] 222°). A sample of the free base was sublimed at 130–135°/0.5 mm. The sublimate melted at 205–206°.

Anal. Calcd. for $C_6H_9N_3$: C, 58.52; H, 7.37; N, 34.13. Found: C, 58.52; H, 7.33; N, 33.94.

The above desulfurization was repeated on a sample of IIIa prepared from 4-amino-5-bromomethyl-2-methylpyrimidine hydrobromide and thioglycolic acid as described above. The product which was obtained was identical with an authentic sample and with the product isolated above. Mixed melting points of the free base and of its picrate salt showed no depression.

(*b*) *Isolation of the acetic acid fragment from the Raney-nickel desulfurization of* IIIa. The desulfurization reaction described above was repeated on a 4.0 g. sample of IIIa with 40 g. of Raney-nickel. The hot reaction filtrate was acidified to *p*H 4 with dilute hydrochloric acid and distilled in order to separate the acetic acid into the distillate. The latter was adjusted to *p*H 9 with 10% sodium hydroxide and evaporated to dryness. The residue was dissolved in 5 ml. of water and treated with one gram of *p*-bromophenacyl bromide according to the procedure described by Shriner and Fuson.[18] The *p*-bromophenacyl acetate was recrystallized from alcohol, m.p. 86–87° (lit.,[18] 85°); the yield was 150 mg.

2,5-Dimethyl-4-hydroxypyrimidine (Vb). (*a*) *Raney-nickel desulfurization of* IIIb (*from oxythiamine and thioglycolic acid*). The desulfurization of 5.2 g. (0.024 mole) of IIIb and 50 g. of Raney-nickel in 175 ml. of water was accomplished as described above for the desulfurization of IIIa. After the second filtration, the filtrate was evaporated to dryness. The residue was extracted with three 50-ml. portions of hot chloroform. The combined chloroform extract was evaporated to dryness and the residue, 1.64 g. (55%), m.p. 175–176°, was sublimed at 135–140°/0.5 mm. The sublimate, m.p. 176–177°, on recrystallization from acetone afforded 1.43 g. (48%) of product, m.p. 176–177°, (lit.,[17b] 174°).

Anal. Calcd. for $C_6H_8N_2O$: C, 58.05; H, 6.49; N, 22.57. Found: C, 57.92; H, 6.47; N, 22.43.

The *p*-bromophenacyl acetate was prepared from the chloroform insoluble residue as described above.

(*b*) *From 4-amino-2,5-dimethylpyrimidine* (Va). A solution of 3.0 g. (0.024 mole) of Va in 100 ml. of 6*N* hydrochloric acid was refluxed for 8 hr. and evaporated to dryness. The residue was dissolved in 50 ml. of water, adjusted to *p*H 5, and evaporated to dryness. This residue was extracted with three 50-ml. portions of chloroform. The chloroform extract yielded 2.7 g. (90%) of product, m.p. 174.5–176°, on evaporation. This material was sublimed at 135–140°/0.5 mm. to give 2.3 g. (77%) of sublimate, m.p. 176–177°. Recrystallization from acetone afforded 2.0 g. (67%) of product, m.p. 176–177°. Mixed melting point with the product obtained from IIIb above showed no depression.

Anal. Calcd. for $C_6H_8N_2O$: C, 58.05; H, 6.49; N, 22.57. Found: C, 58.25; H, 6.58; N, 22.72.

The chloroform insoluble residue when treated with dilute sodium hydroxide and warmed, evolved ammonia.

Acknowledgment. We are indebted to: Merck and Co. Inc., Rahway, N. J., for having furnished the 5-(β-hydroxyethyl)-4-methylthiazole and 4-amino-5-bromomethyl-2-methylpyrimidine hydrobromide; Miss Cecelia Vitiello of the Schering Corp., Bloomfield, N. J., for the infrared analyses reported in this paper; Dr. F. A. Buhler, Mr. A. A. Sirotenko, and Mr. J. F. Alicino for the microanalyses.

NEW YORK 58, N. Y.

(25) R. Mozingo, D. E. Wolf, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).

(26) H. Adkins, "Reactions of Hydrogen," The University of Wisconsin Press, Wis., 1946, p. 22.

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE UNIVERSITY OF SANTA CLARA, SAN JOSE STATE COLLEGE, AND THE JOHNS HOPKINS UNIVERSITY]

Products from *Serratia marcescens*[1,2]

A. J. CASTRO, A. H. CORWIN, F. J. WAXHAM, AND A. L. BEILBY

Received July 21, 1958

Procedures for the isolation of pure prodigiosin from *Serratia marcescens* are described. Prodigiosin occurs in the bacterial strain studied mainly, if not entirely, as an acid derivative. Palmitic acid and an amide, $C_{24}H_{42-44}O_7N_2$ are isolable from the bacterium.

The specta of ethyl and isopropyl alcohol solutions of the perchlorate are influenced due to the interaction of the perchlorate with the solvent, which functions as a Lewis base.

Prodigiosin, obtainable from the red pigment produced by the bacterium *Serratia marcescens*, is reportedly[3] 2,2′2″-(4-*n*-amyl-4′-methoxy-5-methyl)tripyrrylmethene. The proposed structure is unique for a naturally occurring polypyrryl type compound and is of further interest in view of the suggested role of tripyrrylmethanes in the biosynthesis of porphyrins.[4] However, the product used in the original structural study was of questionable purity.[5] Furthermore, assuming the purity to be adequate for the structural study, the proposed formula is not definitely established and merits reinvestigation.

Morgan and Tanner[6] reported the isolation of purified prodigiosin through a procedure involving chromatography on alumina. We have isolated the compound from the reaction of prodigiosin perchlorate with sodium hydroxide *via* solvent extraction and chromatography on powdered sugar. A far more convenient process than column chromatography is to simply stir a petroleum ether solution of the crude compound with magnesium oxide. The dark color is removed from the solution and pure prodigiosin can be obtained through crystallization. The infrared and ultraviolet-visible absorption spectra for the purified compound are shown in Figures 1 and 2,[7] respectively.

The value for ϵ_{max} at 466 mμ is 4.3×10^4. The properties reported for pure prodigiosin by Morgan and Tanner are, for the most part, identical with those for our product. However, distinct absorption bands shown by our product at 7.14, 8.14, and 11.37 μ are not described by them. It was considered that possibly prodigiosin was changed during the Morgan and Tanner procedure. Starting with our product we repeated their process. From melting point data the product and starting compound appeared to be identical, and the infrared spectra were found in fact to be the same, rather than different. Accordingly, the earlier report is apparently incomplete. It is of interest that although the infrared spectrum for prodigiosin is consistent with certain features[8] of the provisional formula, opposing opinions[10-12] have been registered concerning the tripyrrylmethene linkage. A study aimed at the elucidation of the structure of prodigiosin is in progress by us.

Molecular weights of 520 and 540 were found for prodigiosin in benzene at 30° using the method of Signer.[13,14] From these measurements, calculation for

$$(C_{20}H_{25}ON_3)_2 \rightleftarrows 2C_{20}H_{25}ON_3$$

given an equilibrium constant of $1.3\text{–}1.4 \times 10^{-3}$.

(1) Presented in part before the Division of Organic Chemistry at the 132nd National Meeting of the American Chemical Society, New York, N. Y., September 10, 1957.

(2) This investigation was supported in part by a research grant, E-541, from the National Microbiological Institute, Public Health Service, to San Jose State College and in part by a research grant, E-1335, from the National Institute of Allergy and Infectious Diseases, Public Health Service, to the University of Santa Clara.

(3) F. Wrede and A. Rothhaas, *Z. physiol. Chem.*, **226**, 95 (1934).

(4) W. J. Turner, *J. Lab. Clin. Med.*, **26**, 323 (1940).

(5) C. M. Weiss, *J. Cellular Comp. Physiol.*, **34**, 467 (1949).

(6) E. N. Morgan and E. M. Tanner, *J. Chem. Soc.*, 3305 (1955).

(7) The weak absorption near 540 mμ arises from a trace of acid in the solution. In three solutions examined there was no apparent relationship between intensity and concentration.

(8) The broad absorption starting at 2.78 and extending to 3.32 μ is in the region for pyrrole NH and CH stretchings; the 3.45, 3.53, 6.84–6.90 and 7.30–7.37 μ bands can be associated with CH stretching and bending modes of the substituents appearing in the suggested formula; the band at 13.73 μ can be interpreted as arising from rocking vibrations of the methylene groups in the amyl substituent; the 6.16 and 6.44 μ bands are in the region appropriate to C=N stretching and NH bending modes, respectively; the 8.69–8.98 μ band complex falls in the region where C—O stretching vibrations of a methoxyl group attached to a pyrrole ring might appear.[9]

(9) Assignments in this article are based upon private communication with Professor Nelson Fuson (Fisk University), to whom we are indebted in this connection and otherwise, and comparisons with the data contained in L. J. Bellamy's *The Infrared Spectra of Complex Molecules*, Methuen and Co., Ltd., London, 1954.

(10) R. Hubbard and C. Rimington, *Biochem. J.*, **46**, 220 (1950).

(11) A. Treibs and K. Hintermeier, *Ann.*, **605**, 35 (1957).

(12) A. Treibs and R. Galler, *Angew. Chem.*, **70**, 57 (1958).

(13) A. Steyermark, *Quantitative Organic Microanalysis*, The Balkiston Co., New York, 1951, p. 292.

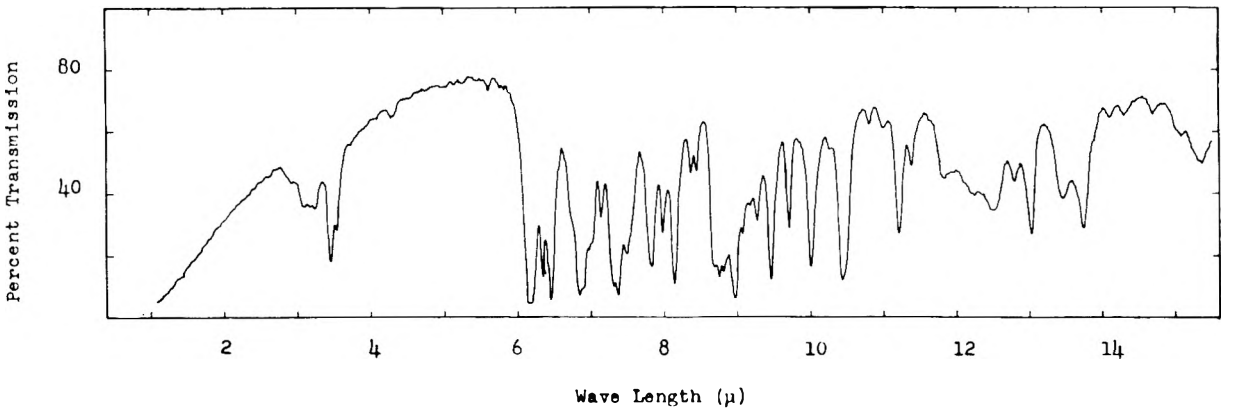


Fig. 1. Infrared spectrum for prodigiosin (KBr).

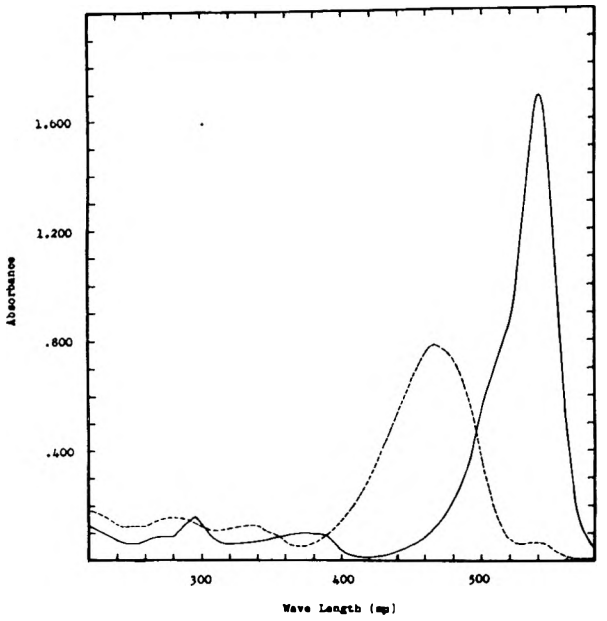


Fig. 2. ---Prodigiosin, 0.580 mg./ml. isopropyl alcohol solution. —Prodigiosin perchlorate in acidified isopropyl alcohol. Solution 13 of Table I.

Wrede's isolation[16] of the zinc-prodigiosin complex from growth of the bacterium on a solid medium containing a zinc salt indicates that prodigiosin is truly a bacterial product. Our attempts to isolate the free base directly from the bacterium through solvent extraction and chromatography were unsuccessful. Instead, a red grease having a green sheen was obtained. The ultraviolet-visible absorption spectrum for this fraction is like that for prodigiosin perchlorate (Fig. 2) with λ_{max} at 534 mμ in 95% ethyl alcohol and upon treatment with perchloric acid, prodigiosin perchlorate was formed. Furthermore, while the isolation of prodigiosin in the preceding fashion was not fruitful, when the bacterial growth is treated with sodium hydroxide in ethyl alcohol, the mixture immediately changes color from a red to an orange, corresponding to the change from an acid derivative of prodigiosin to the free base, and prodigiosin was isolated from the mixture. A magenta colored oil which was separated from the bacterial pigment gave similiar results. It is concluded that prodigiosin exists principally, if not entirely, as an acid derivative in the strain of *Serratia marcescens* studied by us.[17]

Prodigiosin hydrochloride[18] was isolated in a small amount, along with prodigiosin, from the mixture derived from the reaction of prodigiosin perchlorate with alkali. Its presence is attributed to an artifact.[20] In addition, palmitic acid and a compound, $C_{2*}H_{42-44}O_7N_2$, were isolated from the bacterium. The infrared spectrum for the latter in a mineral oil mull contains a strong carbonyl band at 5.81 μ. In addition, bands at 3.02, 6.04 (shoulder at 6.11) and 6.46 μ are consistent with a secondary amide group.

Prodigiosin perchlorate exhibits an absorption spectrum in 95% ethyl alcohol which is dependent upon its concentration. The decrease in the molecular extinction coefficient at 536–538 mμ with dilution, as shown in the accompanying table, is accompanied by a rise in absorption in the neighborhood of the maximum for the free base. This sug-

(14) From Wrede and Hettche's crypscopic measurements[15] in benzene, we calculate molecular weights for their product of 603 and 630. As in the present study, the higher value was obtained for the more concentrated solution. A benzene solution of prodigiosin at a concentration of 6 g./l., which is more concentrated than either of the solutions studied by us, does not show a Tyndall effect. Hence, our results, which are not questionable from the standpoint of purity, must be due to association.[15]

(15) F. Wrede and O. Hettche, *Ber.*, 22, 2678 (1929).

(16) F. Wrede, *Z. physiol. Chem.*, 210, 125 (1932).

(17) A narrow orange zone that occured at the leading edge of the principal pink zone, from which the red grease was obtained, may possibly have arisen from some free prodigiosin, but this was not investigated.

(18) At the time our original manuscript was submitted this compound had not been identified and the similarity in its properties with that which Efimenko, Kuznetsova, and Yakimov[19] claimed to be the hydrochloride was noted. Since then the nature of the compound has been established.[20]

(19) O. M. Efimenko, G. A. Kuznetsova, and P. A. Yakimov, *Biokhimiya*, 21, 416 (1956), kindly translated by Dr. W. Graf.

(20) A. J. Castro, J. F. Deck, M. T. Hugo, L. R. Williams, and M. R. Zingg, *J. Org. Chem.*, 23, 1232 (1958).

gested a proton exchange reaction involving the perchlorate and the alcohol, which functions as a Lewis base. In agreement with this, as shown in the table, in the presence of added perchloric acid, all of the solute is kept in the protonated form and the dilution effect is eliminated. Similar results were obtained with isopropyl alcohol as the solvent.

TABLE I

ABSORPTION MAXIMUM FOR PRODIGIOSIN PERCHLORATE

No.	Solvent	Perchlorate Conc. mg./100 ml.	λ_{max} mμ	ϵ_{max}
1	95% EtOH	0.64	536–538	6.5×10^4[a]
2		0.400	536–538	5.6[a]
3		0.107	536–538	2.6[a]
4	Acidified 95% EtOH	0.604	537	11.6[b,d]
5		0.400	538	11.4[b,d]
6		0.400	538	11.8[b,d]
7		0.200	537	11.4[b,d]
			Avg.	11.6×10^4
8		0.63	536	11.1[c,e]
9		0.400	538	11.4[c,d]
10		0.106	538	11.2[c,e]
			Avg.	11.2×10^4
11	i-PrOH	0.624	542	10.2
12		0.497	542	9.7
13	Acidified i-PrOH	0.624	540	11.5[c,f]

[a] Average of two measurements. [b] Perchlorate dissolved in solvent containing perchloric acid. [c] Perchlorate dissolved in solvent followed by addition of perchloric acid. [d] 1.00 ml. of 0.0829*M* $HClO_4$ per 100 ml. solution. [e] 0.99 ml. of *ca.* 1*M* $HClO_4$ per 100 ml. solution. [f] 1.00 ml. of *ca.* 1*M* $HClO_4$ per 100 ml. solution.

EXPERIMENTAL[21]

Bacterium growth. The organism, a substrain of the Stanford Z-4 strain, exhibited the characteristics described[22] for *Serratia marcescens.* Growth at room temperature on Lack's solid medium[23] showed good red pigmentation having a green metallic sheen. A modification of the Lack medium, wherein the quantity of beef extract was reduced to 1.5 g./l. and an additional 1.5 g./l. of Difco autolyzed yeast was added, also give satisfactory results. For large scale production the bacterium was grown on the medium contained in paper covered, 8 × 10 in. enamel Cesco photography trays. Alternately, the paper covers were removed and the trays stored in pairs in an upright and inverted fashion, so that the upper tray served as a cover for the lower one. Sterile apparatus and media were used. The bacterial growth was scraped from the medium 3–7 days after inoculation and stored in a refrigerator. Eighteen kg. of bacterial mud was obtained from 627 l. of medium.

Prodigiosin perchlorate. The perchlorate was prepared essentially by the method of Wrede and Hettche.[16] The yield of crude product averaged 1.8 g./kg. of bacterial growth. After further recrystallization, the purple solid when examined microscopically appears as clusters of red blades, m.p. 226.0–228.0° (dec.). Some difficulty was experienced in determining the decomposition point, for it is somewhat hard to judge. A decomposition point as high as 234.0–236.0° was recorded for one sample.

Anal. Calcd. for $C_{20}H_{26}O_5N_3Cl$: C, 56.67; H, 6.18; N, 9.91; Cl, 8.37. Found: C, 56.69; H, 6.31; N, 9.89; Cl, 7.89.

In the purification of this compound it was found necessary to remove the oily film that forms on the surface of the hot solution of the crude perchlorate. Furthermore, the perchlorate was found occasionally to be accompanied by a brown filamentous solid, which is apparent under a microscope. This can be removed through recrystallization.

Prodigiosin. (*a*) *Purification through chromatography on powdered sugar.* Two g. of prodigiosin perchlorate, m.p. 226–228° (dec.), in 350 ml. of 95% ethanol was treated with somewhat more 10% aqueous sodium hydroxide than that necessary to change the color of the mixture from deep red to orange-brown, and the mixture was extracted with ligroin (d, 0.67–0.69). The ligroin extract was washed with water, filtered, and applied to a column of California and Hawaiian confectioners powdered sugar, 9.5 cm. (diam.) × 65 cm. After development with ligroin several different colored zones were apparent preceding the principal zone which was pink in color and occupied the major portion of the column. An orange eluate was collected. The principal pink zone was removed, sucked dry on a Büchner funnel and the orange filtrate was combined with the orange eluate from the column. The resulting solution was concentrated and applied to a second column of powdered sugar. Evaporation of the orange eluate which was collected yielded an orange oil having a distinct green sheen. The oil crystallized and after two recrystallizations from ligroin, prodigiosin was obtained as red crystals showing a little green reflex, m.p. 151.5–152.9° (dec.).

The perchlorate was prepared by addition of 5% aqueous perchloric acid to a hot 95% ethanol solution of prodigiosin, boiling the mixture for a short time and allowing it to stand. Red crystals deposited which after one recrystallization from a mixture of 95% ethyl alcohol and 5% aqueous perchloric acid melted at 235.0–236.0° (dec.). The product gave a positive Beilstein test.

Anal. Calcd. for $C_{20}H_{26}O_5N_3Cl$: N, 9.91. Found: N, 9.56.

The ultraviolet-visible absorption spectrum for this compound is the same as that for authentic prodigiosin perchlorate.

The dye which remained absorbed after the main pink zone from the first chromatogram had been sucked dry was eluted with chloroform and the solvent evaporated. The portion of the residue that was insoluble in ligroin was successively crystallized from 95% ethyl alcohol and a mixture of benzene and iso-octane. This yielded 0.0333 g. of prodigiosin hydrochloride,[20] a magenta colored solid, m.p. 146.9–151.2° (dec.). Recrystallization from a mixture of benzene and iso-octane gave a product which melts with decomposition at 150.0–150.5°.

(*b*) *Magnesium oxide purification.* A 0.532 g. sample of prodigiosin perchlorate, m.p. 226.8–229.1° (dec.), in 95% ethyl alcohol was decomposed with sodium hydroxide as before. The resulting water washed, sodium sulfate dried petroleum ether extract of crude prodigiosin was concentrated and stirred with magnesium oxide. The discolored magnesium oxide was removed by filtration, rinsed with solvent, and the combined petroleum ether filtrates were concentrated. The bright red solution that remained was allowed to evaporate in the dark yielding 0.2169 g. of red crystals, m.p. 152.0–153.0° (dec.). From the mother liquor after further treatment with magnesium oxide, a second crop of crystals weighing 0.0672 g. (combined yield 70%), m.p.

(21) Melting points were taken with a Fisher-Johns apparatus, and are uncorrected. Ultraviolet-visible absorption spectra were measured with a Beckman Model DU Spectrophotometer or a Cary Model 11M. The latter was made available to us through the courtesy of Professor William Mansfield Clark, to whom we are indebted. Infrared spectra were determined with a Model 21 Perkin-Elmer Spectrophotometer using a sodium chloride prism.

(22) E. S. Breed, E. G. D. Murray, and A. P. Hitchens, *Bergey's Manual of Determinative Bacteriology,* The Williams and Wilkens Co., Baltimore, 6th ed., 1948, p. 479.

(23) A. Lack, *Proc. Soc. Exptl. Biol. Med.,* **72,** 656 (1950).

150.1–152.0° (dec.), was obtained. A mixture melting point of prodigiosin purified in this fashion with that from a powdered sugar chromatogram showed no depression.

A sample of crude prodigiosin obtained from the Parke, Davis Co. was purified similarly and after crystallization from iso-octane melted at 151.0–152.5°. The infrared spectra for this and the preceding product are the same as that from powdered sugar.

Anal. Calcd. for $C_{19}H_{22}N_3(OCH_3)$: C, 74.27; H, 7.79; N, 12.99; OCH_3, 9.60. Found: C, 74.36, 74.42; H, 7.59, 7.89; N, 12.65; OCH_3, 9.55.

(*c*) *Adsorption on alumina.* Prodigiosin, m.p. 150.2–152.1° (dec.) was treated essentially according to the procedure described by Morgan and Tanner[6] for the isolation of the pure compound. Aluminum Co. of America activated alumina, grade F-20, was used as an adsorbent. The product, m.p. 152.3–153.7° (dec.), was dark red and exhibited considerable green reflux. A mixture melting point with authentic prodigiosin showed no depression.

(*d*) *Isolation from the alkali digestion product from Serratia marcescens.* Following substantially the Lack and Botts[24] modification of Wrede and Hettche's procedure,[15] 1181 g. of bacterial mud was digested overnight with approximately an equal volume of 10% sodium hydroxide. A volume of 95% ethanol equal to that of the alkali was added and the mixture was extracted repeatedly with ligroin. The combined, water washed ligroin extracts were concentrated, and upon standing a brown gelatinous mass precipitated. This was moved by filtration, dried and stored. When examined about 34 months later, crystals of prodigiosin were apparent in the solid. The mixture was extracted with cyclohexane in a Soxhlet apparatus. The extract was evaporated and prodigiosin, m.p. 151.0–152.5° (dec.) was obtained from the residue *via* the magnesium oxide procedure. The infrared spectrum for this product agrees with that for prodigiosin obtained from the perchlorate.

(*e*) *Isolation from alkali digestion of magenta oil from Serratia marcescens.* Ten g. of the magenta oil, isolated from *Serratia marcescens*, as described below, was dissolved in 25 ml. of methanol. To this, 1.55 g. of sodium hydroxide dissolved in a little water and 15 ml. of methanol was added, followed by a 10 ml. methanol rinse. The mixture was stirred for an hour and shaken with an ether–petroleum ether–cyclohexane mixture. Sodium chloride was added to break the emulsion that formed and the hydrocarbon-ether solution was separated. The aqueous layer and the dark solid remaining were extracted with ether. The water washed, combined, sodium sulfate dried extracts were applied to a column of alumina (Woelm, non-alkaline, activity grade I) and the main scarlet band, after elution with ethyl alcohol and subsequent treatment with magnesium oxide as in the preceding, gave a dark semicrystalline mass. Upon the application of this in petroleum ether to a second column of alumina and development with ethyl alcohol the principal zones were orange and red with the former above the latter. As these moved down the column the region occupied by the latter decreased. The two were eluted with alcohol and the product from the eluate after treatment with magnesium oxide as before yielded 0.0407 g. of prodigiosin, m.p. 150.3–152.0° (dec.). The infrared spectrum for this product was the same as that for the product from the powdered sugar chromatogram.

Molecular weight of prodigiosin. The Signer apparatus, mounted in a constant temperature water bath held at 30°, was rotated slowly so that the solutions alternately filled the burets and the corresponding bulbs. Volumes were read periodically until constant. Equilibrium was reached with the following benzene solutions: 2.194 mg. of prodigiosin per 0.7512 ml. and 1.309 mg. of fluorenone per 1.2937 ml., 3.519 mg. of prodigiosin per 0.8080 ml. and 3.294 mg. of 2,2′-(3,3′,5,5′-tetramethyl-4,4′-dicarbethoxy)dipyrrylmethene per 1.1848 ml. From the first experiment, the molecular weight for prodigiosin is 520 and the equilibrium constant is 1.4×10^{-3}; from the second, 540 and 1.3×10^{-3}.

Solvent extract of Serratia marcescens. Repeated extraction of 4.9 kg. of the bacterial growth with cold 95% ethyl alcohol followed by evaporation of the extracts at reduced pressure yielded 186 g. of a viscous red liquid. To a solution of this in 800 ml. of 95% ethyl alcohol, an equal volume of ligroin was added followed by 300 ml. of water. This caused the separation of a dark ligroin layer, a dark aqueous alcohol layer, and a dark solid. The aqueous alcohol layer and dark solid were extracted together repeatedly with ligroin, the dark insoluble solid was removed, and the extraction of the aqueous alcohol layer continued until successive extracts showed only a small, if any, difference in color. The combined, water washed ligroin extracts were evaporated at diminished pressure and the oily residue, 96.3 g., was stored in a refrigerator. After three days, 7.8 g. of a dark red oily solid had precipitated. Upon further standing in the cold an additional 2.8 g. of a red solid precipitated and a magenta oil remained. The latter was noted to contain a little water.

Crude fractions of palmitic acid were isolated from the red oily solid through a series of operations involving successive crystallizations, using petroleum ether as the most common solvent, chromatography of the residual oil and subsequent crystallization of the red oil which was isolated from the chromatogram. In the chromatography step, powdered sugar was used as an adsorbent and a 2:1 mixture[25] of petroleum ether and ethyl ether was used to develop the column and elute the red fraction. Crude portions of the acid were also isolated from the magenta oil following chromatography of one portion on powdered sugar and another on celite (Analytical Filter Aid), in a manner like that of the foregoing case, followed by successive crystallizations of the resulting red oil obtained from these, and repetition of these steps. The crude fractions of palmitic acid were combined, decolorized with charcoal in methanol, and crystallized from aqueous methanol. The purified acid was obtained as shiny white crystals, m.p. 62.3–63.7°. The second red solid, wt. 2.8 g., that had precipitated from the ligroin soluble portion of the bacterial extract was similarly decolorized and crystallized yielding an additional quantity of the acid, m.p. 63.1–63.9°.

Anal. Calcd. for $C_{16}H_{32}O_2$: C, 74.94; H, 12.58; Neut. Eq., 256. Found: C, 74.94; H, 12.52; Neut. Eq., 258.

A mixture melting point with an authentic sample of palmitic acid showed no depression and the two samples show identical infrared absorption spectra.

The red aqueous alcohol solution obtained in the initial solvent fractionation of the bacterial extract was concentrated at reduced pressure and a red tar, 53.6 g., mixed with a brown aqueous solution remained. Through a process of crystallization from aqueous ethyl alcohol, mechanical separation, decoloration with charcoal in ethyl alcohol, and recrystallization from aqueous ethanol 0.53 g. of white needles, m.p. 154.3–156.0°, were isolated from 10 g. of the red tar.

Anal. Calcd. for $C_{24}H_{42}O_7N_2$: C, 61.25; H, 9.00; N, 5.95. Calcd. for $C_{24}H_{44}O_7N_2$: C, 60.99; H, 9.38; N, 5.93. Found: C, 61.00, 61.25; H, 9.08, 9.13; N, 5.39, 6.11.

Mol. wt. Calcd. for $C_{24}H_{42}O_7N_2$: 471. Calcd. for $C_{24}H_{44}O_7N_2$:473. Found[26] (Rast; camphor): 460, 477.

In another experiment, the ethyl alcohol extract of the bacterium was transferred to cyclohexane and the cyclohexane solution was applied to a column of powdered sugar. The main pink zones from this and a similar column after elution with chloroform or benzene were combined and after evaporation a red oil remained. A ligroin solution of the oil

(24) A. Lack and E. D. Botts, private communication.

(25) R. P. Williams, J. A. Green, and D. A. Rappoport, *J. Bacteriol.*, **71**, 115 (1956).

(26) G. Weiler and F. B. Strauss, 164, Banbury Road, Oxford, England.

applied to a column of powdered sugar gave a principal dark pink colored zone. The center portion of the dark pink zone was eluted with chloroform and a red grease having a green metallic sheen remained after removing the solvent. Qualitative analysis of the product like this obtained from another experiment showed that it contained nitrogen; sulfur and halogen were absent. Treatment of the red grease in 95% ethyl alcohol with perchloric acid in the described fashion gave prodigiosin perchlorate, m.p. 224.5–226.0° (dec.).

Anal. Calcd. for $C_{20}H_{26}O_5N_3Cl$: Cl, 8.37. Found: 8.40.

The ultraviolet-visible absorption spectrum for the perchlorate is the same as that for authentic prodigiosin perchlorate.

Acknowledgment. We are grateful to Mrs. J. C. Kurtz, Mr. M. Bilitch, Dr. A. E. Blood, Mr. D. K. Fisher, Mr. J. Walter, and Dr. George C. Kleinspehn for assistance with certain phases of this investigation and to Mr. Martin Black of the Parke, Davis Co. for a supply of prodigiosin.

SANTA CLARA, CALIF.

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Unsymmetrically Substituted Piperazines. XII.[1] Benzhydrylpiperazines and Related Compounds with Spasmolytic and Anti-Fibrillatory Action[2]

WALTER S. IDE, EMIL LORZ, ARTHUR P. PHILLIPS, PETER B. RUSSELL, RICHARD BALTZLY, AND ROBERT BLUMFELD

Received October 17, 1958

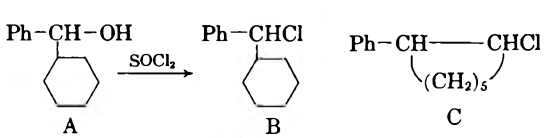
In a study of compounds showing activity against artificial fibrillation, a number of *o*-substituted benzhydrylpiperazines and related benzhydrylamines have been prepared.

In the course of work on piperazines having spasmolytic action, it was found that monoquaternary salts of *ortho*-substituted benzhydrylpiperazines[3] and of partially reduced benzhydrylpiperazines[4] had strong atropine-like action. A number of the ditertiary bases intermediate to these quaternary salts were also submitted to pharmacological screening. Some of these, especially those having *o*-alkyl substitution in the benzhydryl moiety, showed considerable activity in suppressing artificial fibrillation in experimental animals.[5]

In following up this lead we prepared the series of piperazine derivatives, data on which are presented in Table I. Since, *a priori*, it could not be assumed that the observed activity was dependent on a piperazine portion or indeed on any single feature of this type of substance, there were also prepared for comparison a number of benzhydrylamines, substituted ethylenediamines, *etc.* Many of these have already been reported from other sources but some appear to be new compounds. Their physical properties are shown in Table II and in the experimental part. The physiological studies showed that in fact the anti-fibrillatory action was not a function of the piperazine moiety although favorably influenced thereby. The critical requirements seem to be those of an antihistaminic. Activity is augmented, however, by *ortho*-substitution in the benzhydryl moiety.

The quaternary salts, data on which are presented in Table III, were largely prepared as spasmolytics. Compounds XXX, XXXIII, and XXXV have anti-cholinergic activities on isolated tissue of the same general order as atropine. Compounds XXVII–XXIX were tested for anthelmintic activity in mice against *Syphacia obvelata*;[6] of these the most active was XXVIII.

The quaternary salts XXX–XXXVI were prepared by quaternization of hexahydrobenzhydryl-*N'*-methylpiperazine[7] or of Compound III with the appropriate alkyl iodide, usually in acetone. The preparation of these ditertiary bases was initially rather troublesome, resulting in poor yields and leading to a search for an alternate route of synthesis.[4,8] Because of these poor yields and the apparent impurity of the bases as initially obtained, it was suspected that hexahydrobenzhydryl chloride might undergo a rearrangement either in formation from the carbinol, on refluxing with thionyl chloride, or in reaction with *N'*-alkyl piperazine in the sense:



(1) Paper XI in this series, M. Harfenist and E. Magnien, *J. Am. Chem. Soc.*, **80**, 6257 (1958).

(2) The work reported here is part of a joint research carried out in cooperation with the Pharmacology Department of these laboratories.

(3) R. Baltzly, W. S. Ide, and E. Lorz, *J. Am. Chem. Soc.*, **77**, 4809 (1955).

(4) P. B. Russell and R. Baltzly, *J. Am. Chem. Soc.*, **77**, 629 (1955).

(5) C. H. Ellis, *Ann. N. Y. Acad. Sci.*, **64**, 552 (1956); C. H. Ellis and L. N. Sivertsen, *Arch. intern. pharmacodynamie*, **116**, 17 (1958).

(6) H. W. Brown, K. L. Hussey, K. F. Chan, M. Harfenist, R. V. Fanelli, and E. Magnien, in preparation.

(7) R. Baltzly, S. Dubreuil, W. S. Ide, and E. Lorz, *J. Org. Chem.*, **14**, 775 (1949).

(8) R. Baltzly, E. Lorz, P. B. Russell, and F. M Smith, *J. Am. Chem. Soc.*, **77**, 624 (1955).

TABLE I

N-SUBSTITUTED PIPERAZINES: R—N⟨CH₂CH₂⟩N—R′

Cpd. No.	R	R′	Empirical Formula of Salt	M.P., °C.	Analyses C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
I	$PhCH(CH_2)_3CH_3$	Me	$C_{16}H_{26}N_2 \cdot 2HCl$	248[a]	60.2	59.8	8.8	9.2
II	$PhCH(CH_2)_4CH_3$	Me[b]	$C_{17}H_{28}N_2 \cdot 2HCl$	252	61.3	61.3	9.0	9.0
III	$PhCHC_6H_{11}$	Et	$C_{19}H_{31}N_2 \cdot HCl$	266	63.5	63.6	9.0	8.8
IV	Ph_2CH	$CHMe_2$	$C_{20}H_{26}N_2 \cdot 2HCl$[c]	218	65.4	65.1	7.7	7.4
V	$MeO_2CCH_2CH_2$	Ph_2CH	$C_{21}H_{26}N_2O_2 \cdot 2HCl$	190–191	61.3	61.0	6.9	7.0
VI	p-$H_2NC_6H_4CO$	Me	$C_{12}H_{17}N_3O \cdot HCl$	238	56.5	56.8	7.0	7.1
VII	p-$H_2NC_6H_4CO$	$PhCH_2$	$C_{18}H_{21}N_3O \cdot 2HCl \cdot 2H_2O$	[d]	55.7	55.5	6.5	6.4
VIII	p-$H_2NC_6H_4CO$	Ph_2CH	$C_{24}H_{25}N_3O \cdot 2HCl \cdot 2H_2O$	[d]	62.3	62.2	6.3	6.7
IX	o-MeC_6H_4CHPh	COOEt	$C_{21}H_{26}N_2O_2 \cdot HCl$	206	67.3	66.7	7.3	7.0
X	o-MeC_6H_4CHPh	H	$C_{19}H_{22}N_2 \cdot HCl$	246	71.4	71.8	7.7	7.6
XI	m-MeC_6H_4CHPh	$CHMe_2$	$C_{21}H_{28}N_2 \cdot 2HCl$	226	66.1	66.0	7.9	8.4
XII	o-EtC_6H_4CHPh	Me	$C_{20}H_{26}N_2 \cdot 2HCl$	223–225	65.4	65.2	7.7	7.5
XIII	o-ClC_6H_4CHPh	$CHMe_2$	$C_{20}H_{25}ClN_2 \cdot HCl$	272	65.7	65.6	7.2	6.8
XIV	$(o\text{-}MeC_6H_4)_2CH$	Me	$C_{20}H_{26}N_2 \cdot 2HCl$	235[a]	65.4	65.2	7.7	7.8
XV	$(p\text{-}MeC_6H_4)_2CH$	Me	$C_{20}H_{26}N_2 \cdot HCl$	244–246[a]	72.6	72.2	8.2	8.1[e]
XVI	$(o\text{-}EtC_6H_4)_2CH$	Me	$C_{22}H_{30}N_2 \cdot 2HCl$	218	66.9	66.8	8.1	8.3
XVII	Ph_3C	Me	$C_{24}H_{26}N_2 \cdot HCl$	186–191[a]	Cl: Calcd. 9.4%. Found: 9.0			

[a] Melts with decomposition. [b] The monomethiodide melts at 119°. *Anal.* Calcd. for $C_{18}H_{31}IN_2$: C, 53.7; H, 7.7. Found: C, 53.7; H, 7.9. [c] The monohydro-iodide has been reported.[3] [d] Foams above 100°, unmelted at 250°. [e] Cl: Calcd. 10.7%. Found: 10.6.

TABLE II

BENZHYDRYLAMINES RELATED TO THE PIPERAZINES OF TABLE I. $PhCHR \cdot NR_2'$

Cpd. No.	R	NR_2'	Empirical Formula of Salt	M.P., °C.	Analyses C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
XVIII	o-ClC_6H_4	NHMe	$C_{14}H_{14}ClN \cdot HCl$	214.5–215	62.7	62.6	5.9	5.9
XIX	o-ClC_6H_4	NMe_2	$C_{15}H_{16}ClN \cdot HCl$	233–233.5	63.9	63.6	6.1	6.1
XX	o-ClC_6H_4	NC_5H_{10}[a]	$C_{18}H_{20}ClN \cdot HCl$	240–241	67.1	67.0	6.5	6.7
XXI	o-MeC_6H_4	NC_5H_{10}[a]	$C_{19}H_{23}N \cdot HCl$	265–266	75.6	75.7	8.0	7.8
XXII	o-MeC_6H_4	NC_4H_8O[b]	$C_{18}H_{21}NO \cdot HCl$	256 (dec.)	71.3	71.4	7.2	7.0
XXIII	o-ClC_6H_4	$NH(CH_2)_2NMe_2$	$C_{17}H_{21}ClN_2 \cdot 2HCl$	183–185	56.4	56.4	6.4	6.4
XXIV	o-MeC_6H_4	$NH(CH_2)_2NMe_2$	$C_{18}H_{24}N_2 \cdot 2HCl$	199–200	63.4	63.4	7.7	7.7
XXV	Ph	$NH(CH_2)_3NMe_2$	$C_{18}H_{24}N_2 \cdot 2HCl$	206–207	63.4	63.0	7.7	7.8
XXVI	Ph	$NH(CH_2)_2NC_4H_8O$[b]	$C_{19}H_{24}N_2O \cdot 2HCl$	243–244	61.8	61.8	7.1	7.3

[a] Piperidino. [b] Morpholino.

TABLE III

BENZHYDRYL AND HEXAHYDROBENZHYDRYLPIPERAZINE QUATERNARY HALIDES: PhCHRN⟨CH₂CH₂⟩N⁺(R′)(R″) X⁻

Cpd. No.	R	R′	R″	M.P., °C.[a]	Empirical Formula	Analyses C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
XXVII	Ph	Me	n-C_7H_{15}	183	$C_{25}H_{37}BrN_2$	67.4	67.4	8.4	8.1
XXVIII	p-ClC_6H_4	Me	n-C_7H_{15}	198	$C_{25}H_{36}BrClN_2$	62.6	63.0	7.6	7.4
XXIX	p-ClC_6H_4	Me	n-$C_{12}H_{25}$	156	$C_{30}H_{46}BrClN_2$	65.5	65.7	8.4	8.4
XXX	C_6H_{11}	Me	Me	214–215	$C_{19}H_{31}IN_2$	55.1	54.8	7.5	7.7
XXXI	C_6H_{11}	Me	Et	173–174	$C_{20}H_{33}IN_2$	56.1	56.1	7.8	7.7
XXXII	C_6H_{11}	Me	n-C_3H_7	182	$C_{21}H_{35}IN_2$	57.0	56.7	8.0	7.9
XXXIII	C_6H_{11}	Me	i-C_3H_7	194	$C_{21}H_{35}IN_2$	57.0	57.1	8.0	8.3
XXXIV	C_6H_{11}	Me	n-C_4H_9	108–110	$C_{22}H_{37}IN_2$	57.9	58.3	8.2	8.6
XXXV	C_6H_{11}	Et	Et	195	$C_{21}H_{35}IN_2$	57.0	57.1	8.0	7.6
XXXVI	C_6H_{11}	Et	i-C_3H_7	216	$C_{22}H_{37}IN_2$	57.9	57.5	8.2	8.5

[a] Most of these compounds melt with decomposition.

Such a rearrangement would be conceivable wherever a reaction passed through a carbonium ion intermediate. The chloride C would, of course, be much less reactive than B.

While the existence of such rearrangements cannot be excluded completely, attempts to demonstrate them have been unsuccessful. Refluxing hexahydrobenzylhydryl chloride with two equivalents of methylpiperazine for 24 hours (presumptive temperature *ca.* 140°) resulted in yields of water-insoluble base as high as 75%. This basic material was subjected to exhaustive chromatography in pentane on alumina and two fractions apparently different chromatographically were isolated. Both gave monohydrochlorides from water melting around 250° alone and mixed. Both gave quaternary salts (XXX, XXXI, and XXXIII) not clearly distinguishable (since these salts melt with decomposition). Finally, the infrared spectra of the monohydrochlorides were indistinguishable from each other.

Most of the compounds of Tables I and II were also prepared by conventional methods. Referring to Table I, Compounds I–IV, IX, and XI–XVII were prepared by reaction of the appropriate halide, RCl with the N′-R′ substituted piperazines. The preparations of XV and XVII were run with equivalent amounts of the two reagents in acetonitrile as solvent at reflux.[9] The other compounds were obtained from reactions with two equivalents of the piperazine without solvent on the steam bath.[7] The preparations of I and II required around two days heating. The benzhydryl halides needed only 4–8 hours for substantially complete reaction. Preparation of XVII had been attempted previously[10] and the base had presumably been obtained but decomposed during extraction with acid (as the dihydrochloride). The monohydrochloride now reported is somewhat unstable in aqueous solution at room temperature and breaks down rapidly on the steam bath with formation of triphenylcarbinol.

Compound V was formed by action of methylacrylate on *N*-benzhydrylpiperazine.[11]

Compound X was obtained by alkaline hydrolysis of IX followed by neutralization of the base, *N*-*o*-methylbenzylhydrylpiperazine. For the preparation of VI–VIII, *p*-nitrobenzoyl chloride was treated with *N*-methyl- *N*-benzyl- and *N*-benzhydryl-piperazines respectively and the resultant *p*-nitrobenzoyl derivatives were reduced with Adams' Catalyst in methanol containing hydrogen chloride.[12]

Of the compounds of Table II, all but XVIII and XIX were prepared by reaction of the appropriate benzhydryl chloride with two or more equivalents of piperidine, morpholine, or the corresponding *N*′-tertiary amino alkylenediamine. Compound XVIII was prepared in 35–40% yield by addition of phenylmagnesium bromide to *o*-chlorobenzalmethylamine. The secondary base was converted to Compound XIX by the Clarke-Eschweiler methylation. The hydrochlorides of these two amines both crystallized as hydrates. Removal of water before analysis required drying in high vacuum (60–70° at 1 μ pressure).

Several previously unreported compounds belonging to the α,α-diphenylpyridine-4-methanol and piperidine-4-methanol series are also described in the experimental section. One of these, 1-methyl-α,α-bis-*o*-tolylpiperidine-4-methanol differed significantly from its diphenyl analog in being quite resistant to dehydration. This may be due to hindrance that prevents coplanarity in the carbonium ion stage, which is generally involved in dehydration under acid conditions.

This tertiary carbinol was prepared in very poor yield by the addition of *o*-tolylmagnesium bromide to ethyl 1-methylisonipecotate. The bulk of the product appeared to be the ketone 1-methyl-4-*o*-methylbenzoylpiperidine.[13]

EXPERIMENTAL

The compounds of Tables I–III were isolated, in general, by previously described techniques: The choice of mono- or dihydrochlorides for the piperazines of Table I was largely a matter of convenience. A considerable number of the monohydrochlorides of benzhydrylpiperazines can be crystallized from water and solutions of such salts have a *p*H in the range 5–5.5. The dihydrochlorides are perhaps more readily crystallized from alcohol-ether mixtures than the monohydrochlorides.

Hexahydrobenzhydryl chloride.[14] One-tenth mole (19.1 g.) of hexahydrobenzhydrol was dissolved in 100 cc. of toluene in a flask with reflux condenser. To this was added 10 cc. (16 g.) of thionyl chloride. After an initial rapid evolution of gas had subsided, the solution was refluxed for 1 hr. After standing overnight the volatile material was removed on a steam bath at water pump vacuum. The residual oil was distilled at 1 mm. pressure. There was obtained 16 g. (a 75% yield) of colorless oil boiling at 99.5–102°.

Anal. Calcd. for $C_{13}H_{17}Cl$: C, 74.8%; H, 8.2%. Found: C, 75.0; H, 8.3.

This material therefore contained no significant amount of unsaturated hydrocarbon, though a small amount could have escaped during the preparation.

(9) This technique, which was originated by Dr. M. Harfenist, is convenient in cases wherein the monohydrochloride of the product crystallizes readily. As might be expected, the first half of the reaction proceeds rapidly, whereas the second half is slow being dependent on gradual release of secondary piperazine nitrogen from an unfavorable equilibrium.

(10) L. P. Albro, R. Baltzly, and A. P. Phillips, *J. Org. Chem.*, 14, 771 (1949).

(11) K. E. Hamlin, A. W. Weston, F. W. Fischer, and R. J. Michaels, Jr., *J. Am. Chem. Soc.*, 71, 2731 (1949).

(12) The reductions of the precursors of VII and VIII were stopped when 3 equivalents of hydrogen had been absorbed to avoid debenzylation.

(13) Similar predominance of ketone over tertiary carbinol from the reaction of Grignard reagents with γ-ω tertiary-amino esters has been reported from other sources: Brit. Patent, 614,567, U.S. Patent, 2,649,444.

(14) P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, 75, 587 (1927).

N-Hexahydrobenzhydryl-N'-ethylpiperazine (III). Eight and three-tenths g. (0.04 mole) of the above halide was added to 9.1 g. (0.08 mole) of *N*-ethylpiperazine and the solution was heated at gentle reflux for 96 hr. The reaction mixture was partitioned between ether and water and the ethereal layer was washed with water until the washings were neutral. The ethereal layer was then shaken with *N* hydrochloric acid and the base was liberated from the aqueous layer. The base was taken into ether, dried over potassium carbonate, and acidified with excess alcoholic hydrogen chloride.

N-Hexahydrobenzhydryl-N',N'-diethylpiperazinium iodide (XXXV). One and six-tenths g. (6 mmole) of base liberated from the above hydrochloride was dissolved in 10 cc. of acetone. To it was added 2 g. of ethyl iodide and the covered flask was placed beside a steam bath (T. *ca.* 40°). After standing 1 day, 1.3 g. of solid, m.p. 194–195° had separated.

N-Hexahydrobenzhydryl-N'-methylpiperazine. Ten g. (0.048 mole) of hexahydrobenzhydryl chloride was added to 20 g. (0.2 mole) of *N*-methylpiperazine in a round-bottomed flask. The solution was heated under reflux for 23.5 hr. and worked up as described for the *N'*-ethyl derivative. The base was distilled at 1 mm., 9.8 g. (75% of the calculated yield). The monohydrochloride can be crystallized from concentrated aqueous solution or from isopropyl alcohol. It darkens on heating above 240° and melts with decomposition about 255°.

N-(4,4'-Dimethylbenzhydryl)-N'-methylpiperazine (XV). Nine g. (0.039 mole) of 4,4'-dimethylbenzhydryl chloride and 4.3 g. (0.043 mole) of *N*-methylpiperazine were dissolved in 100 cc. of distilled acetonitrile. The solution was refluxed for 24 hr. and then placed in the refrigerator. The crystals that separated were filtered off and washed with acetonitrile until colorless. They weighed 8.4 g. (65%) and melted at 245–250° dec. After recrystallization from absolute ethanol the hydrochloride melted at 244–246° dec.

N-Diphenylacetylpyrrolidine. Ten g. of pyrrolidine was added to 12.5 g. of diphenylacetylchloride in 50 cc. of acetone. After the initial vigorous reaction had subsided, the mixture was refluxed 1 hr., cooled, and diluted with water. The precipitated amide was washed with water and recrystallized from ether-methanol mixture, m.p., 162–163°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.5; H, 7.2. Found: C, 81.6; H, 7.3.

N-[β,β-Diphenylethyl] pyrrolidine. The above amide (7.9 g.) was added to a suspension of 1.5 g. of lithium aluminum hydride in 200 cc. of ether. After refluxing for 5 hr., 5 cc. of water was admitted slowly. The ethereal solution was decanted from the precipitated inorganic matter and the latter was further washed with ether. The ethereal solution was extracted with dilute hydrochloric acid and the base was liberated from the aqueous layer. The base was taken into ether, dried over potassium carbonate, and converted to the hydrochloride with alcoholic hydrogen chloride solution. The hydrochloride was recrystallized from acetone-ether mixture and then melted at 174–175°.

Anal. Calcd. for $C_{18}H_{21}N.HCl$: C, 75.4; H, 7.7. Found: C, 75.3; H, 7.6.

N-(β,β-Diphenylethyl)-N'-methylpiperazine. N-Diphenylacetyl-*N'*-methylpiperazine[15] (8.8 g.) reduced with lithium aluminum hydride (2.5 g.) as described for the above pyrrolidine derivative, afforded *N*-diphenylethyl-*N'*-methylpiperazine. The dihydrochloride darkens above 250° and melts with decomposition at 256–257°.

Anal. Calcd. for $C_{19}H_{26}Cl_2N_2$: C, 64.7; H, 7.4. Found: C, 64.7; H, 7.3.

α,α-Diphenylpyridine-4-methanol methiodide. Thirteen g. of diphenyl-4-pyridylcarbinol[16] was dissolved in 150 cc. of methanol and 7 cc. of methyl iodide was added. The solution was refluxed 22 hr. After evaporation to small volume and addition of ether, the quaternary salt separated. It melted at 234–235° after recrystallization from methanol-ether mixture.

Anal. Calcd. for $C_{19}H_{18}INO$: C, 56.6; H, 4.5. Found: C, 56.7; H, 4.8.

α,α-Diphenyl-1-carbomethoxyethylpiperidine-4-methanol. Fourteen g. of α,α-diphenylpiperidine-4-methanol[16] was mixed with 20 cc. of methyl acrylate in 25 cc. of benzene and kept at 45–50° for 24 hr. It was then refluxed 5 hr. and evaporated *in vacuo* to small volume. On addition of hexane, cooling and scratching, crystals separated, m.p. 65–70°. Recrystallization from benzene-hexane raised the m.p. to 93–94°.

Anal. Calcd. for $C_{22}H_{27}NO_3$: C, 74.8; H, 7.7. Found: C, 74.6; H, 8.0.

α,α-Diphenyl-1-methylpiperidine-4-methanol methiodide. Methylation of the secondary base with excess methyl iodide and alkali afforded the quaternary iodide. It melted at 219–220° after recrystallization first from acetone and then from absolute ethanol. As first obtained it appeared to be a hemihydrate.

Anal. Calcd. for $C_{20}H_{26}INO$: C, 56.5; H, 6.2. Found: C, 56.5; H, 6.5.

α,α-Bis-o-tolyl-1-methylpiperidine-4-methanol and 1-methyl-4-o-methylbenzoylpiperidine. A solution of *o*-tolylmagnesium bromide was prepared from 3.7 g. of magnesium turnings and 28 g. of *o*-bromotoluene in anhydrous ether. To this was added over about 15 min. 8 g. of methyl *N*-methylisonipecotate. After 2 hr. reaction at room temperature and 1 at reflux, the reaction mixture was hydrolyzed with iced concentrated sodium hydroxide solution. After filtration from the sludge of magnesia and thorough washing of that with ether, the combined ethereal extracts were dried over potassium carbonate and acidified with ethanolic hydrogen chloride solution. There was obtained 15–17 g. of crude crystalline solid. From this, four crystallizations from alcohol-ether mixtures gave 3 g. of material melting at 183–185°.

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 66.3; H, 8.0. Found: C, 66.1; H, 8.1.

Examination of the material in the mother liquors revealed the presence of a small amount of higher-melting material. After three crystallizations of the second crop obtained from the mother liquors, there was obtained 2 g. of material melting around 300°. The analytical sample melted at 300–302°.

Anal. Calcd. for $C_{21}H_{28}ClNO$: C, 73.0; H, 8.2. Found: C, 73.2; H, 8.2.

From the mother liquors of the above carbinol more material was obtained whose melting point could not be raised above 158°. The composition was that of the ketone hydrochloride. It is not known whether this material is isomeric with the ketone melting at 183–185° or whether a case of dimorphism has been encountered.

Whereas the diphenyl analog of the carbinol melting at 302° is quite readily dehydrated, this carbinol was recovered only slightly impure after 2 hr. refluxing with equal volumes of concentrated hydrochloric and acetic acids. With concentrated sulfuric acid (5 parts by wt.) on the steam bath it suffered extensive decomposition.

N-Benzhydryloxyethyl-N',N'-dimethyl piperazinium iodide. Five g. of benzhydryl chloride and 7.2 g. of *N*-methyl-*N'*-hydroxyethylpiperazine[17] were mixed in a little dry benzene and warmed on the steam bath for 3 days. The reaction mixture was partitioned between ether and water and the

(15) W. S. Ide, E. Lorz, and R. Baltzly, *J. Am. Chem. Soc.*, **77**, 3142 (1955).

(16) Purchased from the Reilly Tar and Chemical Co.

(17) W. S. Ide, E. Lorz, and R. Baltzly, *J. Am. Chem. Soc.*, **76**, 1122 (1954).

ethereal layer was washed with water, sodium carbonate solution, and again with water. The base in the ether layer was dried and converted to the hydrochloride which melts at 200°. The base was liberated from an aqueous solution of the hydrochloride and allowed to react with an excess of methyl iodide in ether. The quaternary salt melted at 181–182° as first obtained and at 182–185° after one crystallization from alcohol-ether mixture.

Anal. Calcd. for $C_{21}H_{29}IN_2O_2$: C, 55.8; H, 6.4. Found: C, 55.5; H, 6.6.

TUCKAHOE 7, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE]

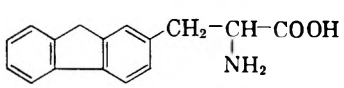
Preparation of DL-*beta*-(2-Fluorenyl)alanine[1]

D. C. MORRISON

Received July 25, 1958

An amino acid derived from fluorene, DL-β-(2-fluorenyl)alanine, was synthesized from fluorene-2-carboxaldehyde or ethyl fluorene-2-carboxylate as starting materials. The physical and chemical properties were determined and the amino acid was characterized as its hydrochloride salt and as the *N*-benzenesulfonyl derivative.

The preparation of DL-β-(2-fluorenyl)alanine was undertaken for work involving cancer chemotherapy with 2-substituted fluorenes containing biologically important polar side chains. The compound was thought to be of interest due to the known carcinogenic activity of 2-fluorenylamines, and because of the desirability of obtaining amino acids derived from the fluorene ring system for growth and antagonism studies. The compound (I) may also be considered as an indenophenyl alanine.



I

The amino acid was synthesized from fluorene-2-carboxaldehyde or from ethyl fluorene-2-carboxylate as starting materials. These substances were reduced with lithium aluminum hydride to the corresponding carbinol, which was transformed to the bromide with phosphorus tribromide. The carbinol and bromide have been previously prepared by another method,[2] but the hydride reduction seemed to be a simpler process. The bromide was used to alkylate the sodium derivative of diethyl acetamidomalonate, and the product was hydrolyzed and decarboxylated with difficulty by hydrochloric acid to the amino acid hydrochloride. The latter gave the desired compound when treated with ammonium hydroxide.

The amino acid is a high melting, very insoluble substance. The physical properties showed some resemblance to those of the corresponding 5-acenaphthenyl alanine,[3] but it was somewhat more stable than the latter, especially in hot alkaline media. The compound was characterized as the hydrochloride and as the *N*-benzenesulfonyl derivative.

EXPERIMENTAL

Melting points are uncorrected and were taken on a Fisher-Johns block.

2-Fluorenemethanol. A. From ethyl fluorene-2-carboxylate. The ethyl ester[4] of fluorene-2-carboxylic acid was employed due to its much greater solubility in solvents compared to the free acid.

A mixture of 8 g. of lithium aluminum hydride and 200 ml. of ether was refluxed for 1 hr. and cooled. To this was added slowly with stirring, a solution of 6.75 g. of the ethyl ester in 50 ml. of benzene. The liquid was then refluxed for 0.5 hr. and excess hydride decomposed with ethanol and dilute hydrochloric acid. The organic solvents were evaporated at room temperature and the aqueous-acid suspension filtered to yield the solid carbinol. Extraction of the latter with ether, and filtration, removed inorganic residues. The filtrate was diluted with petroleum ether and decolorized with Norit, and then filtered and evaporated. After recrystallization from dilute aqueous acetone, the material weighed 5.04 g. or 90.6%. On heating, it softened at about 120° and melted at 125–142° (lit. 131[2]). When the compound was recrystallized twice from ether-petroleum ether, it had m.p. 138–142°, and after 5 more recrystallizations, m.p. 140.5–142.5°. The melting point of the substance is sensitive to impurities but preparative methods and analysis of subsequent products would seem to confirm its identity.

B. From fluorene-2-aldehyde. The aldehyde was prepared by the method of Ayling, Hinkel, and Beynon.[5] Inorganic salts were removed from the product by extraction of the aldehyde with ether, filtration, and evaporation of the solvent.

A solution of 8 g. of lithium aluminum hydride in ether, prepared as above, was treated gradually with a solution of 6.9 g. of the aldehyde in 100 ml. of ether-benzene. A yellow-green color formed together with a light colored precipitate. The solution was refluxed 10 min. and then decomposed by ethanol and dilute hydrochloric acid. The organic solvents were removed at room temperature and the dilute acid suspension of the product was filtered. After washing and drying, the crude aldehyde weighed 6.87 g. or 98.5%. Without further purification, the cream-white solid had m.p. 126–130°. Both preparations of the carbinol gave the same bromide and subsequent derivatives.

(1) The work described in this paper was carried out under a research grant (No. C-327 and CY-2915) to Prof. D. M. Greenberg, from the National Cancer Institute, United States Public Health Service.

(2) J. von Braun and H. Engel, *Ber.*, **57**, 191 (1924).

(3) D. C. Morrison, *J. Org. Chem.*, **23**, 33 (1958).

(4) D. C. Morrison, *J. Org. Chem.*, **23**, 1772 (1958).

(5) L. E. Hinkel, E. E. Ayling, and J. H. Beynon, *J. Chem. Soc.*, 339 (1936).

2-Fluorenylmethyl bromide. The carbinol (2.17 g., 0.011 mole) was added gradually to a solution of 3 ml. of phosphorus tribromide in 20 ml. of benzene. The mixture was shaken until the solid dissolved and then left several days at room temperature. Probably this long reaction time is not necessary. The benzene solution was poured slowly with stirring into a mixture of ether and water. The organic phase was extracted 3 times with water, filtered, and dried over anhydrous sodium sulfate. It was then evaporated to dryness under vacuum. A yield of 2.6 g. (90.7%) of cream colored solid was obtained. This material had m.p. 94–97° (lit.[2] 95°). When stored sealed at 0° for 1 week, the m.p. was lowered to 90–96°. The best preparation obtained showed m.p. 95–100° and all recrystallizations lowered this value, especially if done from aqueous solvents.

Diethyl (2-fluorenylmethyl)acetamidomalonate. A solution containing 0.24 g. of sodium (0.0104 mole) and 2.22 g. of diethyl acetamidomalonate (0.0104 mole) in 150 ml. of anhydrous ethanol (distilled from sodium and diethyl phthalate) was prepared. This was treated with a solution of 2.59 g. of the bromide (0.01 mole) in benzene-ethanol. Little or no heat was evolved and the mixture was refluxed for 16 hr. Acetic acid (5 ml.) was added and the mixture was distilled to a small volume under vacuum. It was then steam distilled for 0.5 hr. An orange oil was left in aqueous suspension and this crystallized on cooling and standing. This product was recrystallized once from aqueous acetone and dried. It weighed 3.5 g. or 88.6%. For purification, the ester was recrystallized from aqueous acetone and from ether-petroleum ether, m.p. 149.5–150.5°.

Anal. Calcd. for $C_{23}H_{25}NO_5$: C, 69.87; H, 6.33. Found: C, 69.64; H, 6.12.

DL-β-*(2-Fluorenyl)alanine hydrochloride.* Hydrolysis and decarboxylation of the ester required long refluxing with hydrochloric acid, or some ester or intermediate product was recovered. The best procedure found is described. A solution of 8.64 g. of the ester in 150 ml. of glacial acetic acid was heated to boiling under reflux and 125 ml. of concentrated hydrochloric acid was slowly added while maintaining reflux. The mixture was refluxed for 6 days and then evaporated to dryness under vacuum. The residue was repeatedly extracted with boiling 3*N* hydrochloric acid and the extracts filtered while above 90°. Storage of the combined filtrates at 0° overnight produced a crystalline deposit which was filtered, washed, and dried. The filtrates were boiled to a small volume and further crops taken. The combined yield of hydrochloride was 5.35 g. or 84.5%. The salt was decolorized in ethanol-benzene solution with Norit and then recrystallized from this solvent 5 times. Recrystallization from boiling dilute hydrochloric acid was less effective in purification. On heating, the hydrochloride sintered and discolored above 230° and melted 240–258° with decomposition, forming an orange-brown melt.

Anal. Calcd. for $C_{16}H_{16}NO_2Cl$: C, 66.32; H, 5.53. Found: C, 66.41; H, 5.35.

DL-β-*(2-Fluorenyl)alanine.* The amino acid hydrochloride was digested with a mixture of equal volumes of concentrated ammonium hydroxide and water on the steam bath until solution was obtained. The hot solution was filtered and the filtrate boiled down to concentrate the solution and to eliminate ammonia. Crystallization of the free amino acid began in the heated solution and was completed on cooling overnight on ice. It was then filtered, washed with water, and dried. From 1.37 g. of hydrochloride, 1.13 g. of amino acid were obtained or 94.3%. The amino acid formed a white powder which could be recrystallized by repeating the solution in hot dilute ammonia and concentrating. The analytical sample was vacuum dried for analysis.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.89; H, 5.93. Found: C, 76.28; H, 6.06.

On heating, the amino acid begins to discolor (light orange-brown) at 210–215° and melts at 225–233° to a brown liquid with decomposition. On further recrystallization of the analytical sample, the melting point was lowered. This amino acid was nearly insoluble in boiling water, but dissolved in hot, dilute acids and alkalies, more readily in the latter. When boiled in suspension in dilute aqueous acetic acid with ninhydrin, the insoluble particles became purple and the liquid light brown, while with excess amino acid the liquid became greenish-brown. No change in appearance of the compound was observed during storage for 2 years.

*N-Benzenesulfonyl-*DL-β-*(2-fluorenyl)alanine.* This derivative was made by acylation of the fluorenylalanine dissolved in an excess of *N* potassium hydroxide, by stirring vigorously with an ether solution of benzenesulfonyl chloride. After several hours stirring, the mixture was filtered and the insoluble potassium salt washed with ether and dried. It was dissolved in hot water and acidified with an excess of dilute hydrochloric acid. The suspension of product was cooled in ice for some time and then filtered, washed with water, and dried. It was recrystallized a number of times from ether, m.p. 184–186°.

Anal. Calcd. for $C_{22}H_{19}NSO_4$: C, 67.18; H, 4.83. Found: C, 67.64; H, 5.14.

BERKELEY, CALIF.

[COMMUNICATION NO. 1969 FROM THE KODAK RESEARCH LABORATORIES]

Dithiocarbamates. I. Quaternary Ammonium Dithiocarbamates

K. C. KENNARD AND D. M. BURNESS

Received June 23, 1958

A series of dithiocarbamates containing tertiary amine groups has been alkylated to give quaternary ammonium or pyridinium dithiocarbamates. Proof of the structure of these products is based largely on their ultraviolet absorption spectra. The ultraviolet spectra of various thiono and dithiocarbamates are compared.

A number of dithiocarbamates have been prepared which contain a tertiary amine group; these have been quaternized to give water-soluble quaternary ammonium or pyridinium dithiocarbamates. The synthesis of the intermediate bases was carried out by an adaptation of the well known metathetical reaction between the alkali metal salt of a dithiocarbamate and an alkyl halide,[1] either or both moieties containing the tertiary

(1) M. Kulka, *Can. J. Chem.*, **34**, 1093 (1956); G. Nachmias, *Ann. Chim.* (Paris), **7**, 584 (1952).

TABLE I

DIALKYLDITHIOCARBAMIC ESTERS WITH TERTIARY AMINE AND QUATERNARY AMMONIUM FUNCTIONS

R_2NCS_2R' ("S" refers to the quaternary salts as indicated)

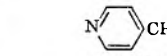
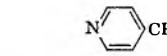
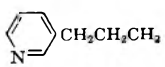
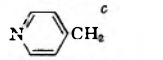
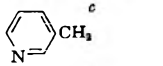
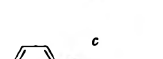
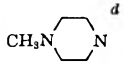
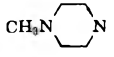
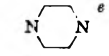
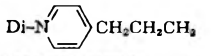
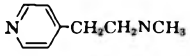
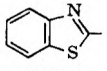
No.	R_2N Amine	R′	% Yield	M.P., °C. and Solvent or B.P., °C. and n_D^{25}	Formula	Analysis								Ultraviolet Absorption Spectra[a]			
						Calculated				Found							
						C	H	N	S	C	H	N	S	λ_{max}	$\epsilon\cdot10^{-3}$	λ_{max}	$\epsilon\cdot10^{-3}$
I	$(CH_3)_2N$		79	62–64 (hexane-chloroform)	$C_{11}H_{16}N_2S_2$	55.0	6.7	11.6		55.0	6.7	11.6		249	12.3	276	9.8
I-S		$(CH_3$, PTS)	70	109.5–111 (acetone)	$C_{19}H_{26}N_2O_3S_3$	53.6	6.1	6.6	22.5	53.8	6.0	6.7	22.8	250	14.2	275	9.8
II	$(C_2H_5)_2N$		60	177 (0.2 mm.); 1.5935[b]	$C_{13}H_{20}N_2S_2$	58.1	7.5	10.4		58.2	7.2	10.0		251	12.3	280	10.8
II-S		(CH_3, ClO_4)	73	101–102 (acetone water)	$C_{14}H_{23}ClN_2O_4S_2$			7.3	16.7			7.2	16.6	254	15.5	279	10.8
III	$(CH_3)_2N$		65	178 (0.4 mm.); 1.6130[b]	$C_{11}H_{16}N_2S_2$	55.0	6.7	11.6		54.7	6.8	11.2		249	11.9	270	11.7
III-S		(CH_3, ClO_4)	50	75–76.5 (acetone)	$C_{12}H_{19}ClN_2O_4S_2$	40.6	5.4	7.9	18.0	40.0	5.4	7.7	18.3	249	10.6	273	12.9
IV	$(CH_3)_2N$		59	67.5–69 (hexane-chloroform)	$C_9H_{12}N_2S_2$	51.0	5.7	12.7		51.4	6.0	12.6		247	12.3	276	9.7
IV-S		$(CH_3$, PTS)	89	93–94 (acetone)	$C_{17}H_{22}N_2O_3S_3$			7.0				6.8		242	12.1	269	11.3
V	$(CH_3)_2N$		68	149–151 (0.2 mm.); 1.6459	$C_9H_{12}N_2S_2$	51.0	5.7	12.7		51.0	5.3	12.3		248	11.8	272	11.5
V-S		$(CH_3$PTS)	87	161–162.5 (methanol acetone)	$C_{17}H_{22}N_2O_3S_3$	51.3	5.6	7.0		51.1	5.9	6.7		243	11.2	270	12.1
VI	$(CH_3)_2N$		81	148–149 (0.25 mm.); 1.6432[b]	$C_9H_{12}N_2S_2$	51.0	5.7	12.7		51.3	5.6	13.1		250	11.0	271	12.5
VI-S		$(CH_3$, PTS)	53	146–147 (dec.) (acetone methanol)	$C_{17}H_{22}N_2O_3S_3$	51.3	5.6	7.0		51.5	5.7	7.0		240	9.5	270	14.1
VII	$(CH_3)_2N$	$(CH_3)_2NCH_2CH_2$[c]	80	88 (0.15 mm.); 1.5733	$C_7H_{16}N_2S_2$	43.6	8.4	14.5		43.4	8.3	14.3		247	8.9	276	10.1
VII-S		$(CH_3$, PTS)	82	153–154.5 (abs. ethanol)	$C_{15}H_{26}N_2O_3S_3$	47.6	6.9	7.4		47.8	6.9	7.2		251	8.5	275	10.2
VIII		$C_6H_5CH_2$		Not isolated													
VIII-S		$(CH_3$, PTS)	52 (yield for 2 steps)	199–200.5 (methanol)	$C_{21}H_{28}N_2O_3S_3$	55.6	6.2	6.2		55.8	6.5	6.2		254	14.0	280	10.5
IX			54	*ca.* 24 (ethyl acetate)	$C_{14}H_{21}N_3S_2$	56.8	7.1	14.2		56.9	7.1	13.9		253	12.7	279	10.9

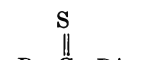
TABLE I (*Continued*)

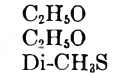
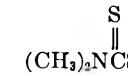
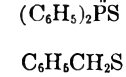
No.	R_2N Amine	R′	% Yield	M.P., °C. and Solvent or B.P., °C. and n^{25}_D	Formula	Analysis Calculated C	H	N	S	Found C	H	N	S	Ultraviolet Absorption Spectra[a] λ_{max}	$\epsilon\cdot10^{-3}$	λ_{max}	$\epsilon\cdot10^{-3}$
IX-S	Very hygroscopic	Di(CH_3, PTS)	50	50.5–52.5 (acetonitrile)	$C_{30}H_{41}N_3O_6S_4$	53.9	6.2	6.3		53.6	6.6	5.9		254	15.7	281	8.8
X			63	131–134 (acetone)	$C_{22}H_{28}N_4S_4$	55.4	5.9			55.6	5.4			255	27.8	281	25.0
X-S	[f]	Di(CH_3, PTS)	62	183–185 (abs. ethanol)	$C_{38}H_{48}N_4O_6S_6$	53.8	5.7	6.6		53.6	5.3	6.7		256	34.5	281	24.8
XI	$(C_6H_5CH_2)_2N$	$(CH_3)_2NCH_2CH_2$	74	Undist. oil 1.6187[b]	$C_{18}H_{24}N_2S_2$	66.3	7.0	8.1	18.6	66.7	6.9	7.8	18.7	254	11.7	282	11.3
XI-S		(CH_3, PTS)	87	143.5–145 (acetone)	$C_{27}H_{34}N_2O_3S_3$	61.1	6.5	5.3		61.4	6.5	4.9		250	13.6	282	14.0
XI-S′	[g]		69	159–160 (acetone (methanol)	$C_{46}H_{56}Cl_2N_4O_8S_4$	55.7	5.7	5.6	12.9	55.8	5.8	5.6	12.9				
XII		$C_6H_5CH_2$	71	87.5–89 (methanol)	$C_{16}H_{18}N_2S_2$	63.6	6.0	9.3	21.2	63.9	6.1	9.6	21.2	252	15.6	279	10.3
XII-S	[h]	(CH_3, ClO_4)	82	120–121.5 (acetone)	$C_{17}H_{21}ClN_2O_4S_2$	48.9	5.1	6.7	15.4	48.6	5.3	6.3	15.5				
XIII	$(CH_3)_2N(CH_2)_3NCH_3$	$C_6H_5CH_2$		Not isolated													
XIII-S		(CH_3, PTS)	30 (Yield for 2 steps)	178–179.5 (methanol)	$C_{22}H_{32}N_2O_3S_3$	56.4	6.9	6.0	20.5	56.2	7.2	5.8	20.6				
XIV	$(CH_3)_2N$	$C_6H_5CH_2CH_2$	73	47 (methanol)	$C_{11}H_{15}NS_2$	58.7	6.7	6.2		58.5	6.7	5.9		249	10.8	276	10.1
XV	$(CH_3)_2N$	$CH_3SCH_2CH_2$[c]	87	114 (0.3 mm.); 1.6192	$C_6H_{13}NS_2$	36.9	6.7	7.2	49.2	37.2	6.1	7.2	49.6	248	10.6	276	10.1
XVI[i]	$(C_2H_5)_2N$			78–79.5 (methanol)	$C_{12}H_{14}N_2S_3$			9.9	34.1			9.8	33.9			276	20.1
XVII	$Di(C_2H_5)_2N$	$—(CH_2)_6—$	43	76–78 (methanol)	$C_{16}H_{32}N_2S_4$	50.5	8.5		33.7	50.5	8.3		33.7	252	19.7	278	21.2

[a] In methanol. For published spectra of dithiocarbamates, see A. D. Ainley, W. H. Davies, H. Gudgeon, J. C. Harland, and W. A. Sexton, *J. Chem. Soc.* (London), 147 (1944); J. R. Robinson *et al.*, *Can. J. Res.*, 34, 1596 (1956); H. P. Koch, *J. Chem. Soc.* (London), 401 (1949). See also: K. Kanamaru, T. Takada, and T. Taniguchi, *J. Soc. Chem. Ind.* (Japan), 42, 47 (1939); J. Chatt, L. A. Duncanson, and L. M. Venanzi, *Nature*, 177, 1042 (1956). [b] Purified chromatographically. [c] Intermediate chloride obtained from Aldrich Chemical Co. [d] 1-Methylpiperazine used; courtesy of Carbide and Carbon Chemicals Co. [e] Disodium *N,N′*-piperazinebis(carbodithioate), prepared according to R. Damiens and R. Delaby, *Compt. rend.*, 236, 931 (1953). [f] The reactants were refluxed in chloroform for 15 min. [g] *p*-Xylylene dibromide and two equivalents of the base (XI) were refluxed in ether for 12 hr., then in methanol for 4 hr. and the product was dissolved in a large volume of 50% aqueous methanol and treated with sodium perchlorate. [h] The base XII was refluxed in methanol for 15 min. with methyl *p*-toluenesulfonate. [i] Prepared according to W. W. Levis, Jr., U. S. Patent 2,697,098 (1954); *Chem. Abstr.*, 49, 15975 (1955).

TABLE II

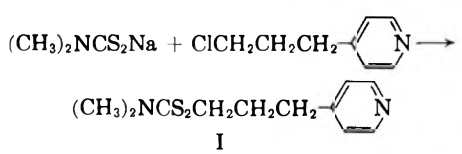
MISCELLANEOUS THIOCARBAMATES



No.	R	R′	% Yield	M.P., °C. and Solvent or B.P., °C. and n_D^{25}	Ultraviolet Absorption Spectra[a] λ_{max}	$\epsilon\cdot10^{-3}$	λ_{max}	$\epsilon\cdot10^{-3}$
XVIII[b]	CH_3CONH	C_2H_5S	..	123 (benzene)	259	13.7	310	11.7
XIX[c]	CH_3CONH	C_2H_5O	..	100–101 (ligroin)	261	12.6	...	...
XX[d]	$(C_2H_5)_2N$	C_2H_5O	68	49–50 (0.3 mm.); 1.4940	249	14.2	...	...
XXI[e]	$NHCH_2CH_2NH$	Di-CH_3S	..	105–107 (benzene)	...	..	270	21.4
XXII[f]	$(CH_3)_2N$		..	150.5–151.5 (benzene)			280	11.6
XXIII[g]	$(CH_3)_2N$		..	107.5–108.5 (benzene)			279	16.3
XXIV	$(C_2H_5)_2N$		77	130–132.5 (benzene-ligroin)			275–6	9.9
XXV[h]	NH_2NH	$C_6H_5CH_2S$		125 (benzene)	274	13.2	299	14.8

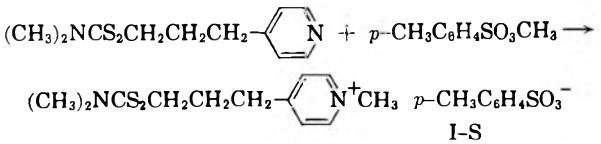
[a] Absorption spectra run in methanol. [b] H. L. Wheeler and H. F. Merriam, *J. Am. Chem. Soc.*, **23**, 290 (1901). [c] G. S. Skinner and H. C. Vogt, *J. Am. Chem. Soc.*, **77**, 5440 (1955); H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **24**, 189 (1900). [d] A. Hantzsh, *Ber.*, **64**, 661 (1931). [e] Anal. Calcd. for $C_6H_{12}N_2S_4$: C, 30.0; H, 5.0; N, 11.6, Found: C, 30.1; H, 5.1; N, 12.0. [f] Eastman Chemical No. P-2089, recrystallized from benzene; Beilstein, m.p. 146°. [g] Eastman Chemical No. P-6255, recrystallized from benzene; Beilstein, m.p. 104°. [h] M. Busch and M. Starke, *J. prakt. Chem.*, **93**, 59 (1916). The authors are grateful to Dr. M. Baron, formerly of these Laboratories, for this sample.

amine group. The reaction of γ-3-chloropropylpyridine with sodium dimethyldithiocarbamate (see Experimental) to give 3-(γ-pyridyl)propyl dimethyldithiocarbamate (I) is illustrative of this reaction.



I

The resulting basic esters are listed in Table I, along with products of their quaternization. The reaction of I with methyl *p*-toluenesulfonate is illustrative of the quaternization reaction. A few

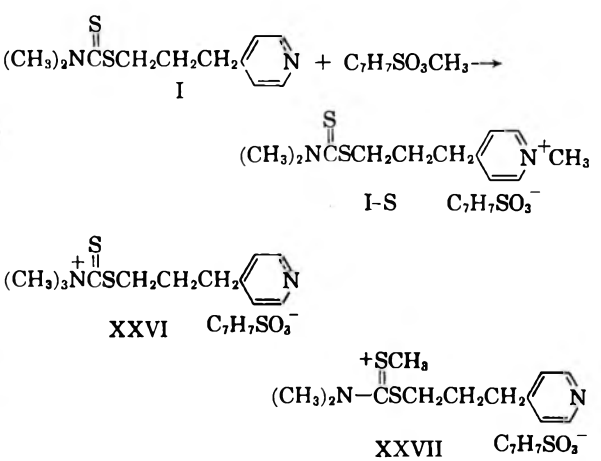


I-S

related compounds pertinent to the discussion are shown in Table II.

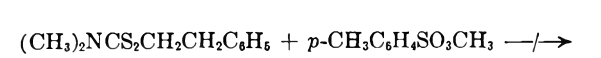
The quaternization of these compounds was accomplished with methyl *p*-toluenesulfonate in ether solution. In those instances of sluggish reaction, methanol was employed. Extended boiling in methanol produced by-products which made subsequent purification difficult. Extensive decomposition also occurred when the reactants were heated on the steam bath without a solvent.

Because of the presence of three basic groups (two nitrogen atoms and one unsaturated carbon sulfur link), the quaternization step is ambiguous. Quaternization of I, for example, might lead to any of the three products shown (I-S, XXVI, or XXVII).



The correctness of the assignment of a I-S type of structure to these compounds is evident from the following considerations:

(1) Attempts to form a salt from β-phenethyl dimethyldithiocarbamate (XIV) with methyl *p*-toluenesulfonate were unsuccessful. Furthermore,



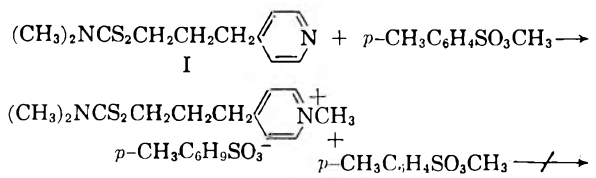
XIV

attempts to react I with *two* moles of methyl *p*-toluenesulfonate were unsuccessful. Only I-S was isolated.

TABLE III

COMPARISON OF ULTRAVIOLET SPECTRA OF MONO- AND DITHIOCARBAMATES

No.	Structure	$\lambda_{max(10^{-3}\epsilon)}$	Res. Contr. Involved	$\lambda_{max(10^{-3}\epsilon)}$	Res. Contr. Involved
XIV	$(CH_3)_2NC(=S)SCH_2CH_2C_6H_5$	249 (10.8)	XXVIIIa	276 (10.1)	XXVIIIb
XX	$(C_2H_5)_2NC(=S)OC_2H_5$	249 (14.2)	XXIXa	...	...
XVIII	$CH_3CNHC(=S)SC_2H_5$	259 (13.7)	XXVIIIa	310 (11.7)	XXVIIIb
XIX	$CH_3CNHC(=S)OC_2H_5$	261 (12.6)	XXIXa	...	...



This showed that the dimethylthiocarbamate moiety is inert under the conditions of quaternization employed.

(2) The infrared spectrum of the free base (I) has a peak at 6.25 mμ, while the salt absorbs at 6.1 mμ; both are characteristic of a pyridine base and its quaternary salt.[2]

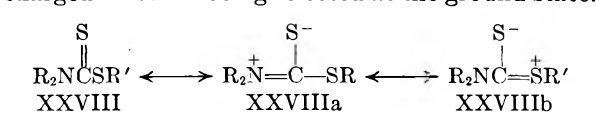
(3) The ease of quaternization (insofar as reaction time and temperature are concerned) paralleled that of the basic group involved, *i.e.*, pyridine in the case of I.

(4) The ultraviolet spectra, which are discussed presently, also are in agreement with a I-S type of structure.

Attempted quaternization of the basic dithiocarbamate esters with bismethanesulfonates or bis-*p*-toluenesulfonates was unsuccessful since, at the higher temperatures required for quaternization with these reagents, extensive decomposition occurred. The only successful synthesis of a true bis-quaternary dithiocarbamate was effected by the use of *p*-xylylene dibromide to give XI-S′ (Table I).

Attempts to form a sulfonium salt analogous to the quaternary salts by heating β-(methylmercapto)ethyl dimethyldithiocarbamate (XV) with methyl *p*-toluenesulfonate, with or without a solvent, were unsuccessful. Similarly, 2-benzothiazolyl diethyldithiocarbamate (XVI) was not quaternized successfully.

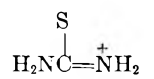
Ultraviolet spectra. The resonance contributors for dialkyldithiocarbamates are as shown, the uncharged XXVIII being selected as the ground state.



(2) Unpublished observations of Thelma Davis, of these Laboratories.

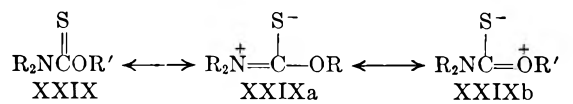
The ultraviolet spectrum of a dithiocarbamate is thus expected to show two peaks, representing the electronic transitions to XXVIIIa and XXVIIIb.[3] Inspection of Table I shows this to be the case.

The ultraviolet peak at lower energy (higher λ_{max}) is assigned to XXVIIIb, while that at higher energy level (lower λ_{max}) is assigned to XXVIIIa. This is in agreement with the spectrum of thiourea which shows the transition to



at about 255 mμ.[3]

This assignment has also been confirmed by the spectra of thionocarbamates (XXIX) (work done in these Laboratories). Since oxygen does not participate in electronic transitions as readily as sulfur, a structure such as XXIXb is not expected



to absorb in the quartz ultraviolet region. The peak related to XXIXa, however, should and does correspond to that caused by XXVIIIa. These facts are clearly illustrated by the data presented in Table III.

The acyldithiocarbamate (XVIII) and the acylthionocarbamate (XIX) absorb at a different wave length from that of the corresponding dialkyl analogs because of their different structure. The similarity of absorption in each series, however, is significant and lends support to the theory.

The ultraviolet spectra of the three sulfides (XXII, XXIII, and XXIV) show broad, less distinct peaks than the dithiocarbamate esters and for this reason are difficult to interpret. The broad peaks may be a fusion of several peaks which normally would be resolved. In any case, the three sulfides show an apparent single absorption at 275–280 mμ.

(3) H. P. Koch, *J. Chem. Soc.*, 401 (1949).

The discussion of the possible electronic transitions of the dithiocarbamates can presumably be extended to include the dithiocarbazates. In accord with the theory, benzyl dithiocarbazate (XXV), the only such compound available, showed absorption maxima at 274 mμ and 299 mμ.

EXPERIMENTAL[4]

A detailed description of the steps leading to γ-[3-(dimethyldithiocarbamato)propyl]-*N*-methylpyridinium *p*-toluenesulfonate (I-S) is illustrative of the methods used in the preparation of these compounds. Significant variations in the procedures are noted subsequently or in the tables, and all the data of value in the characterization of the compounds are collected in Tables I and II.

In those cases in which the intermediate dithiocarbamate bases were oils, it was sometimes necessary (as noted in Table I) to purify them further, after distillation. This was done by passing an ether solution of the distillate through a short column (*ca.* 1 × 10 in.) of activated alumina and elution with fresh ether. Removal of the solvent by warming *in vacuo* produced the pure product.

Occasionally, the *p*-toluenesulfonate salts were hygroscopic, in which event they were converted to the perchlorates by an excess of aqueous sodium perchlorate.

γ-3-Chloropropylpyridine. Thionyl chloride (90 g.) was added dropwise to 68.5 g. of 4-pyridinepropanol (Eastman Kodak Co. No. P5702) in 250 ml. of chloroform over a 25-min. period. When the initial exothermic reaction had ceased, the solution was heated at reflux temperature for 1 hr. The black reaction mixture was poured onto ice, the aqueous layer was made basic to litmus by the addition of 50% KOH solution, and, after thorough shaking in a separatory funnel, the chloroform layer was removed. The aqueous layer was extracted with 150 ml. of chloroform, and the combined chloroform extracts were decolorized with Pittsburgh Type RB activated carbon and dried over magnesium sulfate. The volatiles were then removed *in vacuo*, and the residue was distilled, giving 80–85% of γ-3-chloropropylpyridine:

$$b_{0.3}\ 57\text{–}8°;\ n_D^{25}\ 1.5230$$

Anal. Calcd. for $C_8H_{10}ClN$: N, 9.0 Found: N, 9.2.

This compound was stored at −20° to prevent polymerization which occurs slowly at room temperature. Although a larger quantity may be prepared in one experiment, attempts to distill more than about 125 g. at one time resulted in a lower yield and occasionally led to a violent, exothermic polymerization in the distillation flask.

(4) Melting and boiling points are uncorrected.

3-(γ-Pyridyl)propyl dimethyldithiocarbamate (I). To 10.1 g. of sodium dissolved in 500 ml. of dry methanol was added 73 g. of dimethylammonium dimethyldithiocarbamate (Eastman Kodak Co. No. 812), with stirring. The yellow-to-green solution was treated with 45 g. of γ-3-chloropropylpyridine, and the reaction mixture was heated, with stirring, for 6.5 hr. The volatiles were removed on the steam bath until the volume of solution was about 250 ml. This boiling residue was treated with Pittsburgh Type RB activated carbon and filtered. The filtrate was cooled, and 250 ml. of water was added, with cooling and scratching of the flask with a glass rod. After standing in the refrigerator overnight, the light-brown crystals were filtered and recrystallized from hexane chloroform solution, yielding 41.5 g. (60%) of 3-(γ-pyridyl)propyl dimethyldithiocarbamate which melted at 60.5–63°. Further recrystallization from the same solvent afforded an analytical sample, m.p. 62–64°.

γ-[3-(Dimethyldithiocarbamato)propyl]-N-methylpyridinium p-toluenesulfonate (I-S). To 3.8 g. of 3-(γ-pyridyl)propyl dimethyldithiocarbamate in 50 ml. of dry ether was added 3.5 g. of freshly distilled methyl *p*-toluenesulfonate, and the solution was heated under reflux for 3–6 hr. The precipitate was filtered and recrystallized twice from acetone: m.p. 109.5–111°; yield, 4.8 g. (71%).

Benzyl methyl(2-γ-pyridylethyl)dithiocarbamate (XII). To a solution of 27.2 g. of 4-(2-methylaminoethyl)pyridine[5] and 8 g. of sodium hydroxide in 75 ml. of water was added 15.2 g. of carbon disulfide. The solution was cooled and 100 ml. of methanol added, followed by 25.2 g. of benzyl chloride. After 15 min. at 25°, the mixture was filtered and recrystallized from methanol (see Table I).

Diethylthiocarbamoyl diphenylphosphinothioyl sulfide (XXIV). A mixture of 25 g. of diphenyldithiophosphinic acid[6] and 5.4 g. of sodium methoxide in 600 ml. of benzene was heated under reflux for 15 min., then 200 ml. of benzene methanol azeotrope was distilled off. An additional 400 ml. of benzene was added, followed by a solution of diethylthiocarbamoyl chloride in benzene. The solution cleared, and sodium chloride gradually separated. The mixture was filtered, concentrated, and ligroin was added to the residual oil. The resulting crystalline solid was recrystallized from benzene-ligroin: yield, 28 g.; m.p. 130–132.5°.

Anal. Calcd. for $C_{17}H_{20}NPS_3$: C, 56.0; H, 5.5; N, 3.8; S, 26.3. Found: C, 56.2; H, 5.8; N, 3.6; S, 26.1.

Acknowledgment. The authors are grateful to the following colleagues: Dr. C. F. H. Allen for many helpful suggestions; Mr. D. Ketchum for microanalyses; Miss T. Davis for infrared spectra; and Mr. E. E. Richardson for ultraviolet spectra.

ROCHESTER 4, N. Y.

(5) A. P. Phillips, *J. Am. Chem. Soc.*, 78, 4441 (1956).

(6) Courtesy of The Lubrizol Corp., Cleveland, Ohio.

[COMMUNICATION NO. 1970 FROM THE KODAK RESEARCH LABORATORIES]

Dithiocarbamates. II. The Formation of 1,3-Dithiane, 1,3-Dithiolane, and 1,3-Dithiepane Quaternary Salts

KENNETH C. KENNARD AND JAMES A. VANALLAN

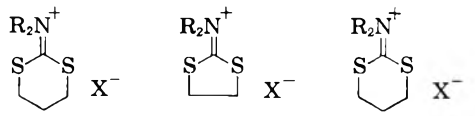
Received June 23, 1958

The hitherto unknown 1,3-dithiolan-, 1,3-dithian-, and 1,3-dithiepan-2-dialkylimmonium salts have been prepared by the reaction of 2-hydroxyethyl, 3-hydroxypropyl, and 4-hydroxybutyl dialkyldithiocarbamate, respectively, with *p*-toluenesulfonyl chloride. 1,3-Dithian-2-diethylimmonium perchlorate is decomposed by alkali to 1,3-propanedithiol, 3-mercaptopropyl diethylthiolcarbamate, and bis(3-diethylthiolcarbamatopropyl)disulfide. The 4-, 5-, and 6-membered ring compounds show a characteristic absorption peak between 262 and 276 mμ.

It has been discovered that certain hydroxyalkyl dialkyldithiocarbamates cyclize in the presence of *p*-toluenesulfonyl chloride. The product of this reaction is a 1,3-dithiane (I), a 1,3-dithiolane (II), or a 1,3-dithiepane (III), depending on whether the starting dithiocarbamate ester is the 3-hydroxypropyl, the 2-hydroxyethyl, or the 4-hydroxybutyl, respectively. Presumably, the *p*-toluenesulfonate ester is an intermediate in this reaction.

$$R_2NCS_2CH_2CH_2CH_2OH + C_7H_7SO_2Cl \longrightarrow R_2NCS_2CH_2CH_2CH_2O_3SC_7H_7$$

$$R_2NCS_2CH_2CH_2CH_2O_3SC_7H_7 \xrightarrow{\Delta} I$$



I II III

The ring closure was effected by two methods. Method A consisted in the addition of *p*-toluenesulfonyl chloride to the dithiocarbamate in dimethylformamide with a flow of nitrogen to entrain the by-product, hydrogen chloride. The product was isolated as the perchlorate or the tetraphenylboron salt.

One drawback to this method is the strong solubilizing effect of the dimethylformamide in the solution from which the product was recovered. The use of a more concentrated reaction solution produced resinous by-products which contaminated the salts.

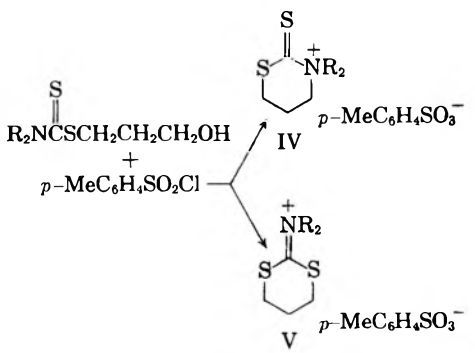
In Method B, the initial reaction was carried out in benzene in the presence of triethylamine. After removal of the triethylamine hydrochloride by filtration, ring closure was effected by heating under reflux. The product was isolated as described previously. This method suffered from the lack of a highly polar solvent which would facilitate the transformation of nonpolar reactants to ionic products. Ultimate yields would probably require the use of a solvent with a high dipole which could be removed after the reaction was completed.

Method B was used to prepare the five-membered ring compound, 1,3-dithiolan-2-diethylimmonium tetraphenylboron, and the seven-membered ring compound, 1,3-dithiepan-2-diethylimmonium perchlorate.

The intermediate hydroxyalkyl dialkyldithiocarbamates are high-boiling or undistillable oils of fair thermal stability. The pure compounds are slightly yellow in color and possess unusually high refractive indices. As may be seen in Table I, their ultraviolet absorption characteristics closely resemble those of other dithiocarbamates.[1]

The dithianes are white, crystalline solids. The *p*-toluenesulfonate salts are hygroscopic and water-soluble, while the perchlorate and tetraphenylboron salts are nonhygroscopic and less water-soluble. The tetraphenylboron salt is especially convenient for homologs bearing small groups on the nitrogen atom. Unlike the dithiocarbamates which show two ultraviolet absorption peaks, the dithianes show only one peak. The dithianes are readily hydrolyzed by dilute alkali. Only one dithiolane and dithiepane were prepared, but they appeared to resemble the dithianes in all respects.

The cyclization of 3-hydroxypropyl dialkyldithiocarbamates conceivably might result in a compound possessing either of two structures. Ring closure on the nitrogen atom would produce the thiazine structure, IV, while alkylation of the un-



IV V

(1) See Part I for a discussion of the properties of the dithiocarbamates.

(2) C. H. Grogan, L. M. Rice, and E. E. Reid, *J. Org. Chem.*, **20**, 50 (1955).

(3) F. Arndt and F. Bielich, *Ber.*, **56**, 2276 (1923).

(4) H. L. Wheeler and B. Barnes, *Am. Chem. J.*, **24**, 60 (1900). H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **24**, 189 (1900). H. L. Wheeler and G. K. Dustin, *Am. Chem. J.*, **24**, 424 (1900).

TABLE I

DITHIOCARBAMATES

$R_2NCS_2(CH_2)_\eta OH$

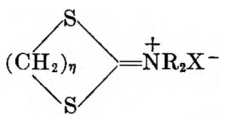
No.	R	η	% Yield	B.P., °C./mm. Hg	n_D^{25}	λ_{max}[a] (mμ)	$10^{-3}\epsilon$	Analysis Calcd./Found % C	% H	% N	% S
XII	CH_3	3	87	139–141/0.5	1.6005[b]	248	9.3	40.2	7.3	7.8	
						276	10.5	40.3	7.4	7.5	
XIII	C_2H_5	3	75	121–122/0.1	1.5726	252	9.4	46.4	8.3	6.8	
						279	10.0	46.1	8.3	6.9	
XIV	n-C_3H_7	3	75	129.5/0.1	1.5559	253	9.3	51.1	9.0	5.9	27.3
						279	10.5	51.0	9.2	5.6	27.4
XV	C_5H_{10}	3	50	162–163/0.2	1.5923			49.4	7.8	6.4	29.2
								48.9	7.7	6.0	28.7
XVI	$C_6H_5CH_2$	3	62	[c]	1.6273	254	11.0	65.3	6.4	4.3	19.2
						282	10.5	65.2	6.4	4.0	19.1
XVII	C_2H_5	2	80	122/0.2	1.5861	25[d]	9.2	43.5	7.8	7.2	
						270	10.9	43.6	7.9	7.1	
XVIII	C_2H_5	4	82	[c]	1.5650					6.3	
										6.2	

XII. 3-Hydroxypropyl dimethyldithiocarbamate.
XIII. 3-Hydroxypropyl diethyldithiocarbamate.
XIV. 3-Hydroxypropyl di-*n*-propyldithiocarbamate.
XV. 3-Hydroxypropyl piperidine-*N*-carbodithioate.
XVI. 3-Hydroxypropyl dibenzyldithiocarbamate.
XVII. 2-Hydroxyethyl diethyldithiocarbamate.
XVIII. 4-Hydroxybutyl diethyldithiocarbamate.

[a] In methanol solution. [b] Temperature of 24°. [c] Purified chromatographically.

TABLE II

QUATERNARY SALTS



No.	R	η	X^-	% Yield	M.P., °C.	λ_{max}[a] (mμ)	$10^{-3}\epsilon$	Analysis Calcd./Found % C	% H	% N	% S
XIX	CH_3	3	$C_7H_7SO_3$	35	136–138	262	12.7	46.7	5.7	4.2	
								46.9	5.7	4.2	
XX	C_2H_5	3	ClO_4[b]	64–69	125.5–127	266	18.4	33.2	5.6	4.8	21.1
								33.3	5.4	5.0	21.1
XXI	n-C_3H_7	3	ClO_4	53	153–155	268	14.8	37.9	6.3	4.4	20.2
								38.0	6.3	4.2	20.2
XXII	C_5H_{10}	3	ClO_4	26	142.5–144.5	268	12.0	35.9	5.4	4.6	21.2
								35.4	5.1	4.5	21.1
XXIII	$C_6H_5CH_2$	3	ClO_4	36	134	271	13.7	52.2	4.9		
								52.1	4.8		
XXIV	C_2H_5	2	$(C_6H_5)_4$[b]	42	208	256[c]	17.2	75.2	6.9		
								75.4	7.0		
XXV	C_4H_5	4	ClO_4	29	99–100	276[a]	11.2	35.6	5.9	4.6	
								35.6	5.8	4.5	

XIX. 1,3-Dithian-2-dimethylimmonium *p*-toluenesulfonate, recrystallized from acetone. This compound is very hygroscopic.
XX. 1,3-Dithian-2-diethylimmonium perchlorate.
XXI. 1,3-Dithian-2-di-*n*-propylimmonium perchlorate, recrystallized from acetone.
XXII. 1,3-Dithian-2-cyclopentamethylenimmonium perchlorate, recrystallized from acetone.
XXIII. 1,3-Dithian-2-dibenzylimmonium perchlorate, recrystallized from alcohol.
XXIV. 1,3-Dithiolan-2-diethylimmonium tetraphenylboron.
XXV. 1,3-Dithiepan-2-diethylimmonium perchlorate, recrystallized from water.

[a] In methanol solution. [b] Tetraphenylboron salt had m.p. 184°. [c] In dimethyl sulfoxide solution. [d] In water solution.

saturated sulfur atom would produce the dithiane structure, V. By analogy with the alkylation of thiourea,[2] monoalkyldithiocarbamates,[3] or thionocarbamates,[4] the dithiane seems to be the obvious answer. Furthermore, alkylation of the amide nitrogen atom, which is required for the thione formation, seems unlikely.

In order to establish the structure of the 1,3-

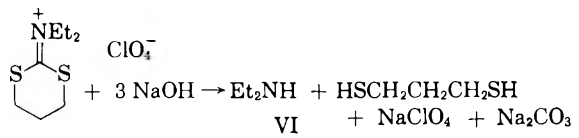
TABLE III

HYDROLYSIS FRAGMENTS

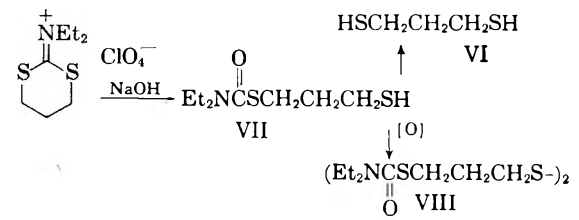
No.	Compound	B.P., °C./mm Hg	n_D^{25}	Analysis Calcd./Found %C	%H	%N	%S
VI	$HSCH_2CH_2CH_2SH$[a]	64/13	1.5406				
VII	$Et_2NC(=O)SCH_2CH_2CH_2SH$[b]	153–154/9	1.5258	46.4 46.4	8.2 8.2	6.8 6.8	30.9 31.2
VIII	$(Et_2NC(=O)SCH_2CH_2CH_2S)_2$[c]	228–230/0.1	1.5522	47.0 47.0	7.7 8.2	7.1 7.0	30.9 31.0

[a] S. D. Simpson, *Can. J. Res.*, 25B, 20 (1947), b.p. 57°; J. R. Meadow and E. E. Reid, *J. Am. Chem. Soc.*, 56, 2177 (1934), n_D^{20} 1.5403. [b] Distillation performed by Dr. Dorothy J. Beavers, of these Laboratories. This substance is a strong skin irritant. [c] The distillate, a slightly brown oil, was further purified chromatographically. Mol. wt. in benzene, 411; calculated, 412.

dithianes, the alkaline hydrolysis of a representative compound was studied. The complete alkaline hydrolysis of 1,3-dithian-2-diethylimmonium perchlorate was expected to proceed as shown in the formula. In practice, several organic fragments were

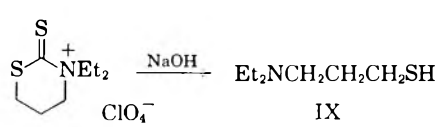


isolated, including 1,3-propanedithiol (VI), 3-mercaptopropyl diethylthiolcarbamate (VII), and bis(3-diethylthiolcarbamatopropyl) disulfide (VIII). Consequently, the hydrolysis scheme can be amended as follows:



That the carbamates were the thiol isomers and not the thione isomers was shown by their transparency to ultraviolet radiation. The properties of the hydrolysis fragments are summarized in Table III.

Under similar hydrolytic conditions, the thione would be expected to provide diethyl-3-mercaptopropylamine (IX). No trace of this amine was detected.

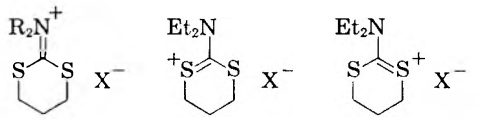


A polarographic study[5] of the alkaline hydrolysis of 1,3-dithian-2-diethylimmonium perchlorate also furnished evidence for the dithian structure. The polarogram recorded immediately after solution of the sample showed an anodic wave at −0.6 volt *vs.* S.C.E. (saturated calomel electrode) and a cathodic wave at −1.2 volts *vs.* S.C.E. These reduction waves were attributed to the sulfhydryl and carbon-nitrogen groups, respectively. After exhaustive hydrolysis, the reduction wave due to the carbon-nitrogen bond was absent, whereas the reduction wave due to the mercaptan appeared to increase.

In an independent experiment, the mercaptan formed in this alkaline hydrolysis was precipitated as the silver salt. Analysis of this precipitate showed the empirical formula of the mercaptide to agree well with 1,3-propanedithiol, the expected hydrolysis product of 1,3-dithian-2-diethylimmonium perchlorate.

Evidence for the presence of the unstable diethylcarbamic acid as a product of the complete alkaline hydrolysis was noted when the alkaline hydrolyzate was made slightly acid (to phenolphthalein) and refluxed. The solution gradually turned alkaline, as evidenced by the reappearance of the phenolphthalein color. The cycle could be repeated by adding more acid and refluxing. This was attributed to the decomposition of diethylcarbamic acid to carbon dioxide and its removal by refluxing.

It has been pointed out (Part I) that dithiocarbamates exhibit several resonance forms, and these have been assigned, both for theoretical and experimental reasons, to specific excited states of the molecule.[1,6] In the dithianes under discussion, there is also opportunity for resonance. Since



two of the states are equivalent, only one ultraviolet absorption peak is expected and only one was observed (Table II).

(5) The authors are grateful to Dr. E. P. Przybylowicz, of these Laboratories, for conducting the work with the polarograph and for analyzing the data.

(6) H. P. Koch, *J. Chem. Soc.*, 401, (1949).

EXPERIMENTAL

The boiling and melting points of all substances described here are uncorrected.

The hydroxyalkyl dialkyldithiocarbamates mentioned here were prepared from 2-bromoethanol, 3-bromopropanol, or 4-chlorobutanol, and the sodium salt of the requisite dithiocarbamic acid, using the general procedure described in Part I.

The syntheses of two of the cyclic quaternary salts, one by Method A and one by Method B, illustrate the general technique employed. The individual compounds are named, associated by Roman numerals, with the data in the tables and accompanied by any pertinent miscellaneous information below them.

Method A. 1,3-Dithian-2-diethylimmonium perchlorate (XX). A solution of 20.7 g. of 3-hydroxypropyl diethyldithiocarbamate (XIV) and 19.1 g. of *p*-toluenesulfonyl chloride in 50 ml. of dimethylformamide, with a stream of nitrogen to dispel the by-product, hydrogen chloride, was maintained for 1 hr. at 60° by intermittent cooling. The reaction solution, without the nitrogen stream, was heated further at 60° for 24 hr. The cooled solution was then poured into 200 ml. of water containing 15 g. of sodium perchlorate. The resulting white crystalline solid was recrystallized from water–acetone solution.

A solution of 0.005 mole of XX in 30 ml. of water was mixed with 0.0055 mole of sodium tetraphenylboron in 30 ml. of water. The resulting white solid was removed by filtration and recrystallized from dimethyl sulfoxide. The pure 1,3-dithian-2-diethylimmonium tetraphenylboron melted at 184°.

Method B. 1,3-Dithiolan-2-diethylimmonium tetraphenylboron (XXIV). A solution of 19.5 g. of 2-hydroxyethyl diethyldithiocarbamate (XVII) in 100 ml. of benzene containing 18 ml. of triethylamine was treated with 22 g. of *p*-toluenesulfonyl chloride. After the solution had been stirred for 3 hr., it was filtered; 16 g. of triethylamine hydrochloride remained on the filter. The filtrate was heated under reflux for 1.5 hr., after which 32 ml. of benzene-insoluble oil was separated. Volatiles were removed *in vacuo* from the warmed oil; the final weight of viscous oil was 20 g. A solution of 1.73 g. of this oil in 25 ml. of water was treated with 1.71 g. of sodium tetraphenylboron in 80 ml. of water. The white crystalline solid was removed from the cooled solution by filtration and recrystallized from dimethylsulfoxide.

Purification of 3-hydroxypropyl dibenzyldithiocarbamate (XVI). This compound appeared to decompose above 200° at a pressure of 0.03–0.04 mm. Consequently, it was purified chromatographically, by means of a 22-in. column of alumina with an outside diameter of 1.25 in., and benzene as the solvent. Fractions of about 50 ml. were collected; only those fractions which gave the proper analysis were employed. The pure compound is a very viscous oil.

Hydrolysis of 1,3-dithian-2-diethylimmonium perchlorate (XX). The relative yields of hydrolysis fragments varied with the mode of hydrolysis. A solution of 87 g. of XX and 48 g. of sodium hydroxide in 300 ml. of water was heated on the steam bath for 4 hr. The reaction solution was cooled, acidified, and extracted with ether. The ether was evaporated and the residual oil was distilled, giving 7 g. of VI, 3 g. of VII, and 21 g. of VIII. VII was further purified chromatographically, using a 24-in. column (outside diameter = 2 in.) filled with alumina and benzene as the solvent.

A solution of 20 g. of XX and 7.5 g. of sodium carbonate in 100 ml. of water was steam-distilled. The distillate was extracted with ether, the ether was evaporated, and the residue was distilled, giving 1 g. of VI and 6 g. of VII.

The polarographic study was made with a Sargent Model XXI polarograph. Polarograms were recorded on millimolar solutions of the dithiane in 0.5*M* ammonium sulfate–ammonium hydroxide buffer containing 50% methanol by volume. The maxima suppressor employed was 0.001% Triton-X-100. Polarograms were recorded on solutions 0, 15, and 30 min. after mixing. The hydrolysis reaction was essentially complete after 30 min.

The silver mercaptide was isolated by precipitating it from an ammoniacal solution of the hydrolyzed dithiane. This salt was dried *in vacuo* and identified by its silver, carbon, hydrogen, and sulfur analyses.

ROCHESTER 4, N. Y.

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

Cyanoethylation of the 5-Aminotetrazoles[1]

DONALD W. RENN[2,3] AND ROBERT M. HERBST

Received July 11, 1958

Cyanoethylation of 5-aminotetrazole gave a mixture of 1- and 2-β-cyanoethyl-5-aminotetrazole. The same mixture of products was obtained by alkylation of 5-aminotetrazole with β-bromopropionitrile. Interaction of 1-benzyl-5-aminotetrazole and acrylonitrile gave both 1-benzyl-5-β-cyanoethylaminotetrazole and 1-benzyl-5-di-β-cyanoethylaminotetrazole. 1-β-Cyanoethyl-5-aminotetrazole was also obtained from β-aminopropionitrile by interaction successively with cyanogen bromide and hydrazoic acid. Under similar conditions β,β′-iminodipropionitrile gave 5-di-β-cyanoethylaminotetrazole. 1-Benzyl-4-β-cyanoethyl-5-iminotetrazoline hydrochloride was formed on alkylation of 1-benzyl-5-aminotetrazole with β-ehloropropionitrile or on benzylation of 1-β-cyanoethyl-5-aminotetrazole.

Many compounds containing active hydrogen atoms will undergo the cyanoethylation reaction.[4] The purpose of this investigation was to determine the conditions for the cyanoethylation of 5-aminotetrazole and to establish the structures of the resulting products. Tautomerism of the 5-aminotetrazole structure[5] makes conceivable the formation of three monocyanoethylated products: 1-β-cyanoethyl-5-aminotetrazole (I), 2-β-cyanoethyl-5-aminotetrazole (II), and 5-β-cyanoethylaminotetrazole (VII). An even greater number of

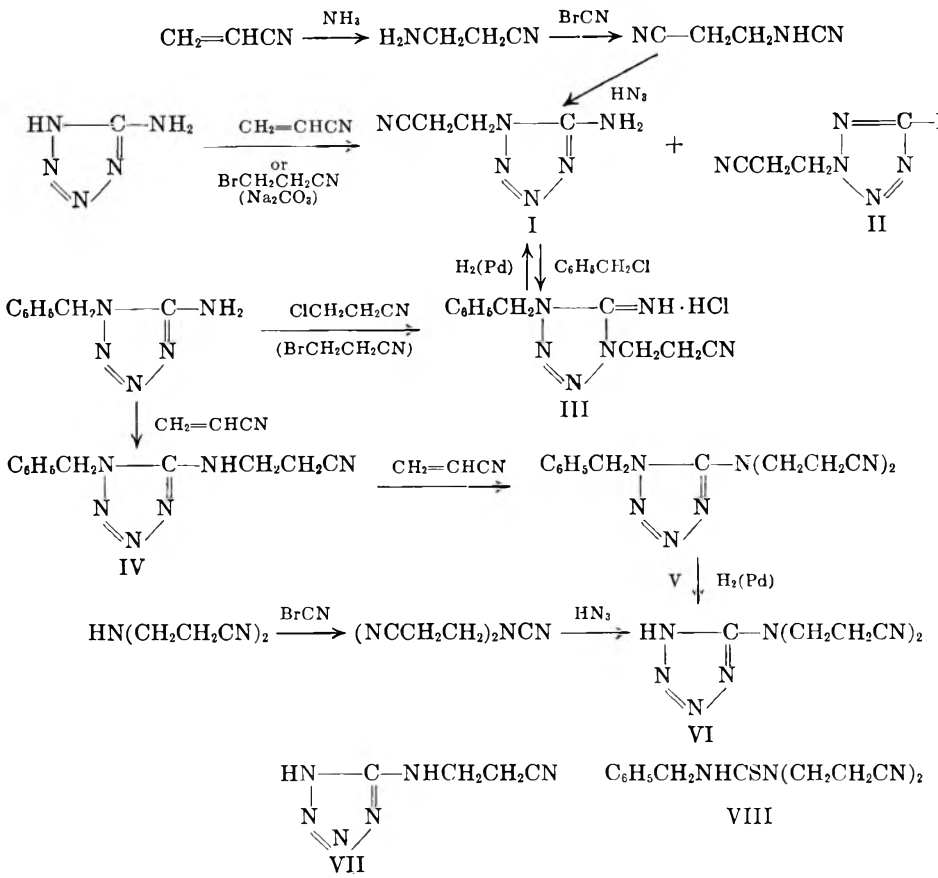
(1) Based on a doctoral thesis submitted to Michigan State University in 1957 by Donald W. Renn.

(2) American Viscose Corporation Fellow, 1955–1956. Monsanto Chemical Company Fellow, 1956–1957.

(3) Present address: John L. Smith Memorial for Cancer Research, Chas. Pfizer and Company, Inc., Maywood, N. J.

(4) H. A. Bruson, *Org. Reactions*, V, 79–135 (1949).

(5) R. M. Herbst, C. W. Roberts, and E. K. Harvill, *J. Org. Chem.*, 16, 139 (1951).



di- and tricyanoethylated products could arise from the reaction of 5-aminotetrazole with acrylonitrile. In order to limit the number of cyanoethylation products the interaction of 1-benzyl-5-aminotetrazole and acrylonitrile was also investigated. Since the benzyl group can be removed from the tetrazole nucleus by hydrogenolysis,[6] the cyanoethylation products of 1-benzyl-5-aminotetrazole can be related to the products obtained from 5-aminotetrazole. Hydrogenolytic removal of the benzyl group from the tetrazole nucleus has been employed on other occasions to elucidate the position of substituent groups.[7-10]

1-β-Cyanoethyl-5-aminotetrazole (I) was prepared as a reference compound by interaction of β-aminopropionitrile successively with cyanogen bromide and hydrazoic acid. It has been shown[11] that the interaction of monosubstituted cyanamides and hydrazoic acid leads to 1-substituted 5-aminotetrazoles. During the formation of 1-substituted 5-aminotetrazoles by the method of von Braun and Keller[12] from alkyl or aryl cyanides and hydrazoic acid in the presence of concentrated sulfuric acid small amounts of the isomeric 5-alkyl aminotetrazoles may be formed.[7] Under these conditions less than one percent of 5-methylaminotetrazole was isolated after interaction of acetonitrile with hydrazoic acid and concentrated sulfuric acid;[7] the major product was 1-methyl-5-aminotetrazole. Similarly, in the application of Thiele's method[13] to 1-alkyl-2-aminoguanidinium salts treatment of the latter with nitrous acid gives primarily 1-alkyl-5-aminotetrazoles (60–80% yields) accompanied by small amounts of 5-alkylaminotetrazoles (2–11%).[7] Only when the highly electronegative nitro group is present, as in 1-amino-2-nitroguanidine, does the primary product appear to be 5-nitraminotetrazole.[14]

Cyanoethylation of 5-aminotetrazole with acrylonitrile in the presence of aqueous benzyltrimethylammonium hydroxide gave a mixture of two monocyanoethylated derivatives that could be separated by extraction with hot ethylene chloride. The material insoluble in ethylene chloride proved to be identical with I while the soluble product appears to be 2-β-cyanoethyl-5-aminotetrazole (II). Both

(6) L. Birkhofer, *Ber.*, **75B**, 429 (1942).
(7) W. G. Finnegan, R. A. Henry, and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953).
(8) R. M. Herbst and D. F. Percival, *J. Org. Chem.*, **19**, 439 (1954).
(9) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.*, **76**, 2894 (1954).
(10) D. F. Percival and R. M. Herbst, *J. Org. Chem.*, **22**, 925 (1957).
(11) W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.*, **18**, 1014 (1953).
(12) J. von Braun and W. Keller, *Ber.*, **65**, 1677 (1932).
(13) J. Thiele, *Ann.*, **270**, 54 (1892).
(14) E. Lieber, E. Sherman, R. A. Henry, and J. Cohen, *J. Am. Chem. Soc.*, **73**, 2327 (1951).

compounds melt at almost the same temperature, 115–116° and 117–117.5°, respectively, but mixture melting points are markedly depressed. The respective acetyl derivatives show widely different melting points. Since 5-alkylaminotetrazoles undergo thermal isomerization to 1-alkyl-5-aminotetrazoles[7,15] and form 1-alkyl-5-acetamidotetrazoles on acetylation,[16] the failure of II to rearrange to I on heating or to form the same acetyl derivative makes rather unlikely the 5-β-cyanoethylaminotetrazole structure (VII) for the soluble product. Although thermal rearrangement of substituted 5-aminotetrazoles is an equilibrium process in homogeneous solutions or undisturbed melts,[17] it should be noted that such melts of alkyl 5-aminotetrazoles contain less than 10 percent of the 5-alkylaminotetrazole isomer.[17] Under other conditions 5-alkylaminotetrazoles have been observed to rearrange completely to the isomeric 1-alkyl 5-aminotetrazoles while 1-aryl-5-aminotetrazoles may rearrange completely to the isomeric 5-arylaminotetrazoles.

Both I and II were also obtained by treatment of the sodium salt of 5-aminotetrazole with an equimolar amount of β-bromopropionitrile. Although the two products were isolated in approximately equal amounts, no quantitative significance as to the relative reactivities of the 1 and 2 positions of the tetrazole ring can be attached to this observation. It is interesting to note that Henry and Finnegan[18] observed the formation of only 1 and 2 substituted products on alkylation of the sodium salt of 5-aminotetrazole with alkyl halides and sulfates. The possibility that the sodium salt of 5-aminotetrazole may have caused dehydrohalogenation of the β-bromopropionitrile cannot be ruled out. In this case formation of the same products could be accounted for if cyanoethylation of 5-aminotetrazole is assumed to occur in a very weakly basic medium. Barkley and Levine[19] have observed cyanoethylation products of certain ketones during interaction with β-chloropropionitrile in absolute ether in the presence of sodamide.

Hydrolysis of I in aqueous barium hydroxide solution caused decyanoethylation; only 5-aminotetrazole could be recovered from the hydrolyzate.

Further support for the structure of I rests upon the formation of 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline hydrochloride (III) when I is heated with benzyl chloride. The same product is obtained from 1-benzyl-5-aminotetrazole on heating with β-chloropropionitrile or β-bromopropionitrile. In the latter case the base was liberated from the crude hydrobromide and converted into the hydrochloride. The formation of the same disubstituted aminotetrazole derivative from either I or 1-benzyl-5-aminotetrazole could take place only if the substituents are symmetrically placed in the 1 and 4 positions.[7–10] The formation of I on hydrogenolysis of III prepared from 1-benzyl-5-aminotetrazole requires that the cyanoethyl group occupy the 4 position.

The interaction of 1-benzyl-5-aminotetrazole with acrylonitrile led to both mono- and dicyanoethylated products depending on conditions. Equimolar quantities of reactants gave chiefly 1-benzyl-5-β-cyanoethylaminotetrazole (IV) while the use of a large excess of acrylonitrile gave primarily 1-benzyl-5-di-β-cyanoethylaminotetrazole (V). It was also possible to convert IV into V by treatment with acrylonitrile. The monocyanoethylated product, IV, is only weakly basic and does not easily form a hydrochloride of constant composition. In this respect it is similar to other 1-alkyl-5-alkylaminotetrazoles which appear to be considerably weaker as bases than the corresponding 1,4-dialkyl-5-iminotetrazolines.[10] The structure of IV is also supported by its conversion to V. Several attempts to prepare 5-cyanoethylaminotetrazole (VII) by hydrogenolysis of IV led only to sirupy products which failed to crystallize and could not be purified by distillation. Acetylation of the crude product gave an acetyl derivative identical with that obtained from I. Since acetylation is known to cause 5-alkylaminotetrazoles to rearrange to 1-alkyl-5-acetamidotetrazoles,[16] the presence of VII in the crude material obtained by debenzylation of IV is possible. Attempted thermal rearrangement of these crude products failed to produce isolable amounts of I.

The structure of V is supported by its conversion to 5-di-β-cyanoethylaminotetrazole (VI) upon hydrogenolysis. The latter was also prepared independently by interaction of β,β′-iminodipropionitrile successively with cyanogen bromide and hydrazoic acid. VI is a weakly acidic product, pK_a 4.85, whose behavior on potentionetric titration is similar to that of other 5-dialkylaminotetrazoles.[20]

Attempts to prepare V from *N*-benzyl-*N*′,*N*′-di-β-cyanoethylthiourea (VIII) were not successful. VIII was prepared by interaction of benzyl isothiocyanate and β,β′-iminodipropionitrile. Treatment of VIII with methyl iodide appeared to give the expected *S*-methylthiuronium iodide which reacted readily with hydrazine in ethanol solution. When the solution of the aminoguanidinium iodide was treated with silver nitrate in the presence of nitric acid, a gummy, pink precipitate formed.

(15) W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.*, **18**, 1269 (1953).

(16) R. M. Herbst and W. L. Garbrecht, *J. Org. Chem.*, **18**, 1283 (1953).

(17) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.*, **76**, 88 (1954).

(18) R. A. Henry and W. G. Finnegan, *J. Am. Chem. Soc.*, **76**, 923 (1954).

(19) L. B. Barkley and R. Levine, *J. Am. Chem. Soc.*, **72**, 3699 (1950).

(20) W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.*, **18**, 1003 (1953).

The latter was soluble only in glacial acetic acid. Attempts to obtain a tetrazole from this material by treatment with nitrous acid were unsuccessful. Similar difficulties were encountered when 4-benzylthiosemicarbazide was treated first with methyl iodide and then with iminodipropionitrile. The benzyl-di-β-cyanoethyl-aminoguanidinium iodide presumably formed from this sequence of reactions gave only a gummy, pink precipitate on attempts to convert it to the nitrate. The product was again soluble only in glacial acetic acid and could not be converted into a tetrazole with nitrous acid.

EXPERIMENTAL[21,22]

1-β-Cyanoethyl-5-aminotetrazole (I). To a solution of 7 g. (0.1 mole) of β-aminopropionitrile[23] in 100 ml. of anhydrous ether was added dropwise a solution of 10.6 g. (0.1 mole) of cyanogen bromide[24] in 50 ml. of anhydrous ether with stirring and cooling below 10°. After complete addition of the reagent the mixture was allowed to stand at room temperature for 2 hr. when the precipitate of amine hydrobromide was filtered off. The filtrate was treated with 40 ml. of xylene containing 4.5 g. (0.1 mole) of hydrazoic acid[24] and heated under reflux for 20 hr. The product that separated on cooling was filtered off and recrystallized from absolute ethanol, yield 4.2 g. (61%), m.p. 115–116°.

Anal. Calcd. for $C_4H_6N_6$: C, 34.8; H, 4.4; N, 60.8. Found: C, 35.0; H, 4.4; N, 60.7.

The *acetyl derivative* was prepared by heating I under reflux with acetic anhydride for 2 hr. and recrystallizing from 95% ethanol, m.p. 104–105°.

Anal. Calcd. for $C_6H_8N_6O$: C, 40.0; H, 4.5; N, 46.6. Found; C, 40.1; H, 4.5; N, 46.8.

Cyanoethylation of 5-aminotetrazole. To a cooled, intimate mixture of 8.5 g. (0.1 mole) of anhydrous 5-aminotetrazole[25] and 4 drops of 40% aqueous benzyltrimethylammonium hydroxide was added 5.3 g. (0.1 mole) of freshly distilled acrylonitrile. After the initial exothermic reaction subsided, the mixture was heated on a steam bath under reflux for 12 hr. The crude, yellow product was extracted with hot ethylene chloride. The material insoluble in ethylene chloride was recrystallized twice from 95% ethanol to give 4.6 g. (33%) of product, m.p. 115–116°, identical with I as evidenced by mixture melting points and comparison of infrared spectra. A second product separated from the ethylene chloride extracts on cooling, was crystallized from 95% ethanol, yield 3.7 g. (27%), m.p. 117–117.5°, and appeared to be 2-β-cyanoethyl-5-aminotetrazole (II). Mixture melting point with I was depressed 20°.

Anal. Calcd. for $C_4H_6N_6$: C, 34.8; H, 4.4; N, 60.8. Found: C, 34.7; H, 4.4; N, 60.7.

II did not rearrange to I on heating above its melting point. The acetyl derivative, prepared by heating with acetic anhydride in chloroform solution, crystallized from chloroform, m.p. 136–137° and depressed the melting point of the acetyl derivative of I.

Anal. Calcd. for $C_6H_8N_6O$: C, 40.0; H, 4.5; N, 46.6. Found: C, 40.2; H, 4.6; N, 46.6.

Alkylation of 5-aminotetrazole with β-bromopropionitrile. To a boiling suspension of 8.5 g. (0.1 mole) of anhydrous 5-aminotetrazole in 150 ml. of 95% ethanol was added slowly with stirring a solution of 6.2 g. (0.05 mole) of sodium carbonate monohydrate in 35 ml. of water followed by dropwise addition of a solution of 13.4 g. (0.1 mole) of β-bromopropionitrile in 15 ml. of 95% ethanol. Stirring and heating were continued for 2 hr. after complete addition of the reagents. The solvent was gradually removed under reduced pressure and replaced with absolute ethanol. After removal of the sodium bromide that separated on cooling, the filtrate was evaporated to dryness. The residue was extracted with hot ethylene chloride. Concentration of the extracts gave a crystalline product which was recrystallized from 95% ethanol, m.p. 116–117°, yield 4.2 g. (32%), whose identity with II was supported by mixture melting point and infrared spectra. The ethylene chloride insoluble fraction was extracted with acetone. Evaporation of the acetone solution left a solid from which a small amount of 5-aminotetrazole was recovered by extraction with cold, dilute sodium hydroxide. The alkali insoluble material was recrystallized twice from 95% ethanol, m.p. 115–116°, yield 3.7 g. (27%), and proved to be identical with I on the basis of mixture melting point and comparison of infrared spectra.

Benzylation of 1-β-cyanoethyl-5-aminotetrazole. A mixture of 0.14 g. of I and 0.13 g. of benzyl chloride was heated at 125°. On stirring the two phase system a vigorously exothermic reaction ensued and was followed by solidification of the mixture. The resulting 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline hydrochloride (III) was crystallized twice from 95% ethanol, colorless needles, m.p. 215–216° with some decomposition, yield 0.24 g. (93%).

Anal. Calcd. for $C_{11}H_{13}ClN_6$: Cl, 13.4; N, 31.8. Found: Cl, 13.4; N, 31.8.

Alkylation of 1-benzyl-5-aminotetrazole with β-chloropropionitrile. A mixture of 1.75 g. (0.01 mole) of 1-benzyl-5-aminotetrazole[19] and 0.88 g. (0.01 mole) of β-chloropropionitrile was heated in an oil bath at 150° for 2 hr. The homogeneous melt solidified on cooling and was recrystallized from 95% ethanol, m.p. 213–215°. The product was identical with III obtained by benzylation of I.

The same product was obtained from 1-benzyl-5-aminotetrazole and β-bromopropionitrile by heating at 145° for 0.5 hr. The base was liberated from the crude hydrobromide and converted into hydrochloride in ether solution.

Debenzylation of 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline hydrochloride. A solution of 1 g. of III, obtained from 1-benzyl-5-aminotetrazole and β-chloropropionitrile, in 75 ml. of 80% ethanol was shaken with 0.2 g. of palladium oxide catalyst at 49 p.s.i. hydrogen pressure for 2.25 hr. After removal of the catalyst the filtrate was neutralized with sodium carbonate, filtered again and concentrated. The crude product was recrystallized from 95% ethanol and proved to be identical with I on the basis of mixture melting point and infrared spectra.

Hydrolysis of 1-β-cyanoethyl-5-aminotetrazole. Barium hydroxide octahydrate (9.6 g.) was heated on a steam bath until self-solution had occurred when a solution of 4.1 g. of I in 50 ml. of hot water was added while keeping the mixture at 85–90°. Heating on the steam bath was continued for 2 hr. after which the solution was diluted with 250 ml. of water and saturated with carbon dioxide. The barium carbonate was removed by filtration and washed thoroughly with hot water. The combined filtrate and washings were evaporated to a small volume under reduced pressure, just enough sulfuric acid was added to remove the remaining barium ion and barium sulfate was removed by centrifugation. Concentration of the filtrate gave a product which after recrystallization from water proved to be 5-aminotetrazole monohydrate, m.p. and mixture m.p. 200–201°.

Cyanoethylation of 1-benzyl-5-aminotetrazole. A. 1-Benzyl-5-aminotetrazole (7 g., 0.04 mole) and 4 drops of 40% aqueous benzyltrimethylammonium hydroxide were intimately mixed, chilled, and treated with 2.1 g. (0.04 mole) of

(21) All analyses were done by Micro-Tech Laboratories, Skokie, Ill.

(22) We are indebted to the Monsanto Chemical Company for samples of acrylonitrile and to the American Cyanamid Company for samples of β,β′-iminodipropionitrile.

(23) S. R. Buc, *Org. Syntheses*, 93 (1955).

(24) All reactions with cyanogen bromide or hydrazoic acid must be done in a well ventilated hood. Exposure to their highly toxic vapors should be avoided.

(25) R. M. Herbst and J. A. Garrison, *J. Org. Chem.*, 18, 941 (1953).

freshly distilled acrylonitrile added dropwise with stirring. The mixture liquefied and then resolidified to a yellow mass. Interaction was completed by heating for 1 hr. on a steam bath. The 1-benzyl-5-β-cyanoethylaminotetrazole (IV) was recrystallized first from ethylene chloride and then from 95% ethanol, m.p. 132.5–133°, yield 5.4 g. (59%).

Anal. Calcd. for $C_{11}H_{12}N_6$: C, 57.9; H, 5.3; N, 36.8. Found: C, 58.1; H, 5.5; N, 36.6.

B. In a similar experiment using a small excess of acrylonitrile 1-benzyl-5-di-β-cyanoethylaminotetrazole (V) separated from the warm solution during crystallization of the reaction mixture from 95% ethanol, shimmering platelets, m.p. 80–81.5°, yield 15%.

Anal. Calcd. for $C_{14}H_{15}N_7$: C, 59.7; H, 5.3; N, 34.9. Found: C, 59.6; H, 5.4; N, 35.1.

Chilling the filtrate gave a crude crystallizate from which IV was separated by recrystallization from 95% ethanol, yield 66%.

C. Interaction of 1-benzyl-5-aminotetrazole with a five-fold excess of acrylonitrile under similar conditions gave 46% of V.

D. A mixture of 2.3 g. of IV, 5 ml. of freshly distilled acrylonitrile and 4 drops of 40% aqueous benzyltrimethylammonium hydroxide warmed at steam bath temperature for 2 hr. gave a product from which V, m.p. 79–81°, was isolated by successive crystallizations from ethylene chloride and 95% ethanol.

5-Di-β-cyanoethylaminotetrazole (VI). A well stirred solution of 24.6 g. (0.2 mole) of β,β′-iminodipropionitrile in 50 ml. of ethyl acetate was kept below 10° while a solution of 10.6 g. (0.1 mole) of cyanogen bromide[24] in 50 ml. of ethyl acetate was added. Stirring was continued for 1 hr. at ice bath temperature and 8 hr. at room temperature. A precipitate of amine hydrobromide was removed by filtration and washed with hot ethyl acetate. The combined filtrate and washings were concentrated to about 50 ml. on a steam bath under reduced pressure.

N,N-Di-β-cyanoethylcyanamide, m.p. 50–51°, may be isolated at this point if the solution is further concentrated and the residue crystallized from 95% ethanol.

Anal. Calcd. for $C_9H_8N_4$: C, 56.7; H, 5.5; N, 37.8. Found: C, 56.3; H, 5.6; N, 36.8.

The concentrated ethyl acetate solution was treated with 100 ml. of benzene containing 15 g. of hydrazoic acid[24] and boiled under reflux for 8 hr., when a second 100 ml. of benzene-hydrazoic acid solution was added and heating continued for 16 hr. The product, (VI), which had started to separate during the heating period was collected after chilling the reaction mixture and recrystallized from 95% ethanol, m.p. 133.5–134°, yield 11.8 g. (62%).

Anal. Calcd. for $C_7H_9N_7$: C, 44.0; H, 4.8; N, 51.2; Neut. equiv., 191. Found: C, 43.9; H, 4.8; N, 51.2; Neut. equiv., 192.

Potentiometric titration of VI in about 0.14*M* aqueous solution with 0.1*N* sodium hydroxide using a Beckman *p*H Meter, Model G, indicated an apparent pK_a of 4.85.

Debenzylation of 1-benzyl-5-di-β-cyanoethylaminotetrazole. A solution of 1 g. of V in 50 ml. of 95% ethanol and 1 ml. of concentrated hydrochloric acid was shaken with 0.1 g. of 5% palladium on charcoal at 49 p.s.i. hydrogen pressure for 5 hr. After removal of the catalyst the solvent was evaporated. The residue was triturated with ether to induce solidification and recrystallized from 95% ethanol. A small amount of product, m.p. 127–129°, identical with VI as evidenced by mixture melting point and comparison of infrared spectra was isolated.

N-Benzyl-N′,N′-di-β-cyanoethylthiourea. Benzyl isothiocyanate (74.5 g., 0.5 mole) diluted with 25 ml. of absolute ethanol was chilled in an ice bath and treated with 61.5 g. (0.5 mole) of β,β′-iminodipropionitrile diluted with 25 ml. of absolute ethanol. The latter was added dropwise with stirring while the temperature was kept below 20°. The resulting solution was boiled under reflux for 1 hr. On chilling only a few crystals separated but on diluting with 500 ml. of hot absolute ethanol and cooling gradually the product crystallized copiously. After two recrystallizations from absolute ethanol the product was obtained as colorless plates, m.p. 145–145.5°, yield 121 g. (89%).

Anal. Calcd. for $C_{14}H_{16}N_4S$: C, 61.7; H, 5.9; N, 20.6; S, 11.8. Found: C, 61.8; H, 6.0; N, 20.4; S, 11.6.

The thiourea derivative reacted smoothly with methyl iodide in ethanolic solution and the resulting *S*-methylthiuronium iodide appeared to react smoothly with hydrazine with elimination of methyl mercaptan. Attempts to convert the aminoguanidinium iodide to the nitrate with silver nitrate in the presence of excess nitric acid gave, in addition to the silver iodide, only an insoluble, gummy, pink precipitate which could not be purified for analysis. Attempts to convert this material or any soluble aminoguanidinium nitrate to the desired tetrazole with nitrous acid were unsuccessful.

An attempt to prepare V from 4-benzylthiosemicarbazide[26] by interaction with methyl iodide followed by treatment of the resulting *S*-methyl hydriodide with β,β′-iminodipropionitrile appeared to give an aminoguanidinium iodide. The same results noted above were encountered on attempts to convert the iodide to the nitrate. Neither the precipitate nor the filtrate after treatment with silver nitrate could be converted into V with nitrous acid.

EAST LANSING, MICH.

(26) G. Pulvermacher, *Ber.*, **27**, 613 (1894).

[CONTRIBUTION NO. 872 FROM THE CHEMISTRY LABORATORIES OF INDIANA UNIVERSITY]

Synthesis of Tetrahydrocarbazoles and Carbazoles by the Bischler Reaction[1,2]

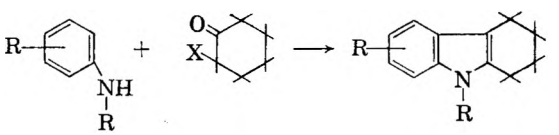
E. CAMPAIGNE AND R. D. LAKE

Received October 20, 1958

The several steps in the synthesis of carbazoles by the Bischler reaction have been studied. The reaction of 2-chlorocyclohexanone with aryl amines was best in a high boiling solvent (Cellosolve) in the presence of sodium carbonate and a small amount of quinoline or pyridine. The resulting 2-arylaminocyclohexanones could be cyclized in high yield, using a mixture of Cellosolves to attain the optimum reflux temperature, and a mixture of anhydrous magnesium chloride and the respective aryl amine as catalyst. Tetrahydrocarbazoles are susceptible to air oxidation, and accurate melting points could be obtained only on samples protected from the air. The improved preparation of a number of substituted 1,2,3,4-tetrahydrocarbazoles is reported, including the 6-phenyl and 7-methyl derivatives, which are new. These were dehydrogenated to the corresponding carbazoles, of which the 3-phenyl derivative is new, and 4-methylcarbazole has been characterized in the pure form for the first time. A color reaction, which distinguished tetrahydrocarbazoles from carbazoles or 2-arylaminocyclohexanones, is described.

The ready availability of a wide variety of aromatic amines and the ease with which 2-chlorocyclohexanone can be prepared from cyclohexanone,[3] combined with consideration of the disadvantages of the traditional synthetic methods, make the Bischler[4] synthesis a potentially attractive method for the preparation of tetrahydrocarbazoles and carbazoles.

Application of the Bischler synthesis to the preparation of tetrahydrocarbazoles was first mentioned in 1923 in a patent by Ott,[5] who claimed that α-halocyclohexanones could be condensed with primary or secondary aromatic amines to give good yields of tetrahydrocarbazoles. In the example described, 2-chlorocyclohexanone was added to



an excess of aniline at 150–160°. The yield of tetrahydrocarbazole was claimed to be nearly quantitative.

Hughes, Lions, Maunsell, and Wright[6] have reported that 6,7-dimethoxy-1,2,3,4-tetrahydrocarbazole was formed in 40% yield by the condensation of 2-chlorocyclohexanone with *p*-aminoveratrole in the presence of sodium acetate. Campbell and McCall[7] have used the Bischler reaction for the synthesis of several methyl, dimethyl, chloro and carbomethoxy derivatives of tetrahydrocarbazole in yields ranging from 13–65%.

Jones and Tomlinson[8] have reported that tetrahydrocarbazoles were formed when 2-hydroxycyclohexanone was heated with the appropriate aromatic amine in the presence of a little mineral acid. The yields reported range from 12–81% but no experimental details were given. The reaction has also been applied to aminocarbazoles.[9] Cummins and Tomlinson[10] describe the preparation of 5-methoxy-1,2,3,4-tetrahydrocarbazole by reaction of 2-hydroxycyclohexanone with 2-chloro-5-methoxyaniline followed by cyclization of the amino ketone and removal of the 8-chloro group.

The preparation of indolocarbazole derivatives by reaction of 2-chlorocyclohexanone with aminocarbazoles has been described by Plant and coworkers.[11]

Interest in the preparation of substituted carbazoles and tetrahydrocarbazoles[12] led us to study carefully the various steps involved in the application of the Bischler synthesis to the preparation of carbazoles. It was found best to prepare first pure arylaminocyclohexanones, cyclize these to the desired tetrahydrocarbazoles under carefully controlled conditions, and then dehydrogenate the purified products.

Preparation of 2-arylaminocyclohexanones. The reaction between 2-chlorocyclohexanone (I) and 2-naphthylamine (II) has been studied thoroughly with respect to the yields of 2-(2-naphthylamino)-cyclohexanone (XIII) that are obtained under

(1) This work was supported by research grant CY-1948 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) Taken from the thesis of R. D. Lake, presented in partial fulfillment of the requirements for the degree doctor of philosophy at Indiana University, September 1956.

(3) M. S. Newman, M. D. Farbman, and H. Hipsher, *Org. Syntheses*, **Coll. Vol. III**, 188 (1955).

(4) P. L. Julian, E. W. Meyer, and H. C. Printy, *Heterocyclic Compounds*, Vol. 3, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, 1952, pp. 22–35.

(5) K. Ott, German Patent **374,098**; *Chem. Abstr.*, **18**, 2175 (1924).

(6) G. K. Hughes, F. Lions, J. J. Maunsell, and L. E. A. Wright, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 433 (1938).

(7) N. Campbell and E. B. McCall, *J. Chem. Soc.*, 2870 (1950).

(8) N. A. Jones and M. L. Tomlinson, *J. Chem. Soc.*, 4114 (1953).

(9) M. L. Swindells and M. L. Tomlinson, *J. Chem. Soc.*, 1135 (1956).

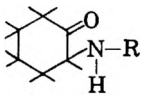
(10) J. A. Cummins and M. L. Tomlinson, *J. Chem. Soc.*, 3475 (1955).

(11) J. A. Hall and S. G. P. Plant, *J. Chem. Soc.*, 116 (1953); P. H. Carter, A. R. Katritzky, and S. G. Plant, *J. Chem. Soc.*, 337 (1955).

(12) E. Campaigne, L. Ergener, J. V. Hallum, and R. D. Lake, *J. Org. Chem.*, **24**, 487 (1959).

TABLE I

2-ARYLAMINOCYCLOHEXANONES



No.	R	Yield, %	M.P., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
III	C_6H_5	60	84.5–85	76.15	75.66	7.99	7.93	7.40	7.66
IV	o-$CH_3C_6H_4$	33	47–48	76.80	77.24	8.43	8.48	6.89	6.97
V	m-$CH_3C_6H_4$	50	70.5–71	76.80	76.58	8.43	8.07	6.89	7.11
VI	p-$CH_3C_6H_4$	65	112–113	76.80	77.08	8.43	8.41	6.89	7.08
VII	p-$CH_3OC_6H_4$	63	100.5–101.5	71.36	71.58	7.83	7.71	6.40	6.65
VIII	p-$C_6H_5C_6H_4$	64	125.5–126	81.47	81.39	7.22	7.22	5.28	5.54
IX	p-ClC_6H_4	57	132–133[a]	64.42	64.71	6.31	6.23	6.26	6.51
X	p-BrC_6H_4	58	141–142[b]	53.74	54.19	5.26	4.92	5.22	5.46
XI	2-Cl-5-$CH_3C_6H_3$	38	79–80	65.68	65.38	6.78	6.61	5.89	6.24[c]
XII	1-$C_{10}H_7$	51	103.5–104.5	80.30	80.20	7.16	7.10	5.85	5.90
XIII	2-$C_{10}H_7$	45	145–146	80.30	80.87	7.16	7.21	5.85	5.93

[a] Campbell and McCall,[7] reported m.p. 132–134°. [b] Reported[3] m.p. 143–144°. [c] Calcd.: Cl, 14.91. Found: Cl, 14.93.

different reaction conditions. Equimolar amounts of I and II (or a slight excess of I) were allowed to react at the boiling point of the solvent, in the presence of an excess of anhydrous sodium carbonate, until the evolution of carbon dioxide had ceased. When sodium carbonate and 2-naphthylamine were the only bases present, 5,6,7,8-tetrahydro-3,4-benzocarbazole (XIV) was formed as a by-product. Addition of a small amount of pyridine or quinoline appeared to eliminate cyclization as a competing reaction and also lessened contamination of the product with colored materials. When the sodium carbonate was omitted (1.1 equiv. of pyridine present) the only product was XIV.

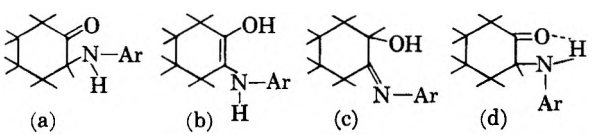
The reaction was very sluggish in dioxane and did not proceed at all in tetrahydrofuran. With dimethylformamide as solvent only a small amount of XIV could be isolated. The use of *n*-propanol in place of ethanol increased the yield of XIII from 32–45%. Higher boiling solvents such as *n*-butanol or cellosolve increased the rate of reaction but failed to bring about any further improvement in yield.

The presence of an excess of II, portionwise addition of II or dropwise addition of I all had a detrimental effect on the yield. Addition of 0.1 equiv. of potassium iodide or replacement of I by 2-bromocyclohexanone also decreased the yield of XIII.

All the remaining 2-arylaminocyclohexanones listed in Table I were prepared by a procedure very similar to that found best for XIII. Equivalent quantities of I and aromatic amine were allowed to react in boiling methylcellosolve, in the presence of 0.1 equiv. of quinoline and an excess of anhydrous powdered sodium carbonate.

All the arylamino ketones having *para*-substituents were quite stable but the others tended to deteriorate upon standing, apparently due to oxidation.

The assumption has been made that the 2-arylaminocyclohexanones exist in the form indicated by the formula (a) rather than in other possible enol forms such as (b) or (c). The infrared



(a) (b) (c) (d)

spectra of several representative compounds of this series (Table II) show quite conclusively that this assumption is correct, at least for the solid state. The NH and CO stretching frequencies fall within normal limits.[13] There was no other absorption which could be attributed to the presence of either hydroxyl or imino groups. The sharpness of the NH bands and the closeness of the carbonyl absorption to that of cyclohexanone itself (1710 cm.$^{-1}$)[13] indicates that hydrogen bonding such as that indicated in formula (d) is probably weak.

TABLE II

NH AND CO INFRARED ABSORPTION BANDS OF 2-ARYLAMINOCYCLOHEXANONES

Substituent	Wave Number, Cm.$^{-1}$ NH	CO
2-$C_{10}H_7NH$	3370	1705
p-$CH_3C_6H_4NH$	3320	1702
o-$CH_3C_6H_4NH$	3420	1715
p-ClC_6H_4NH	3400	1710
$C_6H_5NC_2H_5$	..	1722

Chlorination of 4-methylcyclohexanone, by the same procedure as that used for preparation of I, gave, as expected, two stereoisomeric chloro ketones, which appeared to be interconverted

(13) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, 1954.

TABLE III

CYCLIZATION OF 2-ANILINOCYCLOHEXANONE

Exp.	Catalyst	Solvent	Temp., °C.	Time Hr.	Yield, %
A	$ZnCl_2$	C_2H_5OH	78	12.0	0
B	$ZnCl_2$	$CH_3OC_2H_4OH$	125	12.0	15
C	$ZnCl_2$	n-$C_4H_9OC_2H_4OH$	171	1.0	0
D	$ZnCl_2$	$(CH_3)_2NCHO$	153	12.0	7
E	$ZnCl_2$	CH_3CO_2H	118	12.0	0
F	$(CH_2)_5NH\cdot HCl$[a]	C_2H_5OH	78	6.0	0[b]
G	NH_4Br	Cellosolves[c]	130	4.0	48
H	H_3PO_4	Cellosolves[c]	130	4.0	33
I	CH_3CO_2H	CH_3CO_2H	118	18.0	15
J	$CH_3CO_2H/C_6H_5NH_2$	CH_3CO_2H	118	12.0	74
K	$MgCl_2/C_6H_5NH_2$	CH_3CO_2H	118	12.0	80
L	$C_6H_5NH_2\cdot HCl$	Cellosolves[c]	130	4.0	89
M	$MgCl_2/C_6H_5NH_2$	Cellosolves[c]	130	4.0	88
N	$MgCl_2$	Cellosolves[c]	130	4.0	60
O	$MgCl_2$	C_2H_5OH	78	4.0	0
P	$MgCl_2$	n-C_3H_7OH	97	4.0	18
Q	$MgCl_2$	$CH_3OC_2H_4OH$	125	4.0	30

[a] Piperidine hydrochloride. [b] 80% of IX recovered. [c] 3:2 Mixture of methyl and butylcellosolves.

upon standing. Godchot and Bedos[14] have reported similar results. Only one product was obtained from the reaction of either isomer with II That no rearrangement had taken place is indicated by the fact that ring closure gave the expected 7-methyl-5,6,7,8-tetrahydro-3,4-benzocarbazole.[12] This amino ketone is therefore undoubtedly 4-methyl-2-(2-naphthylamino)cyclohexanone. Reaction of aniline with 2-chloro-4-methylcyclohexanone gave a mixture of isomeric anilino ketones, only one of which was isolated in pure form. These were probably stereoisomers but the possibility that partial rearrangement had occurred and that the product isolated was actually 2-anilino-5-methylcyclohexanone cannot be rigorously excluded. No clue was provided by the result of ring closure, since a mixture of 2- and 3-methyl-1,2,3,4-tetrahydrocarbazoles was obtained. Such rearrangements of arylaminoketone, occurring under ring-closure conditions, are well known.[4]

Preparation of tetrahydrocarbazoles. Both α- and β-naphthylaminocyclohexanones were cyclized in good yield by boiling absolute ethanolic zinc chloride to 5,6,7,8-tetrahydro-1,2-benzocarbazole (XV) or 5,6,7,8-tetrahydro-3,4-benzocarbazole (XIV), respectively. However, attempted extension of the alcoholic zinc chloride method of ring closure to the case of 2-anilinocyclohexanone (III) gave only an intractable oil. As indicated in Table III (Experiment B), zinc chloride in methylcellosolve gave a small amount of 1,2,3,4-tetrahydrocarbazole (XVI) but at the higher temperature provided by butylcellosolve, no XVI could be isolated. It was apparent that the amino ketone was largely destroyed under these conditions. In this connection it is to be noted that zinc chloride in acetic acid gave no tetrahydrocarbazole, but acetic acid alone afforded a small yield of XVI.

Phosphoric acid, ammonium bromide, or anhydrous magnesium chloride in a mixture of methyl and butylcellosolves gave XVI in yields of 33, 48, and 60%, respectively. The catalytic effect of aromatic amines was clearly demonstrated by the fact that a combination of magnesium chloride and aniline afforded XVI in 88% yield (*cf.* Table III. Experiments M, N). This result was expected on the basis of the reaction mechanism proposed by Bischler[15] involving formation of an ene-diamine by reaction of the aromatic amine with the amino ketone, which then undergoes ring closure.

The magnesium chloride–amine catalyst proved to be quite satisfactory for the preparation of the methyl tetrahydrocarbazoles (XVII, XIX), 6-methoxy-1,2,3,4-tetrahydrocarbazole (XXI), and 9-ethyl-1,2,3,4-tetrahydrocarbazole (XXVI) (see Table IV). Equimolar quantities of arylamino cyclohexanone and the corresponding amine and two molar equivalents of anhydrous magnesium chloride were refluxed under nitrogen for 4 hr. in a 3:2 mixture of methyl and butylcellosolve. The crude tetrahydrocarbazoles were pure enough to give very high yields of the corresponding carbazoles. 2-(*p*-Biphenylamino) cyclohexanone (VIII) was somewhat more difficult to cyclize and required a higher reaction temperature.

The cyclization of 2-(*m*-toluidino)cyclohexanone (V) gave a mixture of 7-(XVIII) and 5-methyl-1,2,3,4-tetrahydrocarbazole (XX) in a ratio of about three to one. Although others workers[7,16] have reported an inability to isolate pure compounds from this mixture of isomers, it was found that

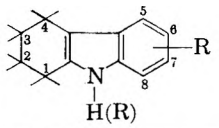
(14) M. Godchot and P. Bedos, *Compt. rend.*, 180, 295 (1925).

(15) A. Bischler and H. Brion, *Ber.*, 25, 2860 (1892).

(16) M. W. G. Coldham, J. W. Lewis, and S. G. P. Plant, *J. Chem. Soc.*, 4528 (1954).

TABLE IV

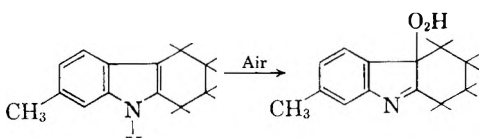
TETRAHYDROCARBAZOLES



No.	R	Yield, %	M.P., °C., Found, *in Vacuo*	M.P., °C., Found *in Air*	Reported	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
XVI	H	88	118.5–119.5	113–118	115–116[a]	84.17	83.81	7.65	7.68	8.18	8.31
XVII	8-CH_3	97	97–98	93–96	97–98[d]	84.28	84.54	8.16	8.10	7.56	7.57
XVIII	7-CH_3	95[e]	148–149	126–138		84.28	84.59	8.16	8.16	7.56	7.63
XIX	6-CH_3	95	145–146	130–142	141–142[d]	84.28	84.42	8.16	8.11	7.56	7.57
XX	5-CH_3	68[f]	150–150.5	140–147	140–147[g]	84.28	84.39	8.16	8.13	7.56	7.55
XXI	6-CH_3O	92	107.5–108.5	92–103	93–105[h]	77.58	77.36	7.51	7.40	6.96	7.16
XXII	6-C_6H_5	63[i]	153–154	149–152		87.41	87.43	6.93	6.82	5.66	5.88
XXIII	6-Cl	90	146–147	143–145	141–143[j]	70.07	69.93	5.88	5.88	6.81	6.94[k]
XXIV	6-Br	60	151.5–152	148.5–150	153[l]	57.62	57.72	4.84	4.77	5.60	5.79[m]
XXV	5-CH_3-8-Cl	70	69–70	67–68.5	64.5[n]	71.06	71.19	6.42	6.44	6.38	6.46[o]
XXVI	9-C_2H_5	61	oil[b,c]			84.37	84.41	8.60	8.70	7.03	6.96

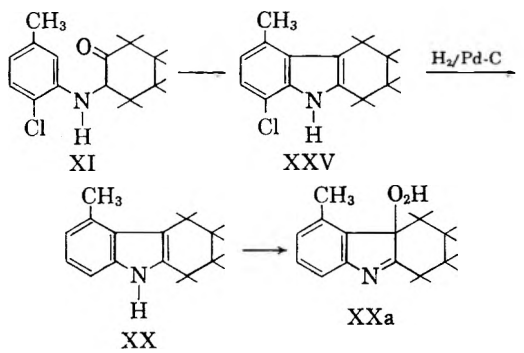
[a] C. U. Rogers and B. B. Corson, *Org. Syntheses*, **30**, 90 (1950). [b] B.p. 105–106° (0.1 mm.), n_D^{25} 1.5912. [c] Adkins and Coonradt[27] report n_D^{25} 1.5498. [d] B. Barclay and N. Campbell, *J. Chem. Soc.*, 530 (1945). [e] Mixture of 5- and 7-methyl isomers. [f] Over-all yield, based on 2-(2-chloro-5-methylanilino) cyclohexanone. [g] Ref. 10. [h] Ref. 20. [i] As the picrate. [j] Ref. 6. [k] Calcd: Cl, 17.24. Found: Cl, 17.29. [l] Ref. 24. [m] Calcd: Br, 31.95. Found: Br, 31.77. [n] K. H. Pausacker and R. Robinson, *J. Chem. Soc.*, 1557 (1947). [o] Calcd: Cl, 16.14. Found: Cl, 16.29.

XVIII could be easily obtained by crystallization. All attempts to separate XX by fractional crystallization or chromatography were unsuccessful. The purity of XVIII was demonstrated by quantitative dehydrogenation to 2-methylcarbazole, which melted sharply without purification. Upon standing exposed to the air in petroleum ether solution, XVIII underwent rapid oxidation to form 11-hydroperoxy-7-methyl-1,2,3,4-tetrahydrocarbazolenine (XVIIIa) which was characterized by elemental analysis, infrared spectrum, solubility in acid, and its ability to oxidize iodide ion.



XVIII XVIIIa

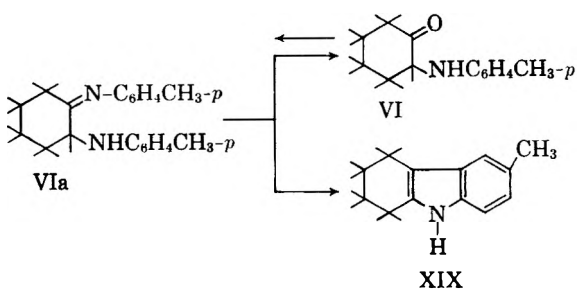
Coldham, Lewis, and Plant[16] have described the synthesis of XX, m.p. 140–146°, from 2-hydrazino-4-methylbenzoic acid and cyclohexanone, followed by decarboxylation. Cummins and Tomlinson[10] have reported the synthesis of a compound, also presumably XX, by hydrogenolysis of 1-chloro-4-methyl-5,6,7,8-tetrahydrocarbazole, but neither product was well characterized. It was therefore considered advisable to synthesize XX in order to characterize it more thoroughly. This was accomplished by cyclization of the amino ketone (XI) and hydrogenolytic removal of the chlorine atom of XXV, a method patterned after that of Cummins and Tomlinson.[10] XX was characterized by its hydroperoxide, picrate, and by dehydrogenation to 4-methylcarbazole.



All attempts to cyclize 2-(*p*-bromoanilino) cyclohexanone (X) with magnesium chloride and *p*-bromoaniline gave only tars. Magnesium chloride and aniline, however, gave a small yield of 1,2,3,4-tetrahydrocarbazole (isolated as the picrate), a result which parallels that of Campbell and McCall.[3] Cyclization of X took place satisfactorily in the presence of *p*-bromoaniline and *p*-bromoaniline sulfate, giving 6-bromo-1,2,3,4-tetrahydrocarbazole (XXIV) in 60% yield. A 90% yield of the 6-chloro-analog (XXIII) was obtained under similar conditions. The difference in reactivity of the chloro- and bromoanilinocyclohexanones was even more evident in the results of Campbell and McCall[7] who reported that *p*-chloroaniline hydrochloride gave XXIII in 22% yield but the *p*-bromo analog was not cyclized under these conditions.

2-*p*-Toluidinocyclohexanone reacted with *p*-toluidine in the presence of zinc chloride to form a compound, $C_{20}H_{24}N_2Cl_2Zn$, believed to be the zinc complex of the diamine (VIa). The free diamine was very unstable but could be hydrolyzed to the parent amino ketone (VI) or cyclized to 6-methyl-

1,2,3,4-tetrahydrocarbazole (XIX). These results are in keeping with the observations of Julian *et al.*[17]



Ring closure of 2-anilino-4-methylcyclohexanone catalyzed by aniline and magnesium chloride led to a mixture of 2- and 3-methyl-1,2,3,4-tetrahydrocarbazoles in good yield. This behavior is like that of 2-anilino-5-methylcyclohexanone, observed by Campbell and McCall.[7] There is a remarkable similarity in the melting points of the two mixtures (78–81° and 77–82°) suggesting that either isomeric amino ketone gives a mixture of the same composition. No conditions could be found under which 2-anilino-4-methylcyclohexanone could be cyclized with formation of only one of the isomeric methyl tetrahydrocarbazoles. On the other hand, the behavior of 2-anilino-4-methylcyclohexanone is in contrast to that of the 2-naphthylamino ketone[12] which gave only one product, a fact which serves further to emphasize the possible fundamental difference between the zinc chloride catalyzed ring closures and those affected by acids in the presence of aromatic amine catalysts.

A few experiments were conducted to test the feasibility of omitting the isolation of the arylaminocyclohexanones. This abbreviated procedure, described in the experimental part, generally gave higher yields, but the tetrahydrocarbazoles so obtained were less pure than those obtained by the two step procedure.

The greater portion of the work with tetrahydrocarbazoles was hindered by the persistent tendency of these compounds to melt over a wide range. This behavior was exhibited by all the tetrahydrocarbazoles studied except the benzo derivatives, but was most pronounced with those having methyl or methoxy substituents (see Table IV). These materials commonly melted higher and more sharply before crystallization than afterward, even though the physical appearance was improved. The melts were invariably yellow. A freshly prepared sample of XVI melted at 117–118°, 113–118° two weeks later, and 111–117° after 16 months, even though there was no visible signs of deterioration. Although Freudenberg has stated[18] that tetrahydrocarbazole is perfectly stable, other writers have commented[19,20] on the wide melting ranges found for apparently pure compounds of this type.

It was found that the melting points of the tetrahydrocarbazoles were higher and much sharper when taken in evacuated capillaries (see Table IV), and the melts were clear and colorless. It is well known that tetrahydrocarbazoles absorb oxygen from the air to form hydroperoxides,[21] especially in inert solvents. Probably the broad melting ranges found after recrystallization are due to traces of hydroperoxides, and formation of hydroperoxides during melting in air tends to depress the melting points of pure tetrahydrocarbazoles. It is therefore recommended that pure samples of tetrahydrocarbazoles be stored in an inert atmosphere, and melting points also be taken in the absence of oxygen.

It was discovered that when a glacial acetic acid solution of any of the tetrahydrocarbazoles studied was treated with bromine, allowed to stand for a few minutes, and then warmed on the steam bath, a green or blue coloration developed. The only exception was 9-ethyl-1,2,3,4-tetrahydrocarbazole for which the test failed. Most tetrahydrocarbazoles not having a substituent on the nitrogen atom gave a very intense color, while those having an *N*-methyl group generally gave comparatively weak colors. The hydroperoxides of 7- or 5-methyl-1,2,3,4-tetrahydrocarbazole also gave a positive test as did indole and pyrrole but the arylamino cyclohexanones and carbazoles failed to give a color reaction. The test was therefore useful in following the success of ring-closure reactions.

Color formation appeared to be catalyzed by acid. No color was formed in acetic acid in the presence of sodium acetate or pyridine, although a considerable quantity of bromine was consumed. The color reaction took place to only a very slight extent or not at all in carbon tetrachloride, but when acetic acid was added the characteristic coloration appeared almost immediately and darkened as the concentration of acetic acid was increased. Addition of a small amount of *p*-toluenesulfonic acid had an even more pronounced effect. The colors were destroyed by a large excess of bromine or chlorine or by small amounts of bases such as sodium acetate or pyridine.

Preparation of carbazoles. Dehydrogenation of the tetrahydrocarbazoles was in most cases easily accomplished by refluxing in xylene in the presence of a 30% palladium on charcoal catalyst. If reasonable precautions were exercised to prevent poisoning of the catalyst, the simple carbazoles were isolated in excellent yield and in a high state of purity

(17) P. Julian, E. Meyer, A. Magnani, and W. Cole, *J. Am. Chem., Soc.*, **67**, 1203 (1945).

(18) W. Freudenberg, in R. C. Elderfield's *Heterocyclic Compounds*, Vol. 3, John Wiley Sons, Inc. New York, 1952, p. 295.

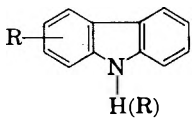
(19) C. V. Rogers and B. B. Corson, *J. Am. Chem. Soc.*, **69**, 2910 (1947).

(20) A. H. Milne and M. L. Tomlinson, *J. Chem. Soc.*, 2789 (1952).

(21) *Cf.* R. J. S. Beer, T. Broadhurst, and A. Robertson, *J. Chem. Soc.*, 4946 (1952), 2440 (1953).

TABLE V

CARBAZOLES



No.	R	Yield, %	M.P., °C. Found	M.P., °C. Reported	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
XXVII	H	91	246–246.5	245[a]						
XXVIII	1-CH_3	95	120.5–121	120.5[b]	86.15	86.21	6.12	6.14	7.73	7.73
XXIX	2-CH_3	99[g]	261–262	259[c]	86.15	85.91	6.12	6.04	7.73	7.89
XXX	3-CH_3	86	206.5–207.5	207[d]	86.15	86.28	6.12	6.06	7.73	7.89
XXXI	4-CH_3	89	129.5–130	115–116[e]	86.15	86.09	6.12	6.09	7.73	7.83
XXXII	3-CH_3O	89	150.5–151	151–152[f]	79.16	79.06	5.62	5.63	7.10	7.06
XXXIII	3-C_6H_5	60	220.5–221.5		88.86	88.33	5.39	5.40	5.76	5.83
XXXIV	9-C_2H_5	79	70–70.5	70[h]	86.12	85.96	6.71	6.68	7.17	7.01

[a] S. H. Tucker, *J. Chem. Soc.*, 546 (1926). [b] F. Ullmann, *Ann.*, *332*, 82 (1904). [c] N. Campbell and B. Barclay, *J. Chem. Soc.*, 530 (1945). [d] S. G. P. Plant and S. H. Oakeshott, *J. Chem. Soc.* 1212 (1926). [e] K. H. Pausacker and R. Robinson, *J. Chem. Soc.*, 1557 (1947). [f] A. H. Milne and M. L. Tomlinson, *J. Chem. Soc.*, 2789 (1952). [g] Yield based on pure 7-methyltetrahydrocarbazole. When a mixture of the 5- and 7-methyl isomers was used, the yield was 74%. [h] F. R. Storrie and S. H. Tucker, *J. Chem. Soc.*, 2255 (1931).

TABLE VI

DERIVATIVES OF TETRAHYDROCARBAZOLES AND CARBAZOLES

No.	Deriv. Type[a] (Color)[b]	M.P., °C.	Empirical Formula	Nitrogen, % Calcd.	Nitrogen, % Found
XVI	P (r.)	146–147[c]	$C_{18}H_{16}N_4O_7$	14.00	14.24
XVII	P (br.)	132–133[d]	$C_{19}H_{18}N_4O_7$	13.52	13.40
XVIII	P (br.)	143.5–144.5	$C_{19}H_{18}N_4O_7$	13.52	13.35
XIX	P (br.)	150–151[e]	$C_{19}H_{18}N_4O_7$	13.52	13.51
XX	P (br.)	155–155.5	$C_{19}H_{18}N_4O_7$	13.52	13.62
XXI	P (r.)	136–137	$C_{19}H_{18}N_4O_8$	13.02	12.88
XXII	P (br.)	152–153	$C_{24}H_{20}N_4O_7$	11.76	11.44[f]
XXIII	T (r.)	184–186	$C_{18}H_{15}ClN_4O_6$	13.38	13.35
XXIV	T (r.)	186–187	$C_{18}H_{15}BrN_4O_6$	12.10	12.28
XXV	P (br.)	151.5–152	$C_{19}H_{17}ClN_4O_7$	12.49	12.49
XXVI	T (r.)	127.5–128.5	$C_{20}H_{20}N_4O_6$	13.59	13.64
XXVIII	T (o.)	165–165.5	$C_{19}H_{14}N_4O_6$	14.21	14.28
XXIX	T (o.)[g]	176–176.5	$C_{19}H_{14}N_4O_6$	14.21	14.50
XXX	P (r.)	181–182[h]	$C_{19}H_{14}N_4O_7$	13.66	13.44
XXXI	P (r.)	168–169[i]	$C_{19}H_{14}N_4O_7$	13.66	13.86
XXXII	T (r.)	158–158.5	$C_{25}H_{17}N_7O_{13}$[j]	15.73	15.70
XXXIII	T (o.)	154.5–155.5	$C_{30}H_{19}N_7O_{12}$[j]	14.65	14.50
XXXIV	P (r.)	104–104.5	$C_{20}H_{16}N_4O_7$	13.21	13.32

[a] T = 1,3,5-trinitrobenzene addition compound, P = Picrate. [b] r. = red, br. = brown, o. = orange. [c] W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, 119, 1831 (1921), give m.p. 147°. [d] Campbell and Barclay, *J. Chem. Soc.*, 530 (1945), give m.p. 131–133°. [e] K. H. Pausacker and C. I. Shubert, *J. Chem. Soc.*, 532 (1945), give m.p. 149°. [f] Calcd: C, 60.50; H, 4.23. Found: C, 60.72; H, 4.45. [g] Picrate, orange needles, m.p. 169–170°, dec. on attempted purification. W. Borsche, A. Witte, and W. Bothe[19] reported: red needles, m.p. 167°. [h] Campbell and Barclay, *J. Chem. Soc.*, 530 (1945) reported m.p. 179–181°. [i] Pausacker and Robinson, *J. Chem. Soc.*, 1557 (1947) reported m.p. 160.5°. [j] Corresponds to two molecules of trinitrobenzene and one of the carbazole per molecule of complex.

merely by removal of the catalyst and evaporation of the solvent. The benzo derivatives, particularly 5,6,7,8-tetrahydro-1,2-benzocarbazole, underwent dehydrogenation with somewhat greater difficulty, but if the catalyst was sufficiently active these, too, were aromatized in satisfactory yield.

EXPERIMENTAL[22]

Materials. Aromatic amines were commercial materials, with the exception of *p*-aminobiphenyl and *p*-chloroaniline, purified by crystallization or distillation. 2-Chlorocyclohexanone (I) was prepared by the method of Newman, Farbman, and Hipsher.[3] Methylcellosolve was fractionated through an efficient column. Cellosolve and butylcellosolve were refluxed with *p*-toluidine prior to distillation. Magnesium chloride was a commercial anhydrous grade supplied by Dow Chemical Co. Palladium on charcoal catalyst was obtained from American Platinum Works and was carefully

(22) Microanalyses by Miss J. Dickey. Melting points are corrected and boiling points uncorrected. Melting points, *in vacuo*, were obtained by sealing the sample in a capillary at 4–5 mm. pressure. At lower pressures sublimation was troublesome.

protected from the laboratory atmosphere in order to maintain the high activity necessary for dehydrogenations.

2-Chloro-4-methylcyclohexanone was prepared by a procedure similar to that used for I. To a vigorously stirred mixture of 336 g. (3.00 moles) of 4-methylcyclohexanone (Eastman Kodak Co., redistilled) and 900 ml. of water was added during 1.25 hr. 215 g. (3.0 moles) of chlorine. The temperature was maintained at 35–45° by cooling in an ice bath. The organic layer was separated and the aqueous layer extracted with three 150-ml. portions of ether. The combined ether extracts were then washed with 150 ml. of water and 150 ml. of saturated sodium chloride solution. After drying over sodium sulfate and removal of the ether, the residue was distilled through a short Vigreux column, 387 g. of distillate (boiling range 55-100°/4 mm.) being collected. The crude product was then fractionated through a 60 × 1.5 cm. column packed with $^3/_{16}$-in. glass helices. After a forerun of 77.8 g., there was obtained 60.3 g. (14%) of a *low boiling isomer*, (b.p. 76–77°/10 mm.) n_D^{18} 1.4720. (Godchot and Bedos[14] reported: b.p. 80–82°/12 mm., n_D^{18} 1.4705, d^{18} 1.0994).

After an intermediate fraction of 25.3 g., boiling range 77–108°/10 mm. (presumably a mixture of isomers) 195.3 g. (44%) of the *high boiling isomer*, b.p. 109–110°/10 mm., n_D^{18} 1.4798, was collected. (Godchot and Bedos[14] reported a high boiling isomer, b.p. 110–112°/12 mm., n_D^{18} 1.4649, d^{18} 1.0749).

After having stood for several months, 134 g. of the high boiling isomer was refractionated, giving 35.0 g. of a low boiling liquid, b.p. 75.0–75.6°/10 mm., n_D^{25} 1.4682–1.4683. A constant boiling middle cut had the following physical constants: n_D^{25} 1.4683, d_{25}^{25} 1.0992, I.R. 1730 cm.$^{-1}$ (CCl_4). After standing at room temperature for 40 hr., the refractive index was 1.4712.

Anal. Calcd. for $C_7H_{11}ClO$: C, 57.34; H, 7.56; Cl, 24.18. Found: C, 56.93; H, 7.52; Cl, 24.19.

After an intermediate fraction of 51.5 g. (n_D^{25} 1.4683–1.4757) 18.2 g. of a high boiling fraction, b.p. 104–104.5°/10 mm., n_D^{25} 1.4757–1.4762, was collected. A middle cut, n_D^{25} 1.4757, d_{25}^{25} 1.1225, I.R. 1740 ,1730 cm.$^{-1}$ (CCl_4), gave a high value for chlorine, apparently due to contamination with polychlorinated by-products. After 40 hr. the refractive index had increased to 1.4770.

Anal. Calcd. for $C_7H_{11}ClO$: C, 57.34; H, 7.56; Cl, 24.18. Found: C, 57.29; H, 7.17; Cl, 25.52.

2-Anilino-4-methylcyclohexanone. A mixture consisting of 9.3 g. (0.10 mole) of aniline, 14.7 g. (0.10 mole) of 2-chloro-4-methylcyclohexanone, 1.3 g. (0.010 mole) of quinoline, 21 g. (0.20 mole) of sodium carbonate and 75 ml. of methylcellosolve was heated under reflux for 0.75 hr. Filtration of the cooled reaction mixture and removal of solvent *in vacuo*, followed by careful crystallization of the residual oil from aqueous methanol provided 8.9 g. (44%) of colorless crystals, m.p. 62–70.5°. Four crystallizations from petroleum ether (b.p. 30–60°) gave colorless prisms, m.p. 73–74°. The crude product was presumably a mixture of isomers, since a sample which had been crystallized two times and melted at 61–72° gave a satisfactory analysis.

Anal. Calcd. for $C_{13}H_{16}NO$: C, 76.80; H, 8.43; N, 6.89. Found: C, 77.13; H, 8.50; N, 7.06.

2-(2-Naphthylamino)cyclohexanone (XIII). (A) *Ethanol solvent.* A mixture of 66.4 g. (0.500 mole) of 2-chlorocyclohexanone (I), 86.0 g. (0.600 mole) of 2-naphthylamine (II), 53 g. (0.50 mole) anhydrous sodium carbonate, and 250 ml. of absolute ethanol was refluxed, with stirring, for 7 hr. and the hot reaction mixture filtered. The product separated from the filtrate after cooling in the refrigerator overnight and was filtered and washed with cold methanol, to give 59.0 g. of pink crystals, m.p. 105–133°. Two crystallizations from *n*-propanol gave 10.0 g. (8%) of pale yellow needles of XIII, m.p. 145–146°.

Dilution of the filtrates from the crystallization of XIII with an equal volume of methanol and cooling in the refrigerator produced 12.3 g. (11%) of 5,6,7,8-tetrahydro-3,4-benzocarbazole (XIV), m.p. 135–138°, undepressed by admixture with an authentic sample.

(B) *Ethanol solvent, pyridine added.* Experiment (A) was repeated on a one-fifth scale with the addition of 1.6 g. (0.02 mole) of pyridine. Crystallization of the crude product from absolute ethanol gave 7.6 g. (32%) of XIII, m.p. 141–144°. Dilution of the filtrate with hexane failed to produce any precipitate.

(C) *Cellosolve solvent.* Repetition of Experiment (B) using Cellosolve as the solvent gave, after a reflux period of 0.5 hr., a 43% yield of XIII. Similar results were obtained using *n*-propanol or *n*-butanol solvents. Other variations in the procedure, such as adding I or II portionwise or using 2-bromocyclohexanone in place of I, had a detrimental effect on the yield.

2-p-Chloroanilinocyclohexanone (IX). A mixture of 38.3 g. (0.300 mole) of *p*-chloroaniline, 39.9 g. (0.300 mole) of I, 3.9 g. (0.030 mole) of quinoline, 48 g. (0.45 mole) of sodium carbonate, and 250 ml. of methylcellosolve was refluxed for 0.75 hr. The hot reaction mixture was quickly filtered and the filter cake washed with three 35-ml. portions of hot methanol. After standing in the refrigerator overnight the mixture was filtered and washed with cold methanol, giving 39.3 g. of crude product, m.p. 129–132.5°. Reduction of the volume of the filtrate to about 100 ml. provided a second crop of 4.1 g., m.p. 127.5–132°. Crystallization of the combined crops from absolute ethanol gave 37.9 g. (57%) of IX as colorless prisms, m.p. 131.5–133°.[7]

2-p-Bromoanilinocyclohexanone (X), *2-p-biphenylylaminocyclohexanone* (VIII), and *2-p-toluidinocyclohexanone* (VI) were prepared in a similar manner. For *2-p-anisidinocyclohexanone* (VII) it was necessary to remove the methylcellosolve and dilute the oily residue with methanol in order to induce crystallization.

2-Anilinocyclohexanone (III). A mixture of 26.6 g. (0.200 mole) of I, 18.6 g. (0.200 mole) of aniline, 2.6 g. (0.020 mole) of quinoline, 30 g. (0.3 mole) of sodium carbonate, and 150 ml. of methylcellosolve was refluxed, with stirring, for 45 min. The cooled reaction mixture was then filtered and the inorganic residue washed with methanol. The solvent was removed *in vacuo* and the oily residue taken up in 60 ml. of chloroform. A little Celite was added and the mixture filtered and washed with two 10-ml. portions of hot chloroform. Removal of the chloroform at reduced pressure, followed by cooling and addition of 80 ml. of hexane caused precipitation of the amino ketone. After cooling in an ice bath for 1 hr., the mixture was filtered and washed with hexane. The yield was 22.7 g. (60%) of light yellow crystals, m.p. 83–84°. Decolorization with Norit and crystallization from a methanol and water mixture provided 17.9 g. of colorless leaves, m.p. 83.5–84.5°.

2-(1-Naphthylamino)cyclohexanone (XII) and *2-m-toluidinocyclohexanone* (V) were prepared in a similar manner. For *2-o-toluidinocyclohexanone* (IV) the work-up was modified as follows: The combined filtrate and washings were distilled through a short Vigreux column, the fraction distilling at 122–127° (0.2 mm.) being collected. The amino ketone crystallized upon cooling and trituration with hexane.

2(N-Ethylanilino)cyclohexanone was prepared in the same way as III, the crude product being obtained in 42% yield as an oil, b.p. 127–128° (0.05 mm.). A solution of 2.00 g. of the crude oil in 90 ml. of hexane was passed through a 75 × 1.6 cm. alumina column. Elution with 180 ml. of 2:1 hexane-benzene and removal of solvent *in vacuo*, produced 0.14 g. of a colorless oil, the infrared spectrum of which was identical to that of 9-ethyl-1,2,3,4-tetrahydrocarbazole.

Elution with 450 ml. of benzene gave 1.53 g. of 2-*N*-ethylanilinocyclohexanone as an amber oil which darkened upon standing, n_D^{25} 1.5607. The infrared spectrum had strong absorption in the carbonyl stretching region (1722 cm.$^{-1}$).

Anal. Calcd. for $C_{14}H_{19}NO$: N, 6.45. Found: N, 6.46.

2-(2-Chloro-5-methylanilino)cyclohexanone (XI). 3-Nitro-

4-aminotoluene[23] was diazotized and converted to the chloro derivative *via* the Gatterman reaction. 3-Nitro-4-chlorotoluene was thus obtained as a pale yellow liquid, b.p. 78–79°[24] (0.4 mm.) m.p. 7°, n_D^{25} 1.5557. Reduction with iron and dilute hydrochloric acid followed by steam distillation gave 3-amino-4-chlorotoluene m.p. 31–32° (previously reported[24] to melt at 29–30°). Reaction with 2-chlorocyclohexanone, by the procedure described above for III, gave, after crystallization from petroleum ether (b.p. 30–60°), XI, m.p. 79–79.5° (38% yield).

Reaction of 2-p-toluidinocyclohexanone (VI) *with p-toluidine and zinc chloride.* Ten g. (0.05 mole) of VI, 5.3 g. (0.05 mole) of *p*-toluidine, 13.4 g. (0.1 mole) of anhydrous zinc chloride, and 250 ml. of absolute ethanol were refluxed under nitrogen for 4 hr. Cooling in an ice bath, filtration, and washing with ethanol gave 17.4 g. (82%) of nearly colorless prisms melting with decomposition at 248°, which were insoluble in most organic solvents, but very soluble in pyridine. This substance gave a white residue upon ignition in a flame which, when dissolved in alkali and partially neutralized with acetic acid, gave a white precipitate upon treatment with hydrogen sulfide. A solution in dilute nitric acid gave a white precipitate when silver nitrate solution was added.

Anal. Calcd. for $C_{20}H_{24}N_2Cl_2Zn$: C, 56.03; H, 5.64; N, 6.54. Found: C, 56.23; H, 5.60; N, 6.80.

Addition of hexane to a pyridine solution of the compound precipitated 92% of the theoretical quantity of zinc chloride as the pyridine complex. Removal of solvent at reduced pressure left a colorless, viscous oil which decomposed rapidly in the presence of air. I.R. (CCl_4): 3350 (NH, shifted to 3140 cm.$^{-1}$ in the $ZnCl_2$ complex), 1670 cm.$^{-1}$ (C=N).

Hydrolysis of the diamine–zinc chloride complex. Two g. of the Zn complex of VIa was dissolved in 50 ml. of warm 10% hydrochloric acid, the solution neutralized with alkali, and just sufficient dilute hydrochloric acid added to bring about solution. Acetic anhydride (5 ml.) and sodium acetate (5 g.) were then added and the mixture was allowed to stand in an ice bath for 15 min. Addition of 10 ml. of concd. hydrochloric acid and filtration gave 0.18 g. of *p*-acetotoluidine, m.p. and mixture m.p. 147.5–148.5°. Adjustment of the filtrate to *p*H 6 gave a solid precipitate (1.13 g., m.p. 102–115°) which, after crystallization from ethanol, melted at 112–114° and did not depress the m.p. of VI.

Ring-closure of VIa. To the oily residue, obtained from 1.00 g. of the complex by removal of zinc chloride with pyridine as described above, were added 25 ml. of Cellosolve and 0.53 g. of anhydrous magnesium chloride. After heating at reflux for 4 hr. and working up in the usual manner, 0.32 g. of crude 6-methyl-1,2,3,4-tetrahydrocarbazole (XIX) (m.p. 140–145°) was obtained. Crystallization from aqueous methanol raised the melting point to 145–146°.

Preparation of tetrahydrocarbazoles. Method A. 5,6,7,8-Tetrahydro-3,4-benzocarbazole (XIV). In a 300-ml. three-neck flask which had been swept out with nitrogen were placed 10.0 g. (0.0418 mole) of 2-(2-naphthylamino)cyclohexanone and 200 ml. of a 20% solution of anhydrous zinc chloride in absolute ethanol. The resulting solution was heated under reflux, in an atmosphere of nitrogen, for 8 hr. The cooled bright red solution was poured into a stirred mixture of 300 ml. of concd. hydrochloric acid and 700 g. of cracked ice. The mixture was filtered, washed with dilute hydrochloric acid and water, and dried in a vacuum desiccator. The yield was 8.5 g. (92%) of buff crystalline solid, m.p. 135–137°. Crystallization from aqueous ethanol gave 6.4 g. of nearly colorless needles, m.p. 137–137.5°, undepressed by admixture with an authentic specimen.[12]

5,6,7,8-Tetrahydro-1,2-benzocarbazole was obtained in 97% yield, m.p. 138–139.5°, in the same manner except that the reflux period was 12 hr. Crystallization from aqueous ethanol provided white plates, m.p. 140–140.5°.[25]

A *picrate* was obtained as brown needles from ethanol, m.p. 170–171°.[26]

Method B. A solution of 0.025 mole of the appropriate aniline derivative and 0.05 mole of anhydrous magnesium chloride in 50 ml. of Cellosolve (or 30 ml. of methylcellosolve and 20 ml. of butylcellosolve) was prepared by boiling under nitrogen for 15 min. After slight cooling, 0.025 mole of the arylaminocyclohexanone was added and the solution heated under reflux in a nitrogen atmosphere for 4 hr. The cooled reaction mixture was then added dropwise to a vigorously stirred mixture of 125 g. of cracked ice and 50 ml. of concd. hydrochloric acid. After stirring for 1 hr. the mixture was filtered, washed with 10% hydrochloric acid and water, and dried in a vacuum desiccator. The crude product was decolorized with Norit and crystallized from aqueous methanol.

6-Phenyltetrahydrocarbazole (XXII) required a modified version of Method B. A mixture of 6.00 g. (0.0227 mole) of 2-(*p*-biphenylylamino)cyclohexanone, 1.92 g. (0.0113 mole) of *p*-aminobiphenyl, 10.8 g. (0.113 mole) of anhydrous magnesium chloride, 100 ml. of butylcellosolve, and 20 ml. of methylcellosolve was refluxed under nitrogen for 8 hr. The cooled reaction mixture was then added slowly to a stirred mixture of 350 g. of cracked ice, 200 ml. of water, and 90 ml. of glacial acetic acid. After standing for several hours, the precipitated product was filtered and washed with 15% acetic acid, 40% aqueous methanol containing 0.5% hydrochloric acid, and finally with water. The yield of crude product was 6.10 g. The impure material was treated with Norit in boiling alcohol, filtered, and 5.2 g. of picric acid in the minimum amount of boiling alcohol were added to the filtrate. The yield of powdery, brown *picrate*, m.p. 151–153.5°, was 6.82 g. (63%). After crystallization from ethanol, 5.33 g. of brown crystals, melting at 153–154°, were recovered. Slow addition of an acetone solution of the picrate to 300 ml. of concd. aqueous ammonia, with stirring and cooling, in an ice bath, followed by filtration, washing with ammonia and water, and drying *in vacuo*, gave 2.54 g. (45%) of buff crystalline powder, m.p. 144–151°. Two crystallizations from ethanol water yielded pale yellow plates, m.p. 153–154° (*in vacuo*).

9-Ethyltetrahydrocarbazole (XXVI). To a solution prepared by boiling 4.4 g. (0.046 mole) of anhydrous magnesium chloride and 2.80 g. (0.0230 mole) of ethylaniline with a mixture of 40 ml. of butylcellosolve and 20 ml. of methylcellosolve, were added 5.00 g. (0.0230 mole) of crude 2-*N*-ethylanilinocyclohexanone. After refluxing under nitrogen for 4 hr., the reaction mixture was cooled, poured into 250 ml. of 10% hydrochloric acid, and extracted four times with a total of 200 ml. of benzene. The combined benzene extracts were then washed with dilute hydrochloric acid, water, and sodium carbonate solution and dried over sodium sulfate. The residue remaining after removal of the benzene was converted to the picrate with 5.9 g. of picric acid in the minimum amount of hot ethanol. Filtration and washing with cold alcohol provided 7.3 g. (75%) of crude *picrate* as brown needles, m.p. 90–93°. Since this compound appeared to be quite unstable no attempt was made to purify it further. It was reported to melt at 92–92.5°.[27]

The picrate was decomposed by stirring for 24 hr. with 750 ml. of 10% sodium carbonate solution. The resulting oily mixture was extracted with ether (250 ml.) and the extract washed with 5% sodium carbonate and water and dried over sodium sulfate. After removal of the ether, the yield of light amber oil was 2.86 g. (61%), n_D^{25} 1.5858. The infra-

(23) W. A. Noyes, *Am. Chem. J.*, 10, 475 (1888).

(24) L. Gattermann and A. Kaiser, *Ber.*, 18, 2600 (1885) reported m.p. 7°.

(25) W. Borsche, A. Witte, and W. Bothe, *Ann.*, 359, 49 (1908), reported 140°.

(26) S. H. Oakeshott and S. G. P. Plant, *J. Chem. Soc.*, 1842 (1928), reported 172°.

(27) H. Adkins and H. L. Coonradt, *J. Am. Chem. Soc.*, 63, 1563 (1941).

red spectrum had no bands in the 3.0 (NH) or 5.8μ (CO regions.

A sample for analysis was prepared by distillation at reduced pressure, giving a viscous yellow oil with a faint rubber-like odor and blue fluorescence in daylight, b.p. 105–106°/0.1 mm., n_D^{25} 1.5912; n_D^{25} 1.5933. (Adkins and Coonradt[27] reported n_D^{25} 1.5498 for a product obtained by catalytic hydrogenation of 9-ethylcarbazole.)

Method C. A mixture of 0.01 mole of the arylaminocyclohexanone, 0.01 mole of the appropriate amine, 0.002 mole of concentrated sulfuric acid, and 30 ml. of Cellosolve was refluxed in an atmosphere of nitrogen for 4 hr. The resulting solution was poured into a mixture of 125 g. of cracked ice and 50 ml. of concentrated hydrochloric acid, and the crude product filtered, washed with dilute hydrochloric acid and water, and crystallized from aqueous ethanol.

8-Chloro-5-methyltetrahydrocarbazole (XXV) was prepared by a modification of the above procedure. A mixture of 23.77 g. (0.100 mole) of 2-(2-chloro-5-methylanilino)cyclohexanone, 14.1 g. (0.100 mole) of 4-chloro-3-aminotoluene, 2.55 g. (0.025 mole) of concd. sulfuric acid and 100 ml. of butylcellosolve was refluxed under nitrogen for 24 hr. The cooled reaction mixture was poured into 1 l. of 10% hydrochloric acid and the resulting violet colored mixture extracted with three 150-ml. portions of chloroform. The combined chloroform extracts were washed with two 500-ml. portions of 10% hydrochloric acid, two 500-ml. portions of water, and two 250-ml. portions of dilute sodium sulfite solution. After adding a few crystals of hydroquinone and drying over Drierite, the solvent was removed at reduced pressure. To the residual oil were added 25.0 g. of picric acid dissolved in 25 ml. of boiling ethanol. The brick-red crystals of the *picrate* were removed by filtration and washing with cold ethanol. The crude material weighed 34.6 g. (77%) and melted at 148–151°. Crystallization from ethanol gave, in two crops, 31.7 g. (71%) of picrate, m.p. 151–152°.

To 1.5 l. of concentrated aqueous ammonia, cooled in an ice bath, was added slowly with stirring, a solution of the picrate in 250 ml. of warm acetone. After stirring for 1 hr., the orange precipitate was removed by filtration, washed with ammonia and water, dissolved in 150 ml. of acetone, and reprecipitated by pouring into 1 l. of ice water. Filtration, washing with water, and drying *in vacuo* provided 15.3 g. (70%) of XXV as amber crystals, m.p. 68.5–69.5° (*in vacuo*). Two crystallizations from methanol water gave an analytical sample of small colorless needles, m.p. 69–70° (*in vacuo*).

5-Methyl-1,2,3,4-tetrahydrocarbazole (XX). To a solution of 0.50 g. (0.0023 mole) of XXV and 0.18 g. (0.0027 mole) of potassium hydroxide in 25 ml. of methanol was added 0.20 g. of 5% palladium-charcoal catalyst. The reaction flask was flushed first with nitrogen then with hydrogen. Hydrogen consumption began as soon as the stirrer was started and ceased after 1.25 hr. when 67 ml. had been taken up. After the catalyst was removed by filtration, the product was precipitated by pouring the methanol solution into cold water. After filtration, washing with water, and drying in a vacuum desiccator the product weighed 0.40 g. (95%) and melted at 150–150.5° (*in vacuo*). A mixture of XX and XVIII melted at 95–118°.[10]

11-Hydroperoxy-5-methyl-1,2,3,4-tetrahydrocarbazolenine (XXa). A solution of 0.182 g. of XX in 30 ml. of hot petroleum ether (b.p. 63–99°) was allowed to stand in a loosely stoppered flask. A precipitate appeared after 10 min. and, after 8 hr., the mixture was filtered and washed with cold hexane, yielding 0.168 g. (77%) of colorless, crystalline hydroperoxide, m.p. 126° (dec.) (Coldham. Lewis, and Plant[16] reported m.p. 125°). The hydroperoxide was soluble in dilute aqueous mineral acid and immediately liberated iodine from acidified potassium iodide solution. The I.R. showed a strong OH stretching band at 3050 cm.$^{-1}$ and a weak OH deformation band at 1020 cm.$^{-1}$, but no NH band in the 3400 cm.$^{-1}$ region.

Anal. Calcd. for $C_{13}H_{15}NO_2$: N, 6.45. Found: N, 6.44.

11-Hydroperoxy-7-methyl-1,2,3,4-tetrahydrocarbazolenine. A hot solution of 0.100 g. of XVIII in 10 ml. of petroleum ether (b.p. 63–99°) was allowed to stand in a loosely stoppered flask overnight. Filtration and washing with hexane gave 0.103 g. (86%) of fine white needles, m.p. 124° (dec.). The hydroperoxide was insoluble in sodium hydroxide solution but very soluble in 10% hydrochloric acid and liberated iodine immediately from acidified potassium iodide solution. The infrared spectrum had no NH band but had a broad band at 3060 cm.$^{-1}$ as well as a band at 1050 cm.$^{-1}$ There was no indication of the presence of any of the isomeric hydroperoxide in the I.R. spectrum.

Anal. Calcd. for $C_{13}H_{15}NO_2$: N, 6.45. Found: N, 6.55.

Color test for tetrahydrocarbazoles. Approximately 5 mg. of the compound to be tested was dissolved in about 1 ml. of glacial acetic acid and shaken with a 2% solution of bromine in glacial acetic acid added dropwise until a definite color persisted. The initial color was usually the pale yellow of bromine but occasionally a light green formed almost immediately. The solution was then allowed to stand in an open test tube for 5–10 min. If a green or blue color had developed, the test was considered positive. If the color had faded, a few more drops of bromine solution were added and the solution warmed on the steam bath for 2–3 min. When the sample was a carbazole the color was generally bleached by heating, but if it were a tetrahydrocarbazole the color changed to a green, blue-green, or blue. Occasionally a purple color was observed, but this always changed to green or blue upon addition of a few additional drops of bromine solution. In most cases the colors were not stable and slowly changed to gray or brown, sometimes with the appearance of a precipitate.

General procedure for dehydrogenation. For each gram of tetrahydrocarbazole, 10 ml. of xylene and 0.25–0.4 g. of 30% palladium on charcoal catalyst were used. After heating the mixture under reflux for 12 hr., it was cooled and in those cases in which a precipitate appeared, sufficient ethyl acetate to dissolve the precipitate was added. The catalyst was removed by filtration and washing with ethyl acetate. The combined filtrate and washings were evaporated to a thick slurry by warming on the steam bath in a stream of air. The slurry was then diluted with an equal volume of hexane, cooled in an ice bath, filtered, and washed with hexane. With the exception of the tetrahydrobenzocarbazoles which were more resistant to dehydrogenation, the crude carbazoles had melting points which were only 1 or 2° below these of the analytical samples. All these were crystallized from ethanol except XXVI and XXXIII, which were crystallized from xylene and methanol, respectively.

1,2-Benzocarbazole. In this case the usual procedure gave a very impure product either because of a greater-than-usual resistance to dehydrogenation or to low activity of the catalyst. From 5.00 g. of crude 5,6,7,8-tetrahydro-1,2-benzocarbazole (XV) (m.p. 138–139.5°), 4.13 g. of product melting at 185–200° were obtained. This material was again dehydrogenated using cumene in place of xylene as the solvent. The yield was 3.65 g. (74% over-all) of 1,2-benzocarbazole, m.p. 231–233°. Crystallization from ethanol gave colorless plates, m.p. 232–233°. (Borsche *et al.*[25] have reported this compound to melt at 225° and Oakeshott and Plant[26] give m.p. 225–226°.)

Anal. Calcd. for $C_{16}H_{11}N$: C, 88.45; H, 5.10; N, 6.45. Found: C, 88.22; H, 4.96; N, 6.73.

The *picrate* formed in maroon needles from alcohol, m.p. alcohol, m.p. 189–191° (dec.). This derivative has been reported[25] to melt at 185°.

Anal. Calcd. for $C_{22}H_{14}N_4O_7$: N, 12.56. Found: N, 12.60.

Abbreviated procedure for preparation of carbazoles. The following procedure for the preparation of carbazoles is typical. A mixture of 6.63 g. (0.0500 mole) of 2-chlorocyclohexanone (I), 4.66 g. (0.0500 mole) of aniline, 10 g. of anhydrous sodium carbonate, 0.65 g. (0.0050 mole) of quinoline, and 30 ml. of Cellosolve was stirred and heated under reflux until the evolution of carbon dioxide had ceased (0.75 hr.).

The reaction mixture was cooled under nitrogen, filtered, and the filter cake washed with three 10-ml. portions of Cellosolve. To the combined filtrate and washings were added 2.33 g. (0.025 mole) of aniline and 12.0 g. (0.125 mole) of anhydrous magnesium chloride, washed into the flask with 15 ml. of Cellosolve. After heating under reflux in an atmosphere of nitrogen for 4 hr. the solution was cooled and allowed to run slowly into a stirred mixture of 100 ml. of concd. hydrochloric acid and 250 g. of cracked ice. After standing overnight, the mixture was filtered and washed with dilute hydrochloric acid, water, and twice with 50% aqueous ethanol. After drying in a vacuum desiccator, the crude *tetrahydrocarbazole* weighed 7.29 g. (85%) and melted at 110–116°.

Dehydrogenation of 2.50 g. of this material in the usual manner gave 2.12 g. (74%, based on 2-chlorocyclohexanone) of XXVII, white plates, m.p. 244–246.5°.

By a similar procedure *1-methylcarbazole* was obtained in 83% yield (crude product, m.p. 118–121°; the yield of purified XXVIII, m.p. 120–121°, was 65%) and *3,4-benzocarbazole* in 40% yield (m.p. 133–134.5°), based on 2-chlorocyclohexanone.

BLOOMINGTON, IND.

[CONTRIBUTION NO. 873 FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

Syntheses of Some Methyl Substituted 3,4-Benzocarbazoles[1,2]

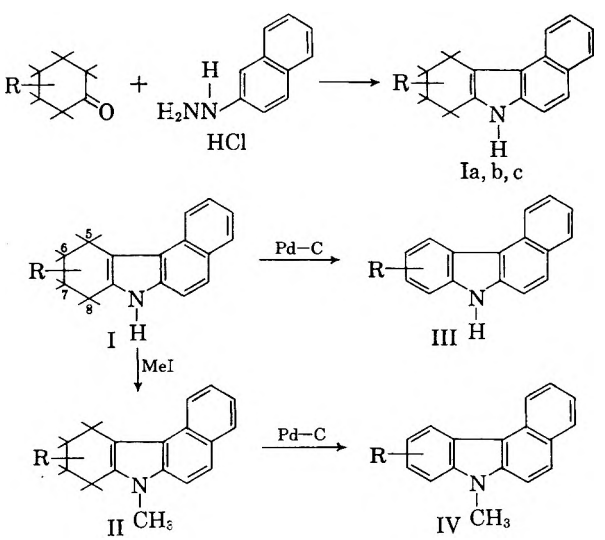
E. CAMPAIGNE, L. ERGENER,[3] J. V. HALLUM,[4] AND R. D. LAKE[5]

Received October 20, 1958

A series of methyl and dimethyl 3,4-benzocarbazoles were prepared by dehydrogenation of the respective 5,6,7,8-tetrahydro-3,4-benzocarbazoles. The latter compounds were obtained by a modified Fischer-Borsche reaction. The product of the reaction of 3-methylcyclohexanone and β-naphthylhydrazine was proved to be 7-methyl-5,6,7,8-tetrahydro-3,4-benzocarbazole, rather than the alternate possible 5-methyl isomer.

The fact that the dibenzocarbazoles are carcinogenic[6–8] has stimulated interest in the synthetic[9,10] and theoretical[11] study of carbazoles. It is known that the tumor producing activity of 1,2,5,6-dibenzanthracene is inhibited by 1,2,5,6-dibenzocarbazole.[12] Partially hydrogenated carbazoles are also of interest because of potential anticarcinogenic activity.[13]

Accordingly, we have undertaken the synthesis of a series of methyl substituted 3,4-benzocarbazoles and 5,6,7,8-tetrahydro-3,4,benzocarbazoles, for use in biological experiments. (Table I). As a result, an extremely convenient technique, involving a modified Fisher-Borsche synthesis,[14] has been developed for the preparation of 5,6,7,8-



Ia–IVa. R = H
Ib–IVb. R = 6-CH_3
Ic–IVc. R = 7-CH_3
Id–IVd. R = 8-CH_3

(1) This work was supported by research grant CY-1948 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) Taken in part from the thesis of R. D. Lake, presented in partial fulfillment of the requirements for the degree Doctor of Philosophy at Indiana University, September, 1956.

(3) U.S.P.H.S. Postdoctoral Fellow, 1952–53. Present address, University of Istanbul, Turkey.

(4) U.S.P.H.S. Postdoctoral Fellow, 1953–54. Present address, Mellon Institute, Pittsburgh.

(5) U.S.P.H.S. Pre-doctoral Fellow, 1953–56. Present address, Mellon Institute, Pittsburgh.

(6) E. Boyland and A. M. Brues, *Proc. Roy. Soc. (London)*, **B122**, 429 (1937).

(7) G. M. Badger, J. W. Cook, C. L. Hewett, E. L. Kennaway, N. M. Kennaway, and R. H. Martin, *Proc. Roy. Soc. (London)*, **B131**, 170, (1942).

(8) L. C. Strong, G. M. Smith, and W. U. Gardner, *Yale J. Biol. and Med.*, **10**, 335 (1938); *Chem. Abstr.*, **32**, 6323 (1938).

(9) E. Sawicki, *J. Am. Chem. Soc.*, **75**, 4106 (1953).

(10) Ng. Ph. Buu-Hoï, Ng. Hoan, and Ng. H. Khoi, *J. Org. Chem.*, **14**, 492 (1949); *Rec. trav. chim.*, **69**, 1053 (1950); *J. Org. Chem.*, **15**, 131 (1950); Ng. Ph. Buu-Hoï, P. Cagniant, Ng. Hoan, and Ng. H. Khoi, *J. Org. Chem.*, **15**, 950 (1950); Ng. Ph. Buu-Hoï, Ng. H. Khoi, and Ng. D. Xuong, *J. Org. Chem.*, **16**, 315 (1951); Ng. Ph. Buu-Hoï and Ng. Hoan, *J. Chem. Soc.*, 2868 (1951); Ng. Ph. Buu-Hoï and P. Jacquignon, *J. Chem. Soc.*, 513 (1954); 1515 (1956).

(11) J. I. Fernandez-Alonzo, L. Carbonell Vila, and R. Domingo, *J. Am. Chem. Soc.*, **79**, 5839 (1957).

(12) G. M. Badger, *Proc. Roy. Soc. (London)*, **B130**, 255 (1942); *cf.*, B. Riegel, W. B. Wartman, W. T. Hill, B. B. Reeb, P. Shubik, and D. W. Stanger, *Cancer Research*, **11**, 301 (1951); W. T. Hill, D. W. Stanger, A. Pizzo, B. Riegel, P. Shubik, and W. B. Wartman, *Cancer Research*, **11**, 892 (1951).

(13) *Cf.*, P. Kotin, H. L. Folk, W. Lijinsky, and L. Zechmeister, *Science*, **123**, 102 (1956).

(14) *Cf.*, W. Borsche, *Ann.*, **359**, 64 (1908).

TABLE I

BENZOCARBAZOLE DERIVATIVES

A. 5,6,7,8-TETRAHYDRO-3,4-BENZOCARBAZOLES

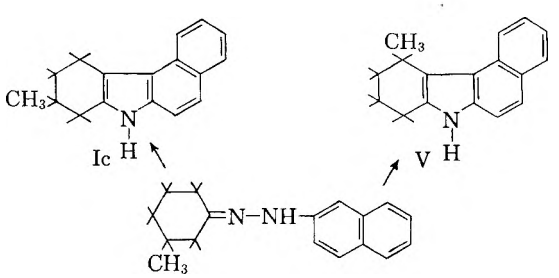
No.	Substituents	Yield, %	M.P.[a] °C	Empirical Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Ia	None	75	136–137[b]	$C_{16}H_{15}N$	86.84	86.22	6.83	6.79	6.33	6.29
Ib	6-methyl	60	129–130[c]	$C_{17}H_{17}N$	86.76	86.67	7.28	7.18	5.95	5.90
Ic	7-methyl	20	137–138	$C_{17}H_{17}N$	86.76	86.55	7.28	7.28	5.95	5.89
Id	8-methyl	17	114–115[d]	$C_{17}H_{17}N$	86.76	86.57	7.28	7.18	5.95	6.29
IIa	9-methyl	68	107–108	$C_{17}H_{17}N$	86.76	87.45	7.28	7.34	5.95	5.95
IIb	6,9-dimethyl	73	102–103	$C_{18}H_{19}N$	86.70	86.41	7.68	7.53	5.62	5.50
IIc	7,9-dimethyl	83	114–115	$C_{18}H_{19}N$	86.70	86.46	7.68	7.55	5.62	5.73
IId	8,9-dimethyl	78	95–97	$C_{18}H_{19}N$	86.70	86.48	7.68	7.64	5.62	5.75
				B. 3,4-BENZOCARBAZOLES						
IIIa	None	73	135–136[b]	$C_{16}H_{11}N$	88.45	88.24	5.10	5.09	6.45	6.39
IIIb	6-methyl	93	181–182[c]	$C_{17}H_{13}N$	88.28	88.26	5.66	5.65	6.06	6.00
IIIc	7-methyl	68	139–140	$C_{17}H_{13}N$	88.28	88.15	5.66	5.72	6.06	6.00
IIId	8-methyl	88	146–147[d]	$C_{17}H_{13}N$	88.28	88.27	5.66	5.51	6.06	6.04
IVa	9-methyl	80	118–119[e]	$C_{17}H_{13}N$	88.28	88.63	5.66	5.79	6.06	6.09
IVb	6,9-dimethyl	70	158–159	$C_{18}H_{15}N$	88.13	87.65	6.16	6.05	5.71	5.68
IVc	7,9-dimethyl	60	133–134	$C_{18}H_{15}N$	88.13	88.15	6.16	6.39	5.71	5.76
IVd	8,9-dimethyl	55	164–165	$C_{18}H_{15}N$	88.13	87.99	6.16	6.19	5.71	5.78

[a] Melting points are uncorrected. [b] S. H. Oakeshott and S. G. P. Plant, *J. Chem. Soc.*, 1840 (1928). [c] Ng. Ph. Buu-Hoï, Ng. Hoan, and Ng. H. Khoi, *Rec. trav. chim.*, 69, 1053 (1950). [d] S. A. Bryant and S. G. P. Plant, *J. Chem. Soc.*, 93 (1931). [e] F. R. Japp and W. Maitland, *Proc. Chem. Soc.*, 174 (1901).

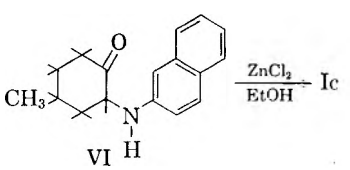
tetrahydro-3,4-benzocarbazole (Ia) and its 6- and 7-methyl derivatives (Ib, Ic). The method failed for 8-methyl-5,6,7,8-tetrahydro-3,4-benzocarbazole (Id), however, apparently due to steric hindrance.

The 5,6,7,8-tetrahydro-3,4-benzocarbazoles (I) were readily methylated by treatment with methyl iodide in the presence of alkali,[9,15] and were dehydrogenated to the corresponding carbazoles (III, IV) with palladium on carbon, a procedure found more convenient than the chloranil method.[16]

The Fischer-Borsche reaction of 3-methylcyclohexanone and β-naphthylhydrazine hydrochloride could produce either or both of the two isomers, 5- or 7-methyl-5,6,7,8-tetrahydro-3,4-benzocarbazole, V or Ic. When these compounds were reacted



as described in the experimental part, an 83% yield of crude product was obtained, which after several recrystallizations from methanol gave only one substance melting sharply at 138°. This product was unequivocally proved to be Ic by its independent synthesis *via* cyclization of 4-methyl-2-β-naphthylaminocyclohexanone (VI).



Although ring-closures of aminoketones may lead to rearrangements,[17] in this case the possible isomer would be 6 methyl-5,6,7,8-tetrahydro-3,4-benzocarbazole (Ib) previously prepared and melting at 129–130°. No rearrangement occurred on ring closure of VI, since a product melting at 137–138° was obtained, identical to the Fischer-Borsche product Ic. Each of these products was independently dehydrogenated to the same sharp-melting 7-methyl-3,4-benzocarbazole, IIIc.

EXPERIMENTAL[18]

5,6,7,8-Tetrahydro-3,4-benzocarbazole (Ia). Five g. (0.026 mole) of β-naphthylhydrazine hydrochloride were suspended in 60 ml. of methanol and 20 ml. of water added. The mixture was stirred for about 5 min. to achieve maximum solution and 2.85 g. (0.028 mole) of cyclohexanone added. Vigorous stirring was continued for about 1 hr. at room temperature and then the mixture was cooled in an ice bath and filtered. The crude yield of tetrahydrobenzocarbazole was 5.2 g. (90%). After decolorizing with Norit, and recrystallizing from methanol, colorless needles of 5,6,7,-8-tetrahydro-3,4-benzocarbazole, melting at 136–137°, were obtained.

(15) T. S. Stevens and S. H. Tucker, *J. Chem. Soc.*, 123, 2140 (1923).

(16) B. Barclay and N. Campbell, *J. Chem. Soc.*, 530 (1945).

(17) E. Campaigne and R. D. Lake, *J. Org. Chem.* 24, 478 (1959).

(18) Melting points are uncorrected. Microanalyses by Miss J. Dickey.

6-, 7- and 8-Methyl-5,6,7,8-tetrahydro-3,4-benzocarbazoles (Ib, Ic, Id). The 6- and 7-methyl derivatives were prepared from 4-methyl- and 3-methylcyclohexanone respectively, as described above for Ia. The 8-methyl isomer (Id) was synthesized by the method of Bryant and Plant.[19]

Proof of structure of Ic. *4-Methyl-2-(2-naphthylamino)-cyclohexanone.* (VI). A mixture of 14.8 g. (0.100 mole) of 2-chloro-4-methylcyclohexanone,[17] 14.4 g. (0.100 mole) of 2-naphthylamine, 2.6 g. (0.020 mole) of quinoline, 20 g. of anhydrous sodium carbonate and 75 ml. of cellosolve were heated and stirred under reflux for 1 hr. The cooled reaction mixture was filtered and the solid material washed with a little methanol. Solvent was removed at reduced pressure and the residual slurry diluted with an equal volume of methanol and allowed to stand overnight. Filtration and washing with cold methanol provided 8.8 g. (35%) of 4-methyl-2-(2-naphthylamino)cyclohexanone, m.p. 116–117°. Crystallization from cyclohexane gave colorless crystals of unchanged melting point.

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.59; H, 7.56; N, 5.53. Found: C, 80.75; H, 7.54; N, 5.65.

7-Methyl-5,6,7,8-tetrahydro-3,4-benzocarbazole (Ic). A solution of 5.00 g. (0.0198 mole) of 4-methyl-2-(2-naphthylamino)cyclohexanone in 100 ml. of 20% absolute ethanolic zinc chloride was refluxed for 18 hr. under nitrogen. The cooled, deep red solution was poured into a mechanically stirred mixture of 150 ml. of concentrated hydrochloric acid and 350 ml. of ice. Filtration, washing with dilute hydrochloric acid and water and drying *in vacuo* gave 4.56 g. of crude product, m.p. 128–135°. Decolorization with Norit and crystallization from ethanol provided 3.51 g. (76%) of colorless needles, m.p. 136.5–138°. A second crystallization raised the melting point to 137–138°. A mixed melting point with a sample prepared as described above showed no depression and the infrared spectra were identical.

The *9-methyl derivatives* (IIa–IId) were prepared by methylation of Ia–Id with methyl iodide in acetone in the presence of concentrated alkali.[9]

Dehydrogenation was carried out as follows: The tetrahydro compound (2 g.), 30% palladium on carbon (0.8 g.) and 25 ml. of xylene were heated at vigorous reflux for 8 to 48 hr. The cooled reaction mixture (diluted with ethyl acetate, when necessary to dissolve precipitated product) was then filtered and evaporated to a thick slurry by heating on the steam bath in a stream of air. The slurry was diluted with hexane, filtered, and crystallized from methanol.

8,9-Dimethyl-3,4-benzocarbazole (IVd) was obtained in impure form by the above treatment. A second dehydrogenation, using *p*-cymene as solvent, followed by crystallization from an ethanol-ethyl acetate mixture gave pure IVd.

BLOOMINGTON, IND.

(19) S. A. Bryant and S. G. P. Plant, *J. Chem. Soc.*, 93 (1931).

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

Studies in Organosilicon Chemistry. XXXV. Preparation of Certain Olefinic and Alkylsilanes

LEONARD D. NASIAK AND HOWARD W. POST

Received October 8, 1958

Several olefinic silanes have been prepared from appropriate Grignard reagents and their infrared spectra are recorded. Hexamethylbis(1,5-chloromethyl)trisiloxane and dimethylallylethoxysilane have also been prepared.

By the action of allylmagnesium bromide on the appropriate chlorosilane, dimethyldiallylsilane, methylphenyldiallylsilane, and diphenyldiallylsilane have been prepared. Similarly, from β methallylmagnesium chloride, dimethylbis(β-methallyl)-silane, methylphenylbis(β-methallyl)silane, and diphenylbis(β-methallyl)silane have been prepared. Cohydrolysis of one molar part of dimethyldichlorosilane and two of dimethylchloromethylchlorosilane yielded hexamethylbis(1,5-chloromethyl)trisiloxane. Dimethylallylethoxysilane has been prepared by the action of allylmagnesium bromide on dimethyldiethoxysilane. Infrared absorption curves are presented for the first three compounds above.

Discussion. The compounds herein described were needed for the carrying out of certain experiments in the formation of polymeric silicon compounds containing sulfur and reported elsewhere in this journal.[1] In general, the principles involved are not novel, but certain modifications in procedure have been developed which are deemed of value. These modifications are based on procedures already in the literature.[2–9] Two compounds are

(1) L. D. Nasiak and H. W. Post, *J. Org. Chem.*, **24**, 000 (1959).

(2) A. D. Petrov, V. F. Mironov, and V. G. Glukhotsev, *Izvest. Akad. Nauk, S.S.S.R., Otdel. Khim. Nauk*, 1123 (1954).

(3) A. D. Petrov and V. F. Mironov, *Doklady Akad. Nauk, S.S.S.R.*, 80, 761 (1951).

(4) A. D. Petrov and G. I. Nikishin, *Izvest. Akad. Nauk, S.S.S.R., Otdel. Khim. Nauk*, 1128 (1952).

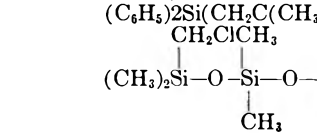
(5) A. D. Petrov and G. I. Nikishin, *Izvest. Akad. Nauk, S.S.S.R., Otdel. Khim. Nauk*, 243 (1956).

(6) R. R. McGregor and E. L. Warrick, U. S. Patent 2,507,316 (1950).

(7) J. L. Speier, *J. Am. Chem. Soc.*, **71**, 273 (1949).

TABLE I

PHYSICAL PROPERTIES

Compound	B.P.	Mm.	n_D^{20}	Yield, %
$(CH_3)_2Si(CH_2CH{=}CH_2)_2$	135.0–136.0[b]	760	1.4402[c]	78.4
$CH_3Si(CH_2CH{=}CH_2)2C_6H_5$	123.5–124.4[d]	20.5	1.5221[e]	72.1
$(C_6H_5)_2Si(CH_2CH{=}CH_2)_2$	183.8–184.4[f]	16	1.5750[g]	66.4
$(CH_3)_2Si(CH_2C(CH_3){=}CH_2)_2$	71.0–71.6[h]	22	1.4538[i]	64.1
$CH_3Si(CH_2C(CH_3){=}CH_2)_2C_6H_5$[a]	142.8–143.1	20	1.5221	63.3
$(C_6H_5)2Si(CH_2C(CH_3){=}CH_2)_2$[a]	193.8–194.1	14.5	1.5693	59.8
	136–138[j]	40	1.4275[k]	21
$(CH_3)2Si(CH_2CH{=}CH_2)OC_2H_5$	123.0–123.4[l]	743	1.4020[m]	74.2

[a] New compound. [b] 135.5° (760 mm.),[2] 136.8° (759 mm.).[3] [c] 1.4420.[2,3] [d] 242° (770 mm.).[2] [e] 1.5220.[2] [f] 140.5 (2 mm.).[2] [g] 1.5750.[2] [h] 178.0–178.5° (760 mm.),[4] 176–179° (760 mm.).[5] [i] 1.4515,[4] 1.4556.[5] [j] 141.9° (40 mm.),[6] 142.0° (40 mm.).[7] [k] 1.4283.[6,7] [l] 122.6°–123.2° (743 mm.).[8,9] [m] 1.4080.[8,9]

herein reported for the first time, methylphenylbis(β-methallyl)silane and diphenylbis(β-methallyl)silane.

Infrared absorption curves have been determined for dimethyldiallylsilane, methylphenyldiallylsilane, and diphenyldiallylsilane. An analysis of the salient features of these curves will be found from the data listed in Table II.

TABLE II

INFRARED DATA (MICRONS)

		Bellamy[10]	Found
C=C	Stretching, no conjugation	6.0	6.1
$CH{=}CH_2CH$	Stretching	3.2	3.2
$CH{=}CH_2CH$	Deformation	10.0	10.6
$CH{=}CH_2CH_2$	Deformation (out of plane)	11.0	11.05
$CH{=}CH_2CH_2$	Deformation (in plane)	7.7	7.6
$Si(CH_3)_2$	Stretching	7.9, 12.3–12.5	7.9, 12.2–12.5
$SiCH_3$	Stretching	7.9, 12.3	7.9, 12.3
SiC_6H_5	Vibration	7.0, 8.9	6.9, 9.0

(10) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*," John Wiley & Sons, Inc., New York (1954).

EXPERIMENTAL

Dimethyldiallylsilane. Magnesium turnings (29.6 g., 1.22 moles) under 500 cc. of anhydrous ether in a 2-l. three necked flask equipped with a mercury stirrer, dropping funnel, and reflux condenser were treated, dropwise, with 180.2 g. (1.49 moles) of allyl bromide in 100 cc. of anhydrous ether under steady reflux. After total addition had been accomplished, the mixture was refluxed for an additional 30 min. Dimethyldichlorosilane (40.0 g., 0.31 mole) in 100 cc. of anhydrous ether was added to the above at a rate sufficient to maintain a steady reflux. After total addition the system was refluxed again for an additional 15 hr. It was then hydrolyzed by slow addition to a chilled 25% solution of ammonium chloride. The ethereal layer was washed with water, dried over calcium chloride, and fractionated yielding dimethyldiallylsilane, yield 78.4%, b.p. (lit.) 135.5° (760 mm.),[2] 136.8° (759 mm.),[3] (found) 135.0–136.0° (760 mm.); n_D^{20} (lit.) 1.4420,[2,3] (found) 1.4402.

Methylphenyldiallylsilane. In similar manner, 1.22 moles of magnesium turnings and 1.49 moles of allyl bromide reacted with 1.49 moles of methylphenyldichlorosilane yielding methylphenyldiallylsilane, yield 72.1%, b.p. (lit.) 242° (770 mm.),[2] (found) 123.5–124.4° (20.5 mm.); n_D^{20} (lit.) 1.5220,[2] (found) 1.5221.

Diphenyldiallylsilane. The above procedure was duplicated using 1.49 moles of diphenyldichlorosilane with the isolation of diphenyldiallylsilane, yield 66.4%, b.p. (lit.) 140.5° (2 mm.),[2] (found) 183.8–184.4° (16 mm.); n_D^{20} (lit.)[2] and (found) 1.5750.

Dimethylbis(β-methallyl)silane. Dimethyldichlorosilane (0.31 mole) reacted with 1.22 moles of β-methallylmagnesium chloride as described above, forming dimethylbis-(β-methallyl)silane, yield 64.1%, b.p. (lit.) 178.0–178.5° (760 mm.),[4] 176–179° (760 mm.),[5] (found) 71.0–71.6° (22 mm.); n_D^{20} (lit.) 1.4515,[4] 1.4556,[5] (found) 1.4538.

Methylphenylbis(β-methallyl)silane. Methylphenyldichlorosilane (1.49 moles) was treated as above with the formation of methylphenylbis(β-methallyl)silane, yield 63.3%, b.p. 142.8–143.1° (20 mm.), n_D^{20} 1.5221.

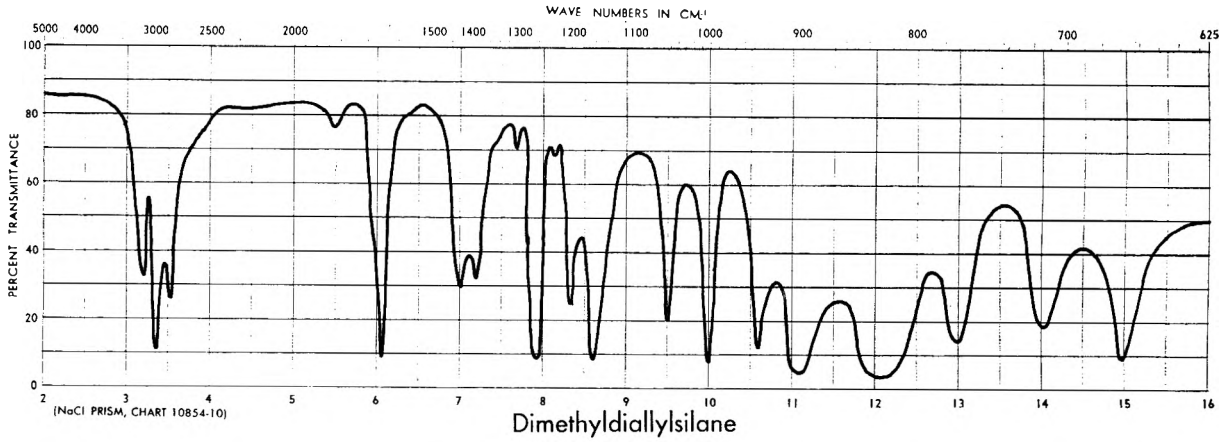
Diphenylbis(β-methallyl)silane. In a similar manner, 1.49 moles of diphenyldichlorosilane reacted to form diphenylbis(β-methallyl)silane, yield 59.8%, b.p. 193.8–194.1° (14.5 mm.), n_D^{20} 1.5693.

Hexamethylbis(1,5-chloromethyl)trisiloxane. To 252.1 g. (3.0 moles) of sodium bicarbonate in 1 l. of water, contained in a 2-l. flask equipped with stirrer, dropping funnel, and reflux condenser, was added a mixture of 286.1 g. (2.0 moles) of dimethylchloromethylchlorosilane and 129.04 g. (1.0 moles) of dimethyldichlorosilane at a slow rate (1 hr.). Vigorous stirring was necessary. After total addition had been accomplished the stirring was continued until an oily layer had clearly separated (1–2 hr.). The oil was separated and washed with distilled water until neutral to litmus. On fractionation, hexamethylbis(1,5-chloromethyl)trisiloxane was isolated, yield 21%, b.p. (lit.) 141.9° (40 mm.),[6] 142.0° (40 mm.),[7] (found) 136–138° (40 mm.); n_D^{20} (lit.) 1.4283,[6,7] (found) 1.4275.

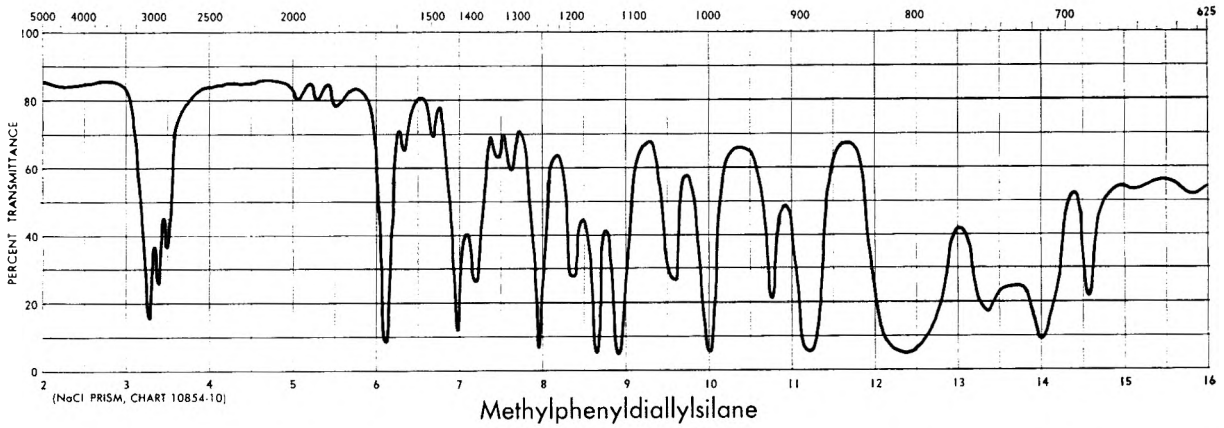
Dimethylallylethoxysilane. Allylmagnesium bromide (1.22 moles) was prepared as described above and treated with 185.6 g. (1.30 moles) of dimethyldiethoxysilane in 100 cc. or anhydrous ether. Hydrolysis was safely carried out with ammonium chloride solution as before and distillation gave

(8) J. Swiss and C. E. Arntzen, U. S. Patent 2,595,729 (1950).

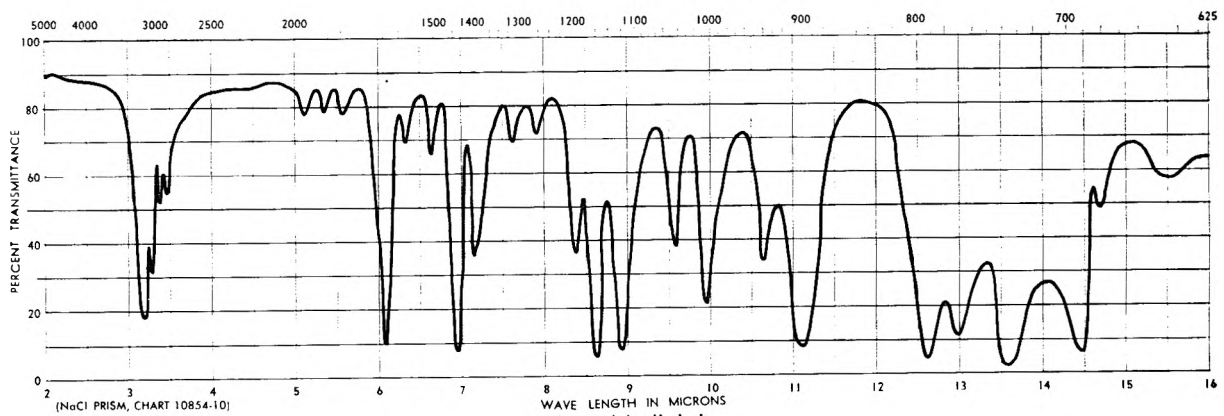
(9) J. Swiss and C. E. Arntzen, Brit. Patent 624,363 (1950).



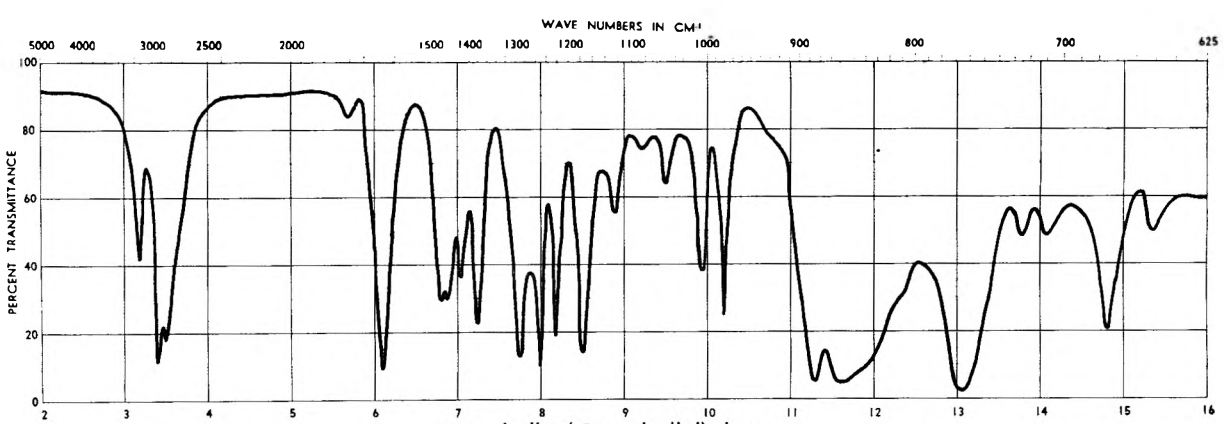
Dimethyldiallylsilane



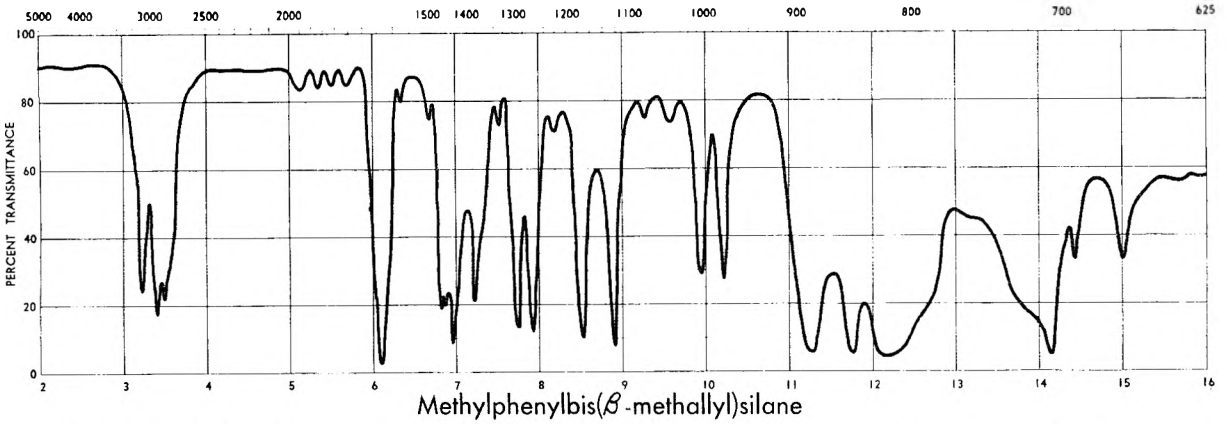
Methylphenyldiallylsilane

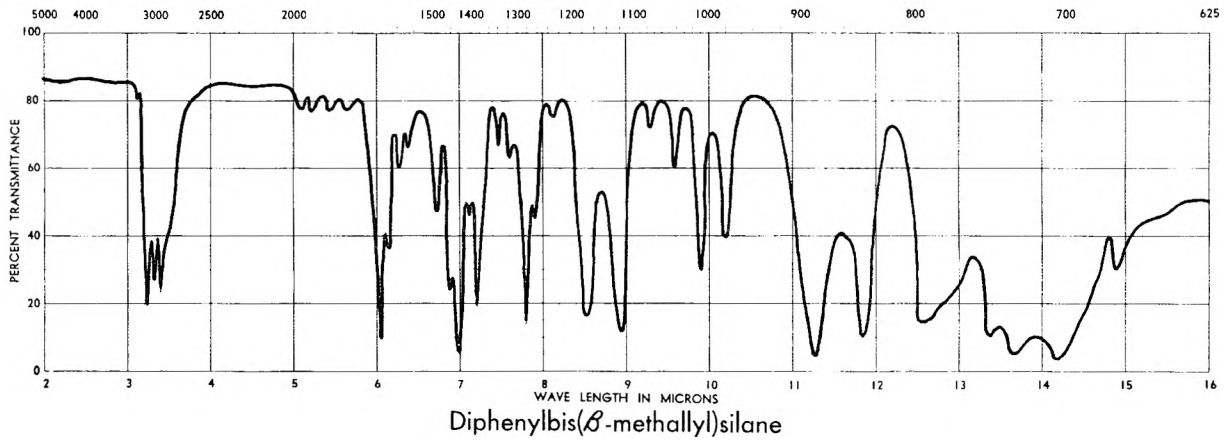


Diphenyldiallylsilane



Dimethylbis(β-methallyl)silane





dimethylallylethoxysilane, yield 74.2% b.p. (lit.) 122.6–123.2° (743 mm.),[8,9] (found) 123.0–123.4° (743 mm.); n_D^{20} (lit.) 1.4080,[8,9] (found) 1.4020.

Dimethylbis(chloromethyl)silane was purchased from Peninsular ChemResearch, Inc. Dimethyldichlorosilane, methylphenyldichlorosilane and diphenyldichlorosilane were purchased from Dow Corning Corp., Midland, Mich., and found to have satisfactory physical constants.

BUFFALO 14, N. Y.

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

Studies in Organosilicon Chemistry. XXXVI. Polymers Containing Sulfur

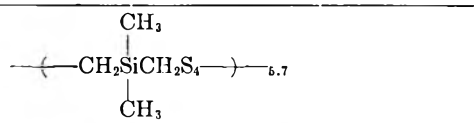
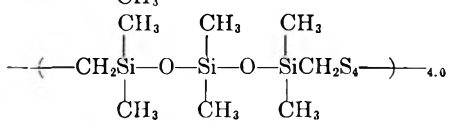
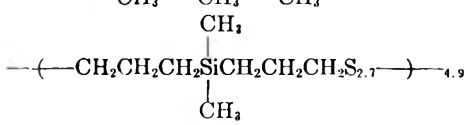
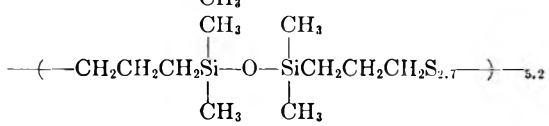
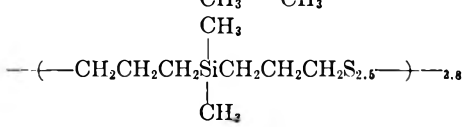
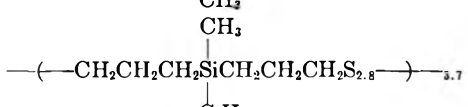
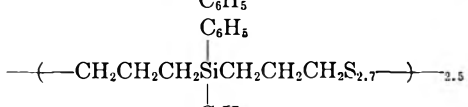
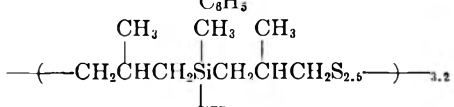
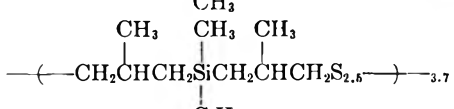
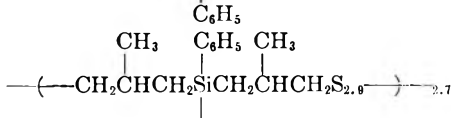
LEONARD D. NASIAK AND HOWARD W. POST

Received October 8, 1958

A number of polymers containing silicon and sulfur have been prepared by both emulsion and solution techniques. Certain properties of the products were investigated.

Emulsion polymerizations have been carried out on the products resulting from the action of sodium tetrasulfide on dimethylbis(chloromethyl)-silane and on hexamethylbis(1,5-chloromethyl)-trisiloxane. Similarly, bulk polymerization is herein reported of the products resulting from the addition of hydrogen polysulfide to dimethyldiallylsilane and to dimethylallylethoxysilane. Solution polymerization has been carried out on the products resulting from the addition of hydrogen polysulfide to dimethyladiallylsilane, methylphenyldiallylsilane, diphenyldiallylsilane, dimethylbis(β-methallyl)silane, methylphenylbis(β-methallyl)-silane and diphenylbis(β-methallyl)silane. The aver-

TABLE I

Physical Data	Inherent Viscosity	Yield, %	Type
	0.13	68.11	Emulsion
	0.13	74.41	Emulsion
	0.13	80.4	Bulk
	0.15	46.10	Bulk
	0.11	65.4	Solution
	0.14	64.1	Solution
	0.14	70.4	Solution
	0.08	68.41	Solution
	0.11	61.8	Solution
	0.11	65.1	Solution

age degrees of polymerization of the above polymers are, respectively, 5.7, 4.0, 4.9, 5.2, 3.8, 3.7, 2.5, 3.2, 3.7, and 2.7.

Calculations of per cent yields are probably too high in all cases. The determinations were very difficult owing to the fact that the samples were small and because of the sticky character of the material itself.

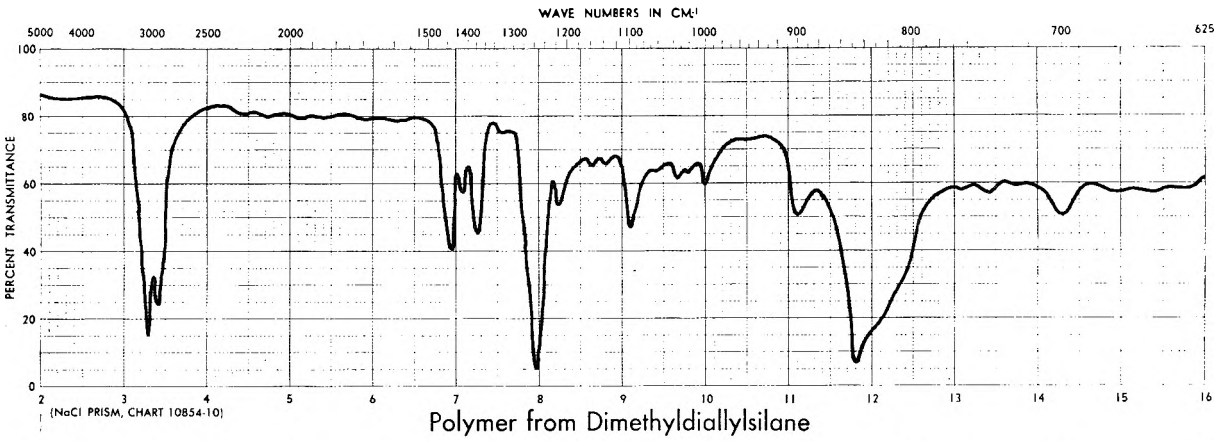
Discussion. Patrick[1] very early reported the preparation of a polysulfide polymer through the interaction of ethylene dichloride and aqueous sodium tetrasulfide. This type of synthesis, as is well known, is to be found in countless other instances and forms the basis for the preparation and manufacture of the various Thiokol elastomers and other products. Modifications of this general procedure have been used for a portion of this work. A wetting agent, Naccosol A, was used to provide maximum contact between monomer and sodium tetrasulfide. Magnesium hydroxide was also introduced. The disagreeable odor which accompanied many of these products could have been due to the presence of mercaptans, even in minute amounts.

There are several references in current literature to the addition of mercaptans across olefinic double bonds and the use of this type of reaction to synthesize polymeric molecules.[2,3] In each case, addition was reported as having taken place contrary

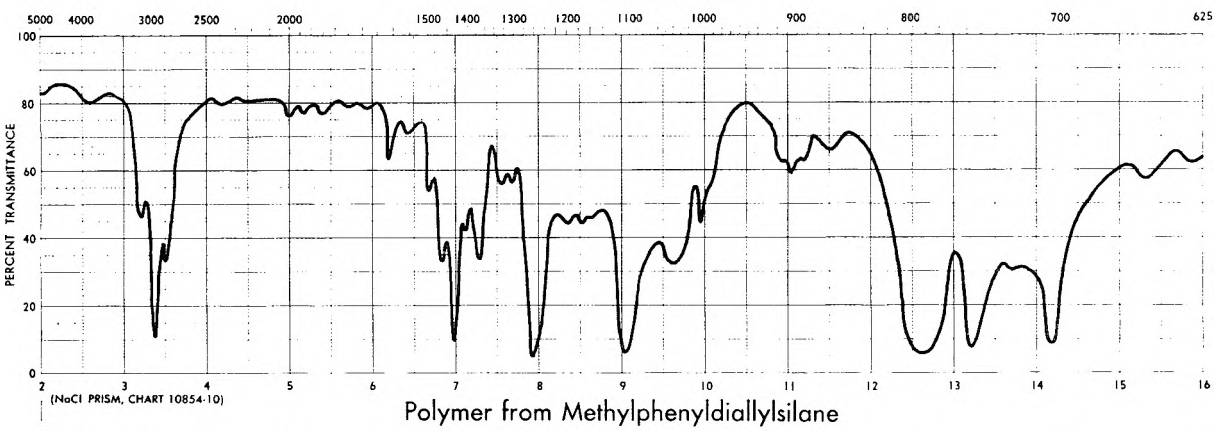
(1) J. C. Patrick, U. S. Patent 1,890,191 (1933).

(2) C. S. Marvel and H. Cripps, *J. Polymer Sci.*, 9, 52 (1952).

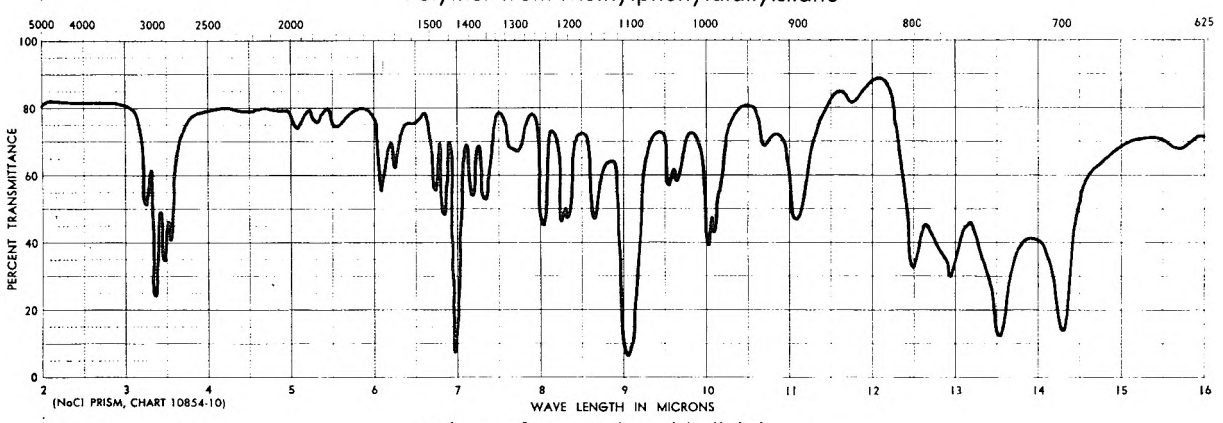
(3) C. Burkhard, *J. Am. Chem. Soc.*, 72, 1078 (1950).



Polymer from Dimethyldiallylsilane



Polymer from Methylphenyldiallylsilane



Polymer from Diphenyldiallylsilane

to the Rule of Markownikoff. Reasoning by analogy the products reported herein which resulted from the addition of hydrogen polysulfide have been assigned analogous formulas.

The molecular weights of the silicon-carbon-sulfur polymers are admittedly low. However, work is now outlined for the application of more advanced techniques to these procedures which should produce products of somewhat higher degree of polymerization.

Infrared absorption curves have been determined for the products from the bulk polymerization of dimethyldiallylsilane and the solution polymerization of methylphenyldiallylsilane and diphenyldiallylsilane with hydrogen polysulfide.

The provisional interpretation of these curves has already been presented in Part XXXV.[4]

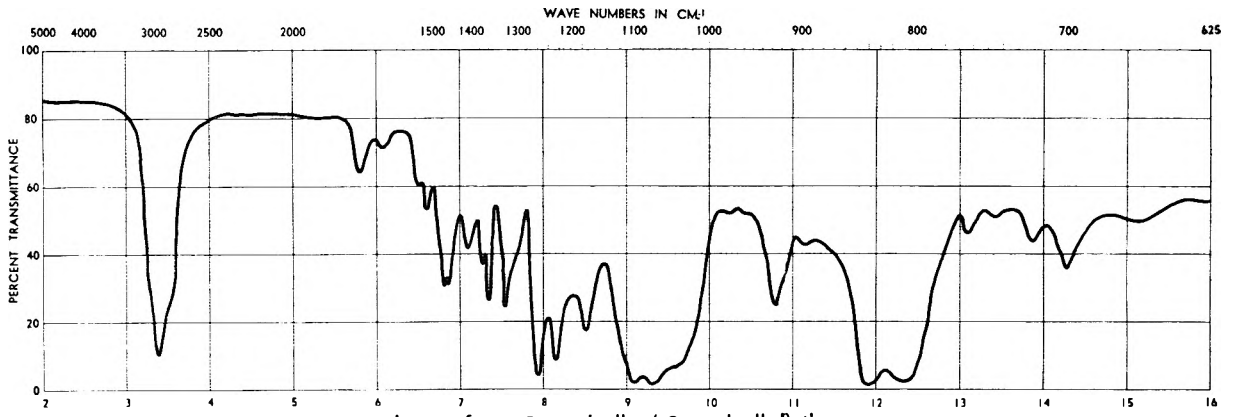
In making calculations as to molar quantities of hydrogen polysulfide, it has been assumed that the compound is a mixture of H_2S_2 and H_2S_3.[5]

EXPERIMENTAL

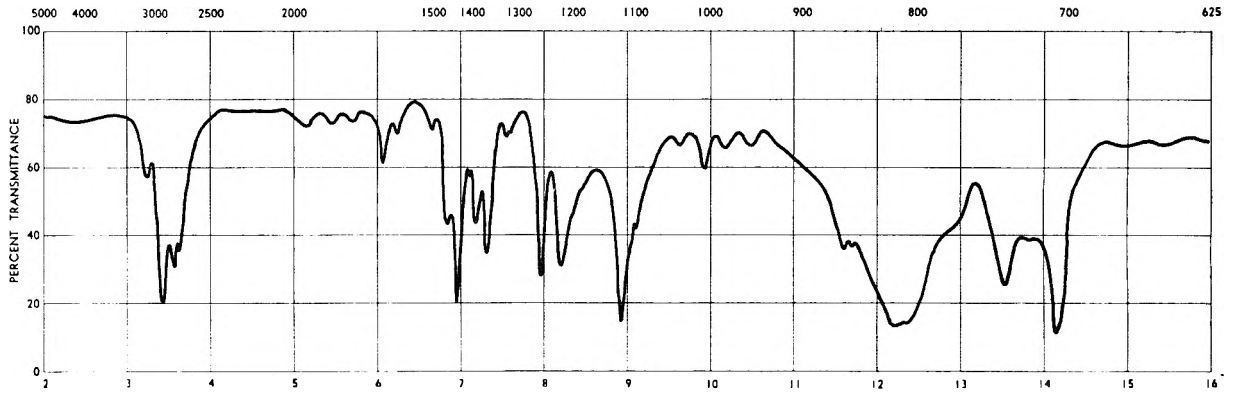
Dimethylbis(chloromethyl)silane and sodium tetrasulfide. Anhydrous sodium tetrasulfide (200 g., 0.46 mole) was placed in a 300-cc. three necked flask equipped with stirrer,

(4) Leonard D. Nasiak and Howard W. Post, *J. Org. Chem.*, **24**, 489 (1959).

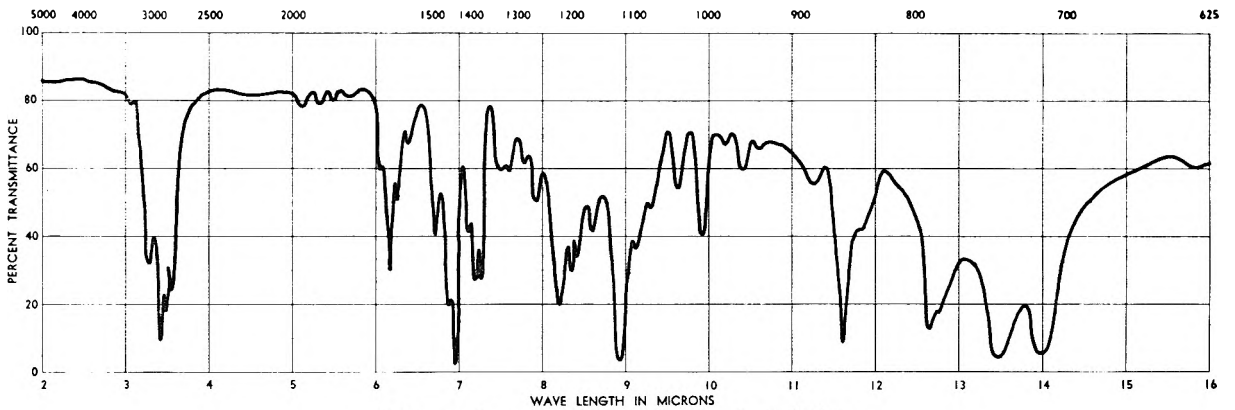
(5) T. Moeller, *Inorganic Chemistry*, John Wiley & Sons, Inc., New York, 1955, p. 516.



Polymer from Dimethylbis(β-methallyl)silane



Polymer from Methylphenylbis(β-methallyl)silane



Polymer from Diphenylbis(β-methallyl)silane

TABLE II

INFRARED DATA, IN MICRONS

		Bellamy[6]	Found
CH	Stretching	3.2	3.3–3.4
$SiCH_3$, $Si(CH_3)_2$	Stretching	7.9	7.9–8.1
		12.3–12.5	12.2–12.5
SiC_6H_5	Vibration	7.0	6.9
		8.9	8.9–9.3
			14.0–14.2

dropping funnel, and reflux condenser, as a 40% aqueous solution. To this solution under vigorous stirring, 1.0 g. of Naccosol A wetting agent and 0.62 g. of sodium hydroxide were added, followed dropwise by 1.55 g. (0.01 mole) of magnesium chloride as a 25% aqueous solution. The system was heated to 60–65° and 20.0 g. (0.13 g. mol.) of dimethylbis(chloromethyl)silane added, dropwise. After complete addition had been accomplished, the mixture was heated to 95–100° and kept at that temperature for 48 hr., with constant stirring. After cooling, the flask was filled with water and the heavy oil extracted with chloroform. After evaporation of the solvent, the viscous tacky oil was heated 4 hr. at 95–100° to facilitate further polymerization, yield 68.1%, based on the silane.

Anal. Calcd. for $(C_4H_{10}SiS_4)_x$: Si, 13.09; S, 37.38. Found: Si, 12.20; S, 36.94; mol. wt. (av.) 1223 (x = 5.7), inherent viscosity (25°) 0.13.

Hexamethylbis(1,5-chloromethyl)trisiloxane and sodium tetrasulfide. In similar manner, the two above named compounds interacted to form an oily polymer, yield 74.4%.

Anal. Calcd. for $(C_8H_{22}Si_3S_4O_2)_x$: Si, 23.21; S, 22.10. Found: Si, 23.75; S, 22.20; mol. wt. (av.) 1456 (x = 4.0), inherent viscosity (25°) 0.13.

(6) L. J. Bellamy, *The Infrared Spectra of Organic Molecules*, John Wiley & Sons, Inc., New York, 1954.

Dimethyldiallylsilane and hydrogen polysulfide (bulk). A mixture of 28.06 g. (0.20 mole) of dimethyldiallylsilane and 16.44 g. (0.20 mole) of hydrogen polysulfide in a 200 cc. beaker equipped with stirrer and thermometer became homogeneous at about 70° when heated in an oil bath, forming a yellow viscous polymer. The temperature was raised to 125–130° and maintained at that level for 4 hr. with constant stirring or until almost all hydrogen sulfide had been evolved (lead acetate paper test). The color of the polymer had meanwhile changed to a deep red with concurrent increase in viscosity and tackiness. The product cooled to a semisolid mass which was washed twice with two 30-cc. portions of methyl alcohol to extract organic materials and dissolved in a minimum amount of chloroform to precipitate as much as possible of dissolved sulfur. The solution was chilled in an ice chest, filtered, and the solvent evaporated. This separation was repeated giving finally a red, viscous tacky polymer, yield 80.4%.

Anal. Calcd. for $(C_8H_{18}SiS_{2.7})_x$: Si, 12.29; S, 37.71. Found: Si, 11.01; S, 38.04; mol. wt. (av.), 1121 (x = 4.9); inherent viscosity (25°) 0.13.

Dimethylallylethoxysilane and hydrogen polysulfide (bulk). The interaction of these two compounds, as described in the preceding experiment, produced a polymeric product in 46.1% yield.

Anal. Calcd. for $(C_{10}H_{24}Si_2S_{2.7}O)_x$: Si, 18.53; S, 28.47. Found: Si, 17.01; S, 28.46; mol. wt. (av.) 1505 (x = 5.2); inherent viscosity (25°) 0.15.

Dimethyldiallylsilane and hydrogen polysulfide (solution). A mixture of 42.10 g. (0.30 mole) of dimethyldiallylsilane and 27.13 g. (0.33 mole) of hydrogen polysulfide in 50 cc. of benzene in a 250-cc. beaker equipped with stirrer and thermometer and heated in an oil bath, was warmed slowly until the benzene had boiled off. A yellow, viscous polymer remained. This polymer was heated at 125–130° for 4 hr. with constant stirring or until very little hydrogen sulfide was being evolved (lead acetate paper test). It cooled to a semisolid mass which was worked up as were the preceding products giving a red, viscous tacky polymer, yield 65.4%.

Anal. Calcd. for $(C_8H_{18}SiS_{2.5})_x$: Si, 12.62; S, 36.05. Found: Si, 11.85; S, 36.91; mol. wt. (av.) 856 (x = 3.8), inherent viscosity (25°) 0.11.

Methylphenyldiallylsilane and hydrogen polysulfide (solution). In like manner, these two compounds reacted to form a polymer of similar physical appearance, in 64.1% yield.

Anal. Calcd. for $(C_{13}H_{20}SiS_{2.8})_x$: Si, 9.49; S, 30.37. Found: Si, 9.30; S, 31.01; mol. wt. (av.) 1084 (x = 3.7); inherent viscosity (25°) 0.14.

Diphenyldiallylsilane and hydrogen polysulfide (solution). These two compounds reacted, as described above, to give a similar red viscous tacky polymer, yield 70.4%.

Anal. Calcd. for $(C_{18}H_{22}SiS_{2.7})_x$: Si, 7.99; S, 24.43. Found: Si, 7.94; S, 24.91; mol. wt. (av.) 872 (x = 2.5); inherent viscosity (25°) 0.14.

Dimethylbis(β-methallyl)silane and hydrogen polysulfide (solution). The reaction between these two compounds was carried out as has already been described to yield an orange-red viscous tacky polymer, yield 68.4%.

Anal. Calcd. for $(C_{10}H_{22}SiS_{2.5})_x$: Si, 11.21; S, 31.99. Found: Si, 10.87; S, 34.95; mol. wt. (av.) 810 (x = 3.2); inherent viscosity (25°) 0.08.

Methylphenylbis(β-methallyl)silane and hydrogen polysulfide (solution). The Interaction of these two compounds resulted in the formation of a similar orange-red viscous tacky polymer, yield 61.8%.

Anal. Calcd. for $(C_{15}H_{24}SiS_{2.5})_x$: Si, 8.98; S, 25.63. Found: Si, 8.49; S, 24.98; mol. wt. (av.) 1141 (x = 3.7); inherent viscosity (25°) 0.11.

Diphenylbis(β-methallyl)silane and hydrogen polysulfide (solution). Using the experimental conditions outlined above, these two compounds interacted to form an orange-red, tacky polymer yield 65.1%.

Anal. Calcd. for $(C_{20}H_{26}SiS_{2.9})_x$: Si, 7.29; S, 23.83. Found: Si, 7.73; S, 24.10; mol. wt. (av.) 1052 (x = 2.7); inherent viscosity (25°) 0.11.

Organosilicon reagents were prepared as described in Part XXXV.[3] Hydrogen polysulfide was prepared by adding 150 cc. of a 40% aqueous solution of sodium tetrasulfide to 500 cc. of hydrochloric acid in a 1-l., three necked flask equipped with stirrer, dropping funnel, and thermometer. The flask was first immersed in a Dry Ice–acetone bath and the acid cooled to −10° to −15°. Agitation was necessary at all times during the addition. After total addition had been attained, the mixture was poured into 1 l. of water and the heavy oily product (hydrogen polysulfide) was separated.

Silicon was determined by incinerating with cold fuming sulfuric acid (15%), heating at low heat for 2 hr., then 1 hr. at maximum heat. After partial cooling, the sample was treated with 3 or 4 drops of fuming sulfuric acid and 5 drops of fuming nitric acid, then again heated slowly increasing to high, for 3 to 4 hr. or until the residue was white. Platinum crucible and contents were then heated to red heat.

Sulfur was determined in the Parr peroxide bomb. Molecular weights were determined by the depression of the freezing point in benzene and inherent viscosity, in dilute solution, by an Ostwald viscometer at 25°. Solutions of 0.1 g. of polymer in 25 cc. of purified chloroform were used.

Sodium tetrasulfide was obtained through the courtesy of Hooker Electrochemical Co., Niagara Falls, N. Y. Wherever anhydrous sodium tetrasulfide was needed, water of crystallization was removed by boiling with toluene.

BUFFALO, N. Y.

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

Acylations with the Acid Chlorides of 2,5-Diphenylfuran-3,4-dicarboxylic Acid and 2,5-Dimethylfuran-3,4-dicarboxylic Acid and Related Compounds

DOROTHY V. NIGHTINGALE AND BERNARD SUKORNICK[1,2]

Received August 18, 1958

The acylation of six aromatic hydrocarbons with 2,5-diphenylfuran-3,4-dicarbonyl chloride and with 2,5-dimethylfuran-3,4-dicarbonyl chloride yielded mainly cyclic diketones and/or open diketones, occasionally accompanied by small amounts of keto acids.

2,5-Diphenylfuran-3,5-dicarboxylic acid anhydride reacted with these hydrocarbons in the presence of aluminum chloride to form keto acids. Phenyl lithium reacted with this anhydride to form a phthalide type of compound.

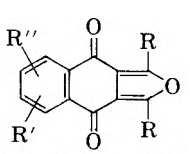
Since little or no work has been done with Friedel-Crafts reactions of 5-membered heterocyclic dicarboxylic acid chlorides having the carboxyl groups on adjacent carbons, 2,5-diphenylfuran-3,4-dicarbonyl chloride III and 2,5-dimethylfuran-3,4-dicarbonyl chloride IV were selected for study. These acid chlorides had not previously been reported in the literature.

The acylation of benzene, toluene, and the three xylenes with III and IV yielded mainly yellow cyclic diketones (9,10-dihydro-4,9-dioxo-1,3-di-R-naphtho[2,3c]furans) and/or colorless 2,5-di-R-3,4-diaroylfurans, occasionally accompanied by small amounts of 2,5-di-R-4-aroylfuran-3-carboxylic acid. No compounds of the phthalide type were isolated. Mesitylene formed only the 2,5-di-R-3,4-dimesitoylfuran as might be expected, in view of the fact that the acylation of this hydrocarbon with phthalyl chloride yielded only *o*-dimesitoylbenzene.[3]

The products of the acylations are summarized in Tables I and II. The preferential formation of cyclic diketones, Series I and II, by intramolecular acylation was surprising, since *o*-phthalyl chloride reacts with benzene and toluene in the presence of aluminum chloride to form mainly diaryl phthalides and only small amounts of anthraquinone.[4] For the most part, the total yield of carbonyl compounds was less in carbon disulfide than in excess hydrocarbon, but the ratio of cyclic diketone to diaroylfuran varied with the hydrocarbon being acylated. It is assumed that toluene and the xylenes acylate and cyclize in the positions usual for these types of reactions.

Benzene and *m*-xylene were also acylated with III in nitrobenzene and in *sym*-tetrachloroethane. The total yield of carbonyl compounds was higher in the latter solvent than in nitrobenzene or in carbon disulfide, but the product distribution was similar to that in excess hydrocarbon as solvent for the reaction.

In the Grignard machine, the cyclic diketones not only added two moles of methylmagnesium



Series I. R = C_6H_5

Ia. R′ = R″ = H
Ib. R′ = 6-CH_3; R″ = H
Ic. R′ = 6-CH_3; R″ = 7-CH_3
Id. R′ = 6-CH_3; R″ = 8-CH_3
Ie. R′ = 5-CH_3; R″ = 8-CH_3

Series II. R = CH_3

IIa. R′ = R″ = H
IIb. R′ = 6-CH_3; R″ = H
IIc. R′ = 6-CH_3; R″ = 7-CH_3
IId. R′ = 6-CH_3; R″ = 8-CH_3
IIe. R′ = 5-CH_3; R″ = 8-CH_3

TABLE I

ACYLATIONS WITH 2,5-DIPHENYLFURAN-3,4-DICARBONYL CHLORIDE[a]

Hydrocarbon	Hydrocarbon Solvent	Yield, %	Carbon Disulfide	Yield, %
Benzene	Cdk Ia	71	Cdk Ia	22
Toluene	Cdk Ib	36	Cdk Ib	61
	Dk	40	Dk	1
o-Xylene	Cdk Ic	78	Cdk Ic	82
m-Xylene	Cdk Id	10	Cdk Id	13
	Dk	75	Dk	43
p-Xylene	Cdk Ie	76	Cdk Ie	42
Mesitylene	Dk	74	Dk	58
ACYLATIONS WITH 2,5-DIMETHYLFURAN-3,4-DICARBONYL CHLORIDE				
Benzene	Cdk IIa	73	Cdk IIa	90
Toluene	Cdk IIb	50	Cdk IIb	68
	Dk	26	Dk	1
o-Xylene	Cdk IIc	82	Cdk IIc	82
			Ka	4
m-Xylene	Cdk IId	6	Cdk IId	13
	Dk	53	Dk	67
p-Xylene	Cdk IIe	68	Cdk IIe	72
Mesitylene	Dk	54	Dk	90
	Ka	8		

[a] Cdk = cyclic diketone. Dk = 2,5-di-R-3,4-diaroylfuran. Ka = 2,5-di-R-4-aroylfuran-3-carboxylic acid.

(1) Abstracted from the Ph.D. dissertation of Bernard Sukornick, University of Missouri, June 1957.

(2) Phillips Petroleum Company Fellow 1956–57. Present address: General Chemical Company, Morristown, N. J.

(3) R. C. Fuson, S. B. Speck, and W. R. Hatchard, *J. Org. Chem.*, 10, 55 (1945).

(4) C. Friedel and J. M. Crafts, *Ann. Chim. Physique*, (6) 1, 523 (1884).

TABLE II

ACYLATION PRODUCTS

Compound	M.P., °C.	Formula	Calcd. C	Calcd. H	Found C	Found H
Ia	225–226	$C_{24}H_{14}O_3$	82.27	4.03	82.45	4.13
Ib	204–205	$C_{25}H_{16}O_3$	82.40	4.42	82.04	4.43
Ic	270–271	$C_{26}H_{18}O_3$	82.52	4.79	82.56	4.94
Id	190–191	$C_{26}H_{18}O_3$	82.52	4.79	83.69	4.81
Ie	223–224	$C_{26}H_{18}O_3$	82.53	4.79	82.53	4.79
2,5-Diphenyl-3,4-di-p-toluoylfuran	151–153	$C_{32}H_{24}O_3$	84.19	5.30	84.32	5.54
2,5-Diphenyl-3,4-bis-(2,4-dimethylbenzoyl)furan	118–119	$C_{32}H_{28}O_3$	84.27	5.82	84.40	5.99
2,5-Diphenyl-3,4-dimesitoylfuran	171–172	$C_{36}H_{32}O_3$	84.34	6.29	84.55	6.95
IIa	171–172	$C_{14}H_{10}O_3$	74.33	4.46	74.34	4.42
IIb	190–191	$C_{15}H_{12}O_3$	74.99	5.03	74.86	5.42
IIc	273–275	$C_{16}H_{14}O_3$	75.57	5.55	75.57	5.98
IId	165–166	$C_{16}H_{14}O_3$	75.57	5.55	75.42	5.59
IIe	161–162	$C_{16}H_{14}O_3$	75.57	5.55	75.48	5.65
2,5-Dimethyl-3,4-bis-(2,4-dimethylbenzoyl)furan	85–86	$C_{24}H_{24}O_3$	79.97	6.71	79.68	6.78
2,5-Dimethyl-3,4-dimesitoylfuran	165–166	$C_{26}H_{28}O_3$	80.38	7.27	80.25	7.51

iodide, but there was also indication of a notable amount of active hydrogen from some of the compounds of Series II. These data are summarized in Table III. 2,5-Dimethylfuran does not undergo a Grignard exchange with methylmagnesium iodide,[5] but the keto groups of the cyclic diketones could activate the hydrogen on the methyl group of the furan nucleus toward the Grignard reagent. As a matter of interest, IIa was allowed to react with methylmagnesium iodide on a 0.02 mole scale. The reaction product was an intractable, very high melting black solid containing no magnesium.

TABLE III

REACTIONS OF SOME OF THE CYCLIC DIKETONES WITH METHYLMAGNESIUM IODIDE

Compound	Heating Time, Min.	Carbonyl Groups per Molecule	Active H per Molecule
Ia	20	2.31	0.11
Ib	20	1.57	0.18
	120	2.42	0.18
Ic	20	1.84	0.28
IIa	20	1.62	0.33
	40	1.55	0.38
	120	1.17	0.95
IIc	20	2.22	1.53
	30	2.22	1.65
	45	2.16	1.78
	110	2.38	1.94
IId	20	2.02	1.03

The infrared absorption spectra of Ia and IIa have strong bands at 5.6 microns and 6.0 microns respectively, the expected region for a carbonyl group conjugated with an unsaturated system.[6] Strong absorption bands at 13.95 and 13.97 microns respectively indicate an *o*-disubstituted benzene ring which is part of a fused system.[7]

Ia, IIa, and IIb formed a mono 2,4-dinitrophenylhydrazone. Although forcing conditions were used, the other cyclic diketones apparently did not react with this reagent, and attempts to prepare other ketone derivatives were unsuccessful.

Acetic anhydride was used to convert acid I to its anhydride V in nearly quantitative yield, but all efforts to convert acid II to an anhydride were unsuccessful. This was surprising in view of the fact that 1-*n*-butyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid formed an anhydride readily.[8] The reaction of I with thionyl chloride yielded V.

The aromatic hydrocarbons reacted with V in the presence of aluminum chloride to form 2,5-diphenyl-4-aroylfuran-3-carboxylic acids in yields of 73–97%. These data are summarized in Table IV.

Efforts to prepare the acid chloride of 2,5-diphenyl - 4 - benzoylfuran - 3 - carboxylic acid by means of phosphorus pentachloride or thionyl chloride yielded only the cyclic diketone Ia. 2,5-Diphenyl-4-mesitoylfuran-3-carbonyl chloride was obtained from the keto acid by means of thionyl chloride, and reacted with di-*n*-butylcadmium and with diphenylcadmium to form respectively a glassy product and an intractable oil.

The anhydride V did not react with phenylmagnesium bromide but with phenyllithium it

(5) C. D. Hurd and K. Wilkinson, *J. Am. Chem. Soc.*, 70, 738 (1948).

(6) L. F. Bellamy, *The Infra-red Spectra of Complex Molecules*, Methuen and Co., Ltd., London, 1954, pp. 119, 129.

(7) Ref. 6, p. 54.

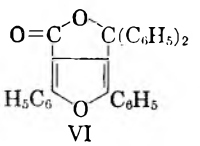
(8) D. V. Nightingale and J. A. Gallagher, *J. Org. Chem.*, 24, 501 (1959).

TABLE IV

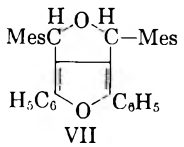
2,5-DIPHENYL-4-AROYL-3-CARBOXYLIC ACIDS

Hydrocarbon	M.P., °C.	Formula	Neut. Equiv. Calcd.	Neut. Equiv. Found	Calcd. C	Calcd. H	Found C	Found H
Benzene	149–150	$C_{24}H_{16}O_4$	368.4	367.5	78.25	4.38	78.23	4.34
Toluene	214–216	$C_{25}H_{18}O_4$	382.4	379.8	78.52	4.99	78.70	4.74
o-Xylene	207–208	$C_{26}H_{20}O_4$	396.4	397.2	78.77	5.09	78.79	5.27
m-Xylene	177–178	$C_{26}H_{20}O_4$	396.4	394.0	78.77	5.09	78.68	5.02
Mesitylene	171–172	$C_{27}H_{22}O_4$	410.5	404.9	79.00	5.69	79.18	5.40

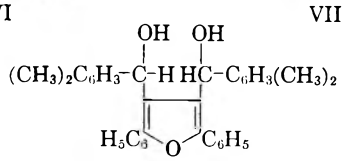
formed the lactone VI of the phthalide type. In the Grignard machine, VI



VI



VII



VIII

added one mole of methylmagnesium iodide and there was no indication of active hydrogen. In ultraviolet light, VI had a blue fluorescence similar to that of other phthalide types of compounds synthesized in this laboratory. The infrared absorption spectrum of VI showed a strong absorption band at 5.7 microns which is characteristic of the γ-lactone structure.[9]

2,5-Diphenyl-3,4-dimesitoylfuran reacted with zinc in alcoholic potassium hydroxide solution to form a compound, the carbon and hydrogen percentages of which agreed with those calculated for the substituted tetrahydrofuranofuran VII, but 2,5-diphenyl-3,4-bis(2,4-dimethylbenzoyl)furan apparently formed a bis-sec-carbinol VIII.

EXPERIMENTAL[10]

The preparation of 2,5-dimethylfuran-3,4-dicarboxylic acid. The procedure for the preparation of 2,5-dimethyl-3,4-dicarbethoxyfuran is an adaptation of the method of Nowlin[11] for the furanization of 1,4-diketones. This method gave a better quality of ester than the cyclization with sulfuric acid.[12] In a liter three-necked flask equipped with a stirrer and thermometer was placed 200 g. of polyphosphoric acid. The flask was heated to 50° and 42 g. (0.16 mole) of the solid β-form of α,α'-diacetoethylsuccinate[13] (m.p. 84–86°) was added in small portions with stirring. The temperature rose to 70° and was maintained at 70–75° for another 20 min. The separated brown complex was decomposed with ice and the mixture was extracted with several 100 ml. portions of ether. The ether solution was dried over magnesium sulfate and distilled to yield 34.8 g. (90%) of the furan ester as a red oil which distilled at 128–148° (1 mm.). Without further purification, this crude ester was saponified by means of 25% alcoholic potassium hydroxide[9] to form the acid II in nearly quantitative yield.

When crude, oily α,α'-diacetosuccinate was cyclized in this manner or with sulfuric acid, the yield of furan ester was only 19%.

Preparation of 2,5-dimethylfuran-3,4-dicarbonyl chloride. In a 500 ml. three-necked flask fitted with a stirrer, thermometer, and a gas outlet was placed 42 g. (0.23 mole) of 2,5-dimethylfuran-3,4-dicarboxylic acid I. To this was added 332 g. (2.8 moles) of thionyl chloride with stirring. After the vigorous evolution of gas had subsided, the mixture was heated at 60–70° for 1 hr. The excess thionyl chloride was removed with an aspirator and the product was distilled under further reduced pressure. Yield, 41 g. (80%), b.p. 117–120° (1 mm.). Efforts to obtain an analytical sample of this acid chloride resulted in a product contaminated with acid.

This acid chloride reacted with aniline in benzene solution to form a *dianilide*, m.p. 203–205°, in 80% yield.

Anal. Calcd. for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43. Found: C, 71.77; H, 5.21.

Preparation of 2,5-diphenylfuran-3,4-dicarboxylic acid. The procedure was identical with that described for the preparation of 2,5-dimethylfuran-3,4-dicarboxylic acid, except that the polyphosphoric acid was heated to 60° prior to the addition of dibenzoylethylsuccinate. From 50 g. (0.13 mole) of solid dibenzoylethylsuccinate and 250 g. of polyphosphoric acid there was obtained 45 g. (95%) of 2,5-diphenyl-3,4-dicarbethoxyfuran, m.p. 84–86°.

An 85% yield of the acid I, m.p. 235–237°, literature value,[14] 238°, was obtained from this ester.

Preparation of 2,5-diphenylfuran-3,4-dicarbonyl chloride. The procedure was essentially that of Hofman and Bridgewater.[15]

To a solution of 11 g. (0.036 mole) of I in 200 ml. of dioxan and 175 g. of chloroform was added 30 g. (0.145 mole) of phosphorus pentachloride. The mixture was shaken vigorously for 20 min. and then filtered. After the solvent had been removed with an aspirator, the residue was dissolved in boiling anhydrous ether. The ether was evaporated and the acid chloride was recrystallized from petroleum ether (b.p. 60–70°); yield 9.3 g. (75%), m.p. 119–120°.

Anal. Calcd. for $C_{18}H_{10}O_3Cl_2$: C, 62.63; H, 2.92. Found: C, 62.89; H, 3.13.

The acylations. The general procedure[3] for all the acylations was as follows: In a 200 ml. three-necked round bottom flask fitted with the usual equipment was placed 30 ml. of aromatic hydrocarbon and 3 g. (0.023 mole) of aluminum chloride. The flask was cooled in an ice bath and the solid acid chloride (3.5 g., 0.01 mole) of I was added slowly from a 60-ml. Erlenmeyer flask connected to the reaction flask by

(9) Ref. 6, p. 153.

(10) The carbon and hydrogen analyses were performed by Mr. Y. C. Lee, Mr. R. Elliot, and Mr. A. Mendel at the University of Missouri, and by the Weiler-Strauss Laboratories, Oxford, England. The melting points and boiling points are uncorrected.

(11) G. Nowlin, *J. Am. Chem. Soc.*, **72**, 5754 (1950).

(12) L. Knorr, *Ann.*, **306**, 332 (1899).

(13) G. H. U. Harrow, *J. Chem. Soc.*, **33**, 425 (1878).

(14) W. H. Perkin and A. Schloesser, *J. Chem. Soc.*, **57**, 944 (1890).

(15) K. Hofman and A. Bridgewater, *J. Am. Chem. Soc.*, **67**, 738 (1945).

rubber tubing. When the addition was complete, the ice bath was removed and the material stirred overnight at room temperature.

The complex was decomposed with iced hydrochloric acid and the mixture steam distilled to remove unreacted hydrocarbon. The separated solid reaction product was triturated with warm 10% aqueous potassium hydroxide solution and the insoluble material collected on a filter and recrystallized from ethanol. When the product consisted of two neutral compounds, they were separated by fractional recrystallization from ethanol. The alkaline filtrate was acidified to precipitate any keto acid if present.

When the hydrocarbons were acylated in carbon disulfide, nitro benzene or *sym*-tetrachloroethane, the amounts of reactants were usually 0.08 mole of hydrocarbon, 15 ml. of solvent, 4.4 g. (0.02 mole) of acid chloride and 6 g. (0.045 mole) of aluminum chloride. The liquid acid chloride of II was added through a separatory funnel.

Yields, physical constants and analyses of the acylation products are summarized in Tables I and II.

Preparation of the anhydride (V) *of 2,5-diphenylfuran-3,4-dicarboxylic acid.* A mixture of 25 g. of I and 200 ml. of acetic anhydride was refluxed for 2 hr. The acetic anhydride was hydrolyzed by the addition of cold water. Recrystallization of the yellow solid from glacial acetic acid gave 23.5 g. of V, m.p. 260–262°, lit.[16] 254–255°.

Acylations with V. The general procedure was as follows: In a 200 ml. round bottom flask fitted with the usual equipment was placed 100 ml. of hydrocarbon and 6 g. (0.045 mole) of aluminum chloride. The flask was cooled in an ice bath and 5.8 g. of V was added during 5 min. with stirring. The ice bath was removed, the mixture stirred at room temperature for 9 hr., and then allowed to stand an additional 15 hr.

The complex was decomposed in the usual manner and excess hydrocarbon removed by steam distillation. The solid residue was triturated with hot 10% aqueous sodium hydroxide solution and the insoluble sodium salt of the keto acid was collected on a filter and extracted with ether to remove any neutral compounds. The sodium salt was suspended in dilute ethanol, hydrochloric acid was added, and the separated keto acid was collected on a filter. Yields were 73% to 97%. Physical constants and analyses of the keto acids are summarized in Table IV.

Reaction of V *with phenyllithium.* A solution of phenyllithium prepared from 6.28 g. (0.04 mole) of bromobenzene was added dropwise with stirring to a slurry of 5.8 g. (0.02 mole) of V in 100 ml. of ether in the conventional apparatus. When the addition was complete, the mixture was stirred at room temperature for 3 hr. and then allowed to stand overnight. The complex was decomposed with 150 ml. of water.

The hydrolyzate was filtered and 0.55 g. of a solid was obtained. The aqueous layer was separated from the ether layer, washed twice with ether, and the ether layers were combined. These combined ether solutions were extracted with 5% sodium carbonate solution and the basic extract added to the original separated aqueous layer.

This basic solution was allowed to stand overnight and during this time a solid precipitated. It was collected and combined with the solid from the first filtration. The combined solids were treated with warm concentrated hydrochloric acid to decompose any remaining metal complex. After recrystallization from ethanol, this solid, the lactone VI, melted at 189–190°; yield 4.1 g. (47.7%). On evaporation of the ether solution, an additional 0.2 g. of VI was obtained.

Anal. Calcd. for $C_{30}H_{20}O_3$: C, 84.09; H, 4.71. Found: C, 83.86; H, 4.76.

The lactone VI showed a strong blue fluorescence in ultraviolet light, and was insoluble in hot concentrated potassium hydroxide solution.

In the Grignard machine, VI added one mole of methylmagnesium iodide but liberated no methane, indicating the presence of one carbonyl group and no active hydrogen.

Acidification of the basic filtrate yielded 1.9 g. of the acid I.

Preparation of 2,5-diphenyl-4-mesitoylfuran-3-carbonyl chloride. In a 200 ml. flask fitted with the conventional equipment was placed 11.0 g. (0.028 mole) of 2,5-diphenyl-4-mesitoylfuran-3-carboxylic acid and 50 ml. of thionyl chloride. After the mixture was stirred for 1.5 hr., the excess thionyl chloride was removed. The residue was recrystallized twice from petroleum ether (b.p. 60–70°) to yield 11 g. (94%) of acid chloride, m.p. 135–138°. Efforts to recrystallize this product further for an analytical sample resulted in decomposition.

This partially purified acid chloride reacted with aniline in benzene solution to form an anilide in 80% yield, m.p. 161–162.5°.

Anal. Calcd. for $C_{33}H_{27}O_3N$: C, 81.62; H, 5.61. Found: C, 81.30; H, 5.95.

Preparation of the 2,4-dinitrophenylhydrazones. The procedure was that of Josten.[17] In a 250 ml. flask was placed 2.0 g. of the ketone IIa, 3.5 g. of 2,4-dinitrophenylhydrazine, 4 ml. of sulfuric acid, and 75 ml. of dioxan. The solution was refluxed for 2 hr. under a slight pressure of nitrogen, then diluted and filtered. The orange brown solid was washed with dilute hydrochloric acid and recrystallized from ethyl acetate to yield, 2.8 g. (76%) of derivative, m.p. 268–269°.

Anal. Calcd. for $C_{20}H_{14}O_6N_4$: C, 59.11; H, 3.47. Found: C, 58.82; H, 3.42.

The *2,4-dinitrophenylhydrazone* of IIb melted at 242–243°.

Anal. Calcd. for $C_{21}H_{16}O_6N_4$: C, 60.00; H, 3.84. Found: C, 59.93; H, 3.68.

The *2,4-dinitrophenylhydrazone* of Ia melted at 233–235°.

Anal. Calcd. for $C_{30}H_{18}N_6O_4$: C, 67.92; H, 3.42. Found: C, 67.92; H, 3.77.

Reaction of 2,5-diphenyl-3,4-dimesitoylfuran with zinc.[3] To 4.3 g. (0.076 mole) of potassium hydroxide dissolved in 425 ml. of 95% ethanol was added 2.0 g. (0.004 mole) of 2,5-diphenyl-3,4-dimesitoylfuran. The mixture was refluxed for 14 hr., cooled, and filtered. The yellow filtrate was poured into dilute acetic acid and the mixture extracted with ether. The ether layer was separated and washed and the solvent removed by distillation. The oily residue was triturated with a mixture of ethanol and petroleum ether and finally solidified. The product V melted at 119–120° after recrystallization from ethanol.

Anal. Calcd. for $C_{36}H_{34}O_2$: C, 86.91; H, 6.87. Found: C, 86.82; H, 7.02.

Reaction of 2,5-diphenyl-3,4-bis(2,4-dimethylbenzoyl)furan with zinc. By the procedure described above this ketone yielded VI, m.p. 156.5–158° after recrystallization from ethanol.

Anal. Calcd. for $C_{34}H_{32}O_3$: C, 83.57; H, 6.60. Found: C, 83.77; H, 6.47.

COLUMBIA, MO.

(16) W. H. Perkin and A. Calman, *J. Chem. Soc.*, 49, 154 (1886).

(17) W. Josten, *Ber.*, 41, 2230 (1931).

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

Acylations with the Acid Chloride and Anhydride of 1-*n*-Butyl-2,5-dimethylpyrrole-3,4-dicarboxylic Acid

DOROTHY V. NIGHTINGALE AND JAMES A. GALLAGHER[1]

Received August 18, 1958

The acylation of benzene, toluene, and the three xylenes with 1-*n*-butyl-2,5-dimethylpyrrole-3,4-dicarbonyl chloride (I) yielded cyclic diketones. The acylation of mesitylene yielded an open diketone.

The anhydride (II) of 1-*n*-butyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid reacted with benzene in the presence of aluminum chloride to form a cyclic diketone. With toluene, the product was a mixture of cyclic diketone and keto acid.

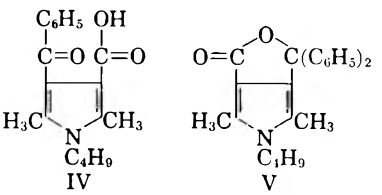
The reaction of II with phenyllithium yielded a phthalide type of compound, but with phenylmagnesium bromide and diphenylcadmium a keto acid was formed.

The fact that the acylation of some aromatic hydrocarbons with the acid chlorides of 2,5-dimethyl- and 2,5-diphenylfuran-3,4-dicarboxylic acids yielded mainly cyclic diketones rather than the phthalide type of compounds[2] led us to investigate acylations of these same hydrocarbons with the acid chloride I of 1-*n*-butyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid and its anhydride II. This acid chloride and the anhydride had not previously been reported in the literature. The hydrogen in the 1-position was replaced by a *n*-butyl group to avoid any possible adverse effect of this hydrogen on the course of some of the reactions.

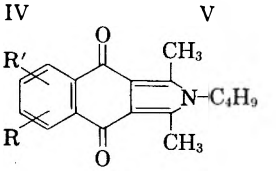
The acid chloride I was prepared from the acid by means of thionyl chloride. When the purification of I was attempted by recrystallization, the odor of hydrogen chloride was noted at each step and finally only II was obtained. After removal of traces of thionyl chloride during two crystallizations, I was sufficiently pure for use in the acylations.

The anhydride II could be obtained in two ways: cyclization of the acid by means of acetic anhydride in the presence of a trace of 85% phosphoric acid or by means of acetyl chloride. Cyclization by means of acetyl chloride was the most convenient procedure. For the acylation of benzene with I, three procedures were tried. The addition of I to the aluminum chloride in excess benzene gave the best yields. When the hydrocarbon was added to I and the aluminum chloride in nitrobenzene, only an intractable red oil was obtained. If the benzene was added to I and the aluminum chloride in carbon disulfide, the yield of IIIa was only 37% as compared with 88% in benzene solution. On the basis of these results, the first procedure was used for all of the acylations.

The acylation of benzene, toluene, and the three xylenes with I yielded only cyclic diketones III (9,10-dihydro-4,9-dioxo-1,3-dimethyl-4-*n*-butylnaphtho[2,3c]pyrroles). These compounds were



IV V



III

IIIa. R = R′ = H
IIIb. R = 6-CH_3; R′ = H
IIIc. R = 6-CH_3; R′ = 7-CH_3
IIId. R = 6-CH_3; R′ = 8-CH_3
IIIe. R = 5-CH_3; R′ = 8-CH_3

yellow and fluoresced yellow in ultraviolet light. No ketoacid, no diaroyl compounds and no phthalide type of compounds were isolated from the reaction mixtures. Mesitylene formed 1-*n*-butyl-2,5-dimethyl-3,4-dimesitoylpyrrole.

The products from the acylation of benzene and *p*-xylene were analyzed in the Grignard machine. Both compounds gave one active hydrogen and two carbonyl groups per molecule when the pot was heated in boiling water for fifteen minutes after the addition of the methylmagnesium iodide. If the mixture was not heated at this point but merely stirred for fifteen minutes at room temperature, only one carbonyl group reacted and there was no evolution of methane. Heating in boiling water for about 8 minutes gave about 0.6 mole of methane and about 1.5 carbonyl groups per molecule. 1-*n*-Butyl-2,5-dimethylpyrrole gave 0.017 mole of methane after heating for fifteen minutes.

The acylation of benzene with II formed only the cyclic diketone IIIa in 12% yield. The acylation of toluene with II under the same experimental conditions formed IIIb and a ketoacid, each in 13% yield. In the furan series, no cyclic diketone was obtained from the corresponding anhydride.

The reaction of II with phenylmagnesium bromide and with diphenylcadmium yielded the keto acid IV. When this keto acid was recrystallized from ethanol, the compound, m.p. 135–

(1) Abstracted from the Ph.D. dissertation of James A. Gallagher, June 1955.

(2) D. V. Nightingale and B. Sukornick, *J. Org. Chem.*, **24**, 497 (1959).

TABLE I

ACYLATIONS WITH 1-*n*-BUTYL-2,5-DIMETHYLPYRROLE-3,4-DICARBONYL CHLORIDE

Hydrocarbon	Yield, % III	M.P., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
Benzene	88	129–130	$C_{18}H_{19}O_2N$	76.84	6.81	76.48	6.88
Toluene	34	135–136	$C_{19}H_{21}O_2N$	77.26	7.17	77.13	6.96
o-Xylene	82	216–217	$C_{20}H_{23}O_2N$	77.64	7.49	77.67	7.65
m-Xylene	83	125–126	$C_{20}H_{23}O_2N$	77.64	7.49	77.28	7.51
p-Xylene	33	102–103	$C_{20}H_{23}O_2N$	77.64	7.49	77.45	7.65
Mesitylene	57[a]	173–174	$C_{30}H_{37}O_2N$	81.22	8.41	81.07	8.38

[a] The open diketone.

136°, apparently crystallized with one molecule of alcohol of crystallization, $C_{18}H_{21}O_3N.C_2H_5OH$, which was not removed by heating in a drying pistol under reduced pressure. The percentages of carbon and hydrogen found agreed with the calculated values for a mono alcoholate. A determination of active hydrogen and carbonyl groups in the Grignard machine gave 1.89 active hydrogens and 2.26 carbonyl groups per molecule. These values are within experimental error for two active hydrogens and two carbonyl groups per molecule. If the crude product was recrystallized only from petroluem ether, the found values for carbon and hydrogen percentages of the compound, m.p. 133–134°, agreed with those calculated for $C_{18}H_{21}O_3N$. A mixture of the two compounds melted at 115–117°.

The reaction of II with phenyllithium formed a phthalide type of compound V as indicated by values from carbon and hydrogen analyses and determination of active hydrogen and carbonyl groups.

The ketoacid IV was reacted with thionyl chloride, but the resulting acid chloride could not be purified without decomposition, or kept for any length of time even in a vacuum desiccator. Immediately after removal of excess thionyl chloride, a toluene solution of the crude acid chloride was added to aluminum chloride in toluene. The The only product isolated from the reaction was the intra molecular acylation product, the cyclic diketone, IIIa rather than an open diketone.

The infrared absorption spectrum of IIIa has strong bands at 6.06 microns and 13.88 microns, the expected region for a carbonyl group conjugated with an unsaturated system and an *o*-disubstituted benzene ring which is part of a fused system.[3]

EXPERIMENTAL[4]

The melting points are uncorrected.

The preparation of 1-n-butyl-2,5-dimethyl-3,4-dicarboxylic acid. The procedure is an adaptation of Knorr's preparation of pyrrole.[5] Solid α,α'-diacetoethylsuccinate (25.8 g., 0.1 mole), 10.9 g. of *n*-butylamine and 300 ml. of water were mixed at room temperature and allowed to stand overnight with occasional stirring. The solution was acidified and extracted with ether, the ether extract was washed with 5% hydrochloric acid and finally with water. After removal of the solvent, the crude ester was recrystallized from ethanol and finally from petroleum ether (60–70°); yield, 21.6 g. (73%) m.p. 61–62°.

Anal. Calcd. for $C_{16}H_{25}O_4N$: C, 65.06; H, 8.53. Found: C, 65.10; H, 8.58.

In a 100-ml. round bottom flask was placed 10 g. of 1-*n*-butyl-2,5-dimethyl-3,4-dicarbethoxypyrrole, 10 g. of potassium hydroxide, 10 ml. of water, and 30 ml. of ethylene glycol. The solution was refluxed overnight, cooled to room temperature, and acidified with 50% acetic acid. After cooling in an ice-salt bath for about an hour, crystals of the desired acid separated and were collected on a filter. The filtrate was acidified with hydrochloric acid to precipitate the remaining acid, which was redissolved in a minimum amount of 10% sodium hydroxide to remove a small amount of hydrochloric acid from the crystals, and the solution acidified with 50% acetic acid. The combined solids were recrystallized from ethyl acetate to yield 7 g. (87%) of 1-*n*-butyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid, m.p. 178–180°.

Anal. Calcd. for $C_{12}H_{17}O_4N$: C, 60.24; H, 7.16. Found: C, 60.12; H, 7.36.

Preparation of the acid chloride of 1-n-butyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid. To 2.28 g. (0.01 mole) of the acid was added 32 g. of thionyl chloride. The reaction began immediately and after it had subsided, the mixture was heated on a steam bath for 30 min. The excess thionyl chloride was removed with an aspirator, the residue was dissolved in dry ether and the solution decolorized with Norite. The solution was filtered and the ether removed with the aspirator. After two recrystallizations, the acid chloride was satisfactory for use in the acylations, but efforts to obtain an analytical sample lead finally to the anhydride. Yields of twice recrystallized acid chloride ranged from 76% to 91%.

Preparation of the anhydride of 1-n-butyl-2,5-dimethylpyrrole 3,5-dicarboxylic acid. Procedure A. In a 100-ml. round bottom flask fitted with a reflux condenser were placed 5 g. (0.021 mole) of the acid and 40 ml. of acetyl chloride. The solution was refluxed for 2 hr. or less on a steam bath and then connected to the aspirator to remove part of the acetyl chloride. The flask was then placed in an acetone dry ice bath and cooled for about 15 min. The precipitated anhydride was collected on a Buchner funnel, then stirred in a beaker with a small amount of ether and with 20 ml. of 5% sodium bicarbonate solution. After standing about 20 minutes, the anhydride was collected on a Buchner funnel and washed with water. Recrystallization from petroleum ether (60–70°) yielded 2.8 g. (61%) of colorless anhydride, m.p. 127–128°.

(3) L. F. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen and Co., Ltd., London, 1954, pp. 119, 129, 54.

(4) The carbon and hydrogen analyses were performed by Mr. Y. C. Lee and Mr. R. Elliot at the University of Missouri.

(5) L. Knorr, *Ber.*, 18, 299 (1885).

Anal. Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83. Found: C, 65.43; H, 6.88.

Procedure B. In a 50-ml. round bottom flask fitted with a six inch column packed with glass helices were placed 8 g. (0.033 mole) of 1-*n*-butyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid, one drop of 85% phosphoric acid, and 20 ml. of acetic anhydride. The flask was heated to 140° and held at this temperature until the head of the column reached 118°, the boiling point of acetic acid. These temperatures were maintained for an hour and then the acetic acid and acetic anhydride were removed with an aspirator. The residue was recrystallized from petroleum ether (60–70°) to yield 4.4 g. (60%) of II, m.p. 127–128°.

Acylations with 1-n-butyl-2,5-dimethylpyrrole-3,4-dicarbonyl chloride.[6] The general procedure is as follows: In a 200-ml. three necked round bottom flask was placed 1.0 mole of the hydrocarbon and 3.04 g. (0.023 mole) of aluminum chloride. The flask was fitted with the usual equipment and cooled in an ice bath. The acid chloride (2.93 g.) (0.01 mole) was added slowly to the cooled hydrocarbon solution, then the ice bath was removed and the mixture was stirred overnight at room temperature. The complex was decomposed in the usual manner with iced hydrochloric acid, the hydrocarbon layer was separated, the aqueous layer was washed with ether, and the ether washings were added to the hydrocarbon layer. The solvents were removed by steam distillation, the organic residue was dissolved in ether, and the solution extracted with sodium hydroxide. The separated ether layer was evaporated at room temperature and the solid residue was recrystallized from ethanol and finally from petroleum ether (60–70°). Yields, physical constants, and analytical data are summarized in Table I.

Acylations with 1-n-butyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid anhydride. In a 500-ml. flask was placed 100 ml. of benzene and 3.20 g. (0.024 mole) of aluminum chloride. The flask was cooled in ice and 2.21 g. (0.01 mole) of the anhydride II was added slowly with stirring. The material in the flask became gummy but after standing overnight, most of the gum had dissolved, and the solution was stirred for 4 hr. at room temperature.

The complex was decomposed with iced hydrochloric acid. The separated solid was collected on a filter and proved to be 1-*n*-butyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid. The hydrocarbon layer was separated, the aqueous layer was extracted with ether, and the ether extract added to the hydrocarbon layer. The ether-benzene solution was extracted with 10% sodium hydroxide, separated, and the solvents steam distilled. The residue was recrystallized from petroleum ether (60–70°) to yield 0.32 g. (12%) of yellow needles, m.p. 126–127°, which were identified as the cyclic diketone IIIa.

Acidification of the sodium hydroxide extract yielded a small amount of the dicarboxylic acid but no ketoacid IV.

The acylation of toluene with 2.20 g. (0.01 mole) of anhydride and 3.20 g. (0.024 mole) of aluminum chloride in the same manner yielded 0.35 g. (13%) of cyclic diketone IIIb, m.p. 134–135°, and 0.50 g. of 1-*n*-butyl-2,5-dimethyl-4-toluoylpyrrole-3-carboxylic acid, m.p. 129–130°.

Anal. Calcd. for $C_{19}H_{23}O_3N$: C, 72.83; H, 7.40. Found: C, 72.93; H, 7.59.

Reaction of II with phenylmagnesium bromide. A solution of phenylmagnesium bromide prepared from 6.28 g. (0.04 mole) of bromobenzene in about 150 ml. of ether was added to 8.70 g. (0.04 mole) of II suspended in 100 ml. of dry ether in a 500-ml. three necked round bottom flask fitted with the usual equipment. After the slightly exothermic reaction, the solution was stirred for about 2 hr.

The complex was decomposed by pouring onto iced hydrochloric acid. The solid which separated contained magnesium and was warmed briefly with hydrochloric acid on the steam bath to complete decomposition. Ether was added, the solution filtered, and the ether layer added to the ether layer initially obtained from the partial decomposition of the complex.

The combined ether solutions were washed with water, sodium bicarbonate, sodium carbonate, and finally with sodium hydroxide.

The sodium bicarbonate and sodium carbonate extracts were acidified dropwise with 10% hydrochloric acid. The first material to separate was a gummy product which was dried in a vacuum desiccator and melted at 118–125°. The gum was completely precipitated at *p*H 7. After removal of the gum, continued acidification to about *p*H 5 yielded a white solid which melted at 124–128°. After removal of this material by filtration, further acidification yielded a small amount of dicarboxylic acid.

The crude solids were recrystallized first from ethanol and finally from aqueous ethanol. Yield, 2.55 g. (21%), m.p. 135–136°. The values from the carbon and hydrogen analyses indicated that this compound was an alcoholate.

Anal. Calcd. for $C_{18}H_{21}O_3N.C_2H_5OH$: C, 69.54; H, 7.88. Found: C, 69.54; H, 7.52.

Tschugaeff-Zerwitinoff determination: 1.89 active hydrogens and 2.26 carbonyl groups per molecule.

The reaction was repeated, but the product was recrystallized only from petroleum ether (60–70°). The yield was 2.86 g. (24%) of white crystals, m.p. 133–134°.

Anal. Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07. Found: C, 71.88; H, 7.37.

A mixture of this product and that recrystallized from alcohol (above) melted at 115–117°.

Reaction of II with diphenylcadmium. To a toluene solution of diphenylcadmium prepared from 10.6 g. of bromobenzene was added 6 g. of II. The reaction flask was heated to 70° and stirred at this temperature for about 2 hr. The complex was decomposed with iced concentrated hydrochloric acid and filtered.

The separated solid (2.55 g.) was unchanged II.

The toluene layer was separated from the aqueous layer, the aqueous layer was washed with ether and these washings combined with the toluene layer. The combined solvents were extracted with 5% sodium carbonate solution and then the alkaline solution was acidified with 50% acetic acid. The product separated as a gummy mass and was removed. It was redissolved in 5% sodium carbonate and 10% acetic acid was added dropwise. The keto acid precipitated and was recrystallized from ethanol. Yield, 0.81 g. (10%), m.p. 135–136°, mixture m.p. with the product (alcoholate) m.p. 135–136° from the reaction with phenylmagnesium bromide 135–136°.

Reaction of II with phenyllithium. A solution of phenyllithium prepared from 3.14 g. of bromobenzene in 100 ml. of dry ether was added to a slurry of 4.42 g. (0.02 mole) of II in 100 ml. of dry ether in a 500-ml. flask fitted with the usual equipment. When the addition was complete, the mixture was allowed to stand overnight. The complex was decomposed with 150 ml. of water, and the solution was filtered to remove 0.3 g. of dicarboxylic acid. The ether layer was separated, the aqueous layer was washed three times with ether and the ether washings added to the original ether layer. This solution was then extracted three times with 1% sodium hydroxide solution and these alkaline washings added to the original aqueous layer. A yellow oil was obtained by evaporation of the ether solution which crystallized on standing.

The aqueous layer was acidified dropwise with 10% hydrochloric acid to about *p*H 8. A solid separated and was collected on a filter. Further acidification yielded 0.4 g. of dicarboxylic acid.

The solid from the ether solution and the solid which separated from the aqueous layer at *p*H 8 were warmed on a steam bath with 5% sodium hydroxide for about 20 min. The insoluble white solid was collected on a filter, and acidification of the filtrate yielded 0.7 g. of dicarboxylic acid.

(6) R. Fuson, S. Speck, and W. Hatchard, *J. Org. Chem.*, 10, 55 (1945).

The white solids (2.4 g., 33%) were recrystallized from aqueous ethanol to yield crystals which melted at 167–167.5°.

Anal. Calcd. for $C_{24}H_{25}O_2N$: C, 80.19; H, 7.01. Found: C, 79.79; H, 7.15.

Tschugaeff-Zerewitinoff determination: 0.12 mole of active hydrogen and 0.85 carbonyl group per molecule.

Acylation of toluene with 1-n-butyl-2,5-dimethyl-3-benzoyl-4-carbonyl chloride. Because this acid chloride could not be purified without extensive decomposition, the crude product from the reaction of 1.40 g. of keto acid and thionyl chloride was dissolved in dry toluene and added dropwise to a mixture of 1.5 g. of aluminum chloride and 50 ml. of toluene in the conventional equipment.

From this reaction there was isolated by the procedures previously described 0.40 g. (29%) of cyclic diketone IIIa, m.p. and mixed m.p. with IIIa from the acylation of benzene with I, 129–130°.

Preparation of 1-n-butyl-2,5-dimethylpyrrole. Acetonylacetone (57 g., 0.5 mole) and 36 g. (0.5 mole) of *n*-butylamine were placed in a flask fitted with a reflux condenser. The exothermic reaction began immediately. The mixture stood overnight and was then distilled. The product boiled at 98–100° (20 mm.), yield 64 g. (85%), n_D^{20} 1.4828.

Anal. Calcd. for $C_{10}H_{17}N$: C, 79.40; H, 11.34. Found: C, 79.08; H, 11.27.

COLUMBIA, MO.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, VANDERBILT UNIVERSITY]

A Study of the Entrainment Method for Making Grignard Reagents

D. E. PEARSON, DOROTHA COWAN, AND J. D. BECKLER

Received October 2, 1958

Modifications of the entrainment method used in this work were: (1) introduction of all of the "inert" halide at the start of the reaction, (2) use of ethylene bromide rather than ethyl bromide as the entrainment reagent, (3) a slow rate of addition (*ca.* 12 hr.) of the entrainment reagent. In this manner, α-chloronaphthalene was converted to α-naphthoic acid in 56% yield and to naphthalene in 66% yield, *p*-bromodimethylaniline to *p*-dimethylaminobenzoic acid in 48% yield and to dimethylaniline in 71% yield, hexachlorobenzene to pentachlorobenzoic acid in 71% yield and pentachloroacetophenone in 31% yield, and *p*-bromoacetophenone azine to *p*-carboxyacetophenone in 34% yield and to phenyl-*p*-acetophenylcarbinol in 9% yield. The yields for the specific compounds are superior to any obtained heretofore by means of the entrainment method and demonstrate the utility of ethylene bromide as an entrainment agent.

A number of "inert" halogen compounds, such, for example, as α-chloronaphthalene, fail to give Grignard reagents under ordinary conditions. Four methods are available for application under these circumstances: the lithium, the reactive solvent, the activated metal, and the entrainment methods. The lithium method[1–3] has been applied occasionally for conversion of "inert" halides to organic lithium compounds, but its main use, stemming from the high reactivity of organic lithium compounds, has been to accomplish additions in a more effective way than with Grignard reagents. In one of the few papers devoted to a comparison of conversion of "inert" halides,[4] Gilman and coworkers state that chlorobenzene, *p*-chlorotoluene, α-chloronaphthalene, and *p*-bromodimethylaniline give better yields of organolithium compounds than of Grignard reagents but that the reverse is true for conversion of dihalides to organometallic compounds. An example of the former conversion is the preparation of *p*-dimethylaminobenzoic acid in 41–56% yields from the *p*-dimethylaminophenyllithium.[5] Braude and Evans have been successful recently in preparing vinyllithium compounds.[6] Examples of conversion of "inert" halides to organolithium compounds are not numerous, however. Perhaps additional factors contributing to this neglect are the possibilities of the organolithium compound being insoluble or of the lithium halide coating the surface of the lithium.

The second method of application, the reactive solvent method, is comparatively recent. Indeed, the most promising results of this method have been published after the work in this laboratory on the entrainment method had been well advanced. The reactive solvent is one which complexes with the Grignard reagent more effectively and in this manner brings about reaction or completion of reaction between magnesium and "inert" halides. Tetrahydrofuran seems to be the solvent of choice although other cyclic ethers are also effective.[7–9] The method is particularly well adapted to synthesis of vinyl Grignard reagents. We must keep in mind, however, that tetrahydro-

(1) *Annotated Bibliography of Organic Lithium Compounds*, Lithium Corp. of America, Rand Tower, Minneapolis 2, Minn.

(2) F. Runge, *Organometallverbindungen*, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1944.

(3) R. G. Jones and H. Gilman, *Organic Reactions*, John Wiley & Sons, New York, N. Y. (1951), Vol. 6, 339. Halogen-Metal Interconversions.

(4) H. Gilman, E. A. Zoellner, and W. M. Selby, *J. Am. Chem. Soc.*, 55, 1252 (1933).

(5) H. Gilman and I. Banner, *J. Am. Chem. Soc.*, 62, 344 (1940).

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

(7) H. Normant, *Compt. rend.*, 240, 1111 (1955) and preceding papers; *Bull. soc. chim. France*, 1444 (1957).

(8) H. E. Ramsden *et al.*, *J. Org. Chem.*, 22, 1202 (1957); 1602 (1957).

(9) C. S. Marvel and R. G. Woolford, *J. Org. Chem.*, 23, 1658 (1958).

furan is a more powerful coordinating solvent than diethyl ether. In the addition of the Grignard reagent complexed with tetrahydrofuran to slowly reacting carbonyl compounds, lower yields or even side reactions may take place.[10,11] With this single reservation of possible retardation of addition of the Grignard reagent, the reactive solvent method is an extremely attractive synthetic route.

The third method, the activated metal method, consists of activation of the magnesium by chemical reaction or by reduction of the size of the metal particles.[12a] Gilman catalyst,[13] a combination of magnesium and iodine, is a well known example of the chemical activator type. A recent example of the use of ground magnesium is the preparation of durylmagnesium bromide, from which a 70% crude yield of adduct was obtained.[14] The latter method has not been tested sufficiently to assess its general use.

In the light of the availability of the above three methods of conversion of "inert" halides to organometallic compounds, we had cause to wonder if the fourth method, the entrainment method, is passé. The yields of products have never been consistently good: of the 29 reactions listed (with yields) by Kharasch and Reinmuth,[12b] the average yield is 38%, and the yields are above 60% in only five instances. Nevertheless, we felt that the entrainment method had never been utilized under the most favorable conditions based on knowledge of the reaction and for this reason deserved further study.

The following important modifications were made for reasons to be described with each. First, all of the "inert" halide was added at the beginning of the reaction, not, as is usual, with the entrainer. In this manner, the activated magnesium surface was exposed to the highest concentration possible of the "inert" halide. Second, and more important, ethylene bromide was used as the entrainment reagent rather than ethyl bromide. With ethylene bromide and magnesium only ethylene and magnesium bromide are formed as products. Thus, only the Grignard reagent of the "inert" halide is present, mixed or complexed with magnesium bromide. With ethyl bromide and magnesium, two Grignard reagents are present, an obvious disadvantage if the carbonyl compound to be added to the Grignard reagent is valuable. We believe we were the first to use ethylene bromide as an entrainment reagent,[15] although anhydrous magnesium bromide has been prepared by reaction of ethylene bromide and magnesium covered with ether.[12c,16,17] Third, the entrainment agent was added over a long period of time (8 hr. or more). The agent acts in the main part as a cleanser and activator of the magnesium surface.[18] A fast rate of addition of entrainer will etch merely the already active surface; a slow rate will permit the "inert" halide to react with these active surfaces without wasting the entrainer by reaction on the same active surfaces. If consumption of entrainer and magnesium are not important, a fast rate of addition of entrainer can also be used with excesses (several equivalents) of each. We found the latter method to be expedient in the preparation of the Grignard reagents of bromoketazines to be described. Since the efficacy of the entrainment reagent was brought about by a mechanical action, in part at least, the amount of entrainer need not be related in any molecular way to the amount of "inert" halide. It is stated, however, that at least one equivalent of entrainer is ordinarily necessary for greatest yield.[12b]

Our first efforts were to study the efficacy of the second and third modifications using α-naphthyl chloride as the "inert" halide. Previous experiments with the Grignard reagent of this halide, made using ethyl bromide as the entrainer, gave a 16% yield of α-naphthoic acid by reaction with carbon dioxide and a 46% yield of naphthalene by reaction with water.[12b] The effect of time of addition of ethylene bromide is shown in Table I.

TABLE I

$\alpha\text{-}C_{10}H_7Cl + Mg \rightarrow \alpha\text{-}C_{10}H_7MgCl \rightarrow \alpha\text{-}C_{10}H_7COOH$

Time of addition of ethylene bromide in hours	2	7	12	26
% Yield as α-naphthoic acid (crude)	0	42	56[a]	58

[a] When isolated as naphthalene, the yield was 66%.

(10) R. N. Lewis and J. R. Wright, *J. Am. Chem. Soc.*, **74**, 1253 (1952). Ethylmagnesium bromide did not add to benzophenone in presence of tetrahydrofuran.

(11) L. Field, J. R. Holsten, and R. D. Clark, *J. Am. Chem. Soc.*, in press. Methylsulfonylmethylmagnesium bromide and benzaldehyde in tetrahydrofuran gave half the yield of the normal adduct from the same reactants in diethyl ether and benzene.

(12) (a) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York (1954), p. 6, (b) p. 38, (c) p. 33.

(13) H. Gilman and R. H. Kirby, *Rec. trav. chim.*, **54**, 577 (1935).

(14) R. C. Fuson, W. C. Hammann, and P. R. Jones, *J. Am. Chem. Soc.*, **79**, 928 (1957).

(15) J. D. Beckler, "Grignard Reagents of *m*- and *p*-Bromoacetophenone Azines," Master's thesis, Vanderbilt University, 1955. A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Bull. Acad. Sciences, U.S.S.R.*, Div. of Chem. Science, 1389 (1957) have used "a few drops" of ethylene bromide in the preparation of the Grignard reagent of α-iodoselenophene.

(16) M. Tissier and V. Grignard, *Compt. rend.*, **132**, 835 (1901).

(17) C. L. Stevens and S. J. Dykstra, *J. Am. Chem. Soc.*, **76**, 4402 (1954).

(18) Part of the facilitation may also be in forming a complex of the Grignard reagent of the entrainer with that of the "inert" halide. In the case of ethylene bromide, a complex of magnesium bromide and the Grignard reagent of the "inert" halide would be formed.

From these results, a time of addition of about 12 hr. was selected for all other experiments. Comparison of ethyl bromide and ethylene bromide as entrainment reagents was next made with the results shown in Table II.

TABLE II

Entrainment Reagent	% Yield as α-Naphthoic Acid	% Yield as Naphthalene
Ethylene bromide	56	66
Ethyl bromide	56	77

From our results, the two entrainment reagents seemed comparable, and all other experiments were conducted using ethylene bromide as the entrainment agent. To demonstrate that ethylene bromide has an advantage in not forming any Grignard reagent, we synthesized α-naphthyl phenyl ketone in 49% yield using benzonitrile as the limiting reagent. With ethylmagnesium bromide, a major proportion, if not all, of the benzonitrile would have been lost as propiophenone.

Other "inert" halides besides α-naphthyl chloride were tested also. The first, hexachlorobenzene, was selected because of its alleged unreactivity. In view of a recent paper,[19] however, this compound probably is of moderate activity since it has been shown to react with amines under relatively mild conditions. Part of its alleged unreactivity is caused no doubt by its insolubility. The results of our conversion of this compound to the Grignard reagent and subsequently to the acid and to pentachloroacetophenone are shown in Table III. A large scale run also gave a 60% yield of pentachlorobenzoic acid.

TABLE III

PREPARATION OF COMPOUNDS USING ETHYLENE BROMIDE AS ENTRAINER

Mono-Grignard of	Reagent	Product	Yield, %
Hexachlorobenzene	CO_2	C_6Cl_5COOH	71
	$(CH_3CO)_2O$	$C_6Cl_5COCH_3$	31
p-Bromodimethylaniline	CO_2	$(CH_3)_2NC_6H_4COOH$	48
	H_2O	$C_6H_5N(CH_3)_2$	71

It is interesting to note that Ramsden and coworkers[8] were unable to obtain pentachlorobenzoic acid although pentachlorophenylmagnesium chloride was shown to be present in 77% yield by titration. Thus, we have one example at least in which the entrainment method is superior to the reactive solvent method. In another example, *o*-bromophenylmagnesium bromide in ether gave a 30% yield of acid on carbonation while the same reagent in tetrahydrofuran gave no acid.[20] Other examples should be found if we can judge from the influence of the environment. In the environment for the entrainment method, magnesium bromide, a Lewis acid, is present which should activate carbonyl compounds in their addition to Grignard reagents.[21-23] In the environment for the reactive solvent method, the strongly complexing solvent should deactivate the Grignard reagent in addition reactions as it appears to do here. However, we must admit that we were unable to see any good or bad influence of magnesium bromide in affecting the yields of acetophenone from phenylmagnesium bromide and acetonitrile[24] and for this reason are not wholly convinced of the generality of magnesium bromide activation. Another "inert" halide, *p*-bromodimethylaniline, was studied not because it was inert but because it tended to form an impervious coating on the magnesium surface. Compounds containing ether, hydroxyl, amino, sulfone, and other groups seem to have this tendency perhaps because of their ability to form associated polymeric Grignard reagents.[25,12b] The entrainment method in this case worked well as noted in Table III, and, as noted in the Experimental section, the time of addition of the entrainer was less critical.

In our last examples of the use of the entrainment method, we chose two halides which had never been converted to Grignard reagents. They were the *m*- and *p*-bromoacetophenone azines. The azine group was selected as a protective grouping because of its resistance to addition reactions compared to the carbonyl group through resonance stabilization: $\rangle C{=}N{-}N{=}C\langle \longleftrightarrow \rangle \overset{+}{C}{-}N{=}N{-}\overset{-}{C}\langle$ and because of considerable reduction of active methylene reactivity through loss of enolization ability.[26] If the haloketazines could be converted to Grignard reagents, derivatives of the ketones would be accessible by a new route. Slow addition of ethylene bromide as an entrainment reagent was not successful, but rapid addition of several equivalents of ethylene bromide was successful in making this Grignard reagent of unusual structure:

(19) A. L. Rocklin, *J. Org. Chem.*, **21**, 1478 (1956).

(20) H. Heaney, F. G. Mann, and I. T. Millar, *J. Chem. Soc.*, 4692 (1956).

(21) C. G. Swain and H. B. Boyles, *J. Am. Chem. Soc.*, **73**, 870 (1951).

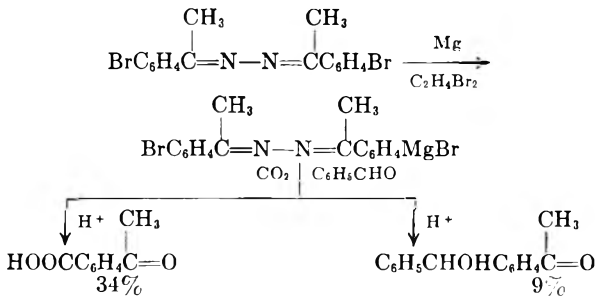
(22) V. Franzen and H. Krauch, *Chem. Ztg.*, **79**, 137 (1955).

(23) E. T. McBee, O. R. Pierce, and D. D. Meyer, *J. Am. Chem. Soc.*, **77**, 83 (1955) demonstrate that complexes between magnesium bromide and carbonyl compounds exist in the ratio 2 to 1.

(24) D. Cowan, "A Study of the Entrainment Method for Preparing Grignard Reagents," Ph.D. thesis, Vanderbilt University, 1959.

(25) L. Field, *J. Am. Chem. Soc.*, **78**, 92 (1956).

(26) E. C. Kooyman, *Rec. trav. chim.*, **74**, 117 (1955).



Although titration indicated that 83% of the two bromine atoms in the azine had been converted to Grignard groups, yields were never more than 50%, indicating that only one bromine atom was converted. For this reason the Grignard reagent of the bromoketazine did not seem attractive as an intermediate for synthesis. To avoid the synthesis of a di-Grignard reagent, as is necessary with bromoketazines, the unsymmetrical dimethylhydrazone of *m*-bromoacetophenone was converted to a Grignard reagent. This reagent however gave only traces of *m*-carboxyacetophenone and considerable amounts of a reduction product, acetophenone. Hydrazone and ketazine Grignard reagents appear to be much less useful intermediates than those for example from ethylene glycol ketals.[27]

Although the experiments with the bromoketazine were not practical (but nevertheless curious) from a preparative viewpoint, we believe that the results of the modifications introduced in this paper are promising enough to consider the entrainment method complementary and even comparable to the other three methods for conversion of "inert" halides to organometallic compounds. The presence of the magnesium bromide may confer upon the organometallic compound certain characteristic properties differing from that of the ordinary preparation in ether or tetrahydrofuran. And, above all, the use of ethylene bromide, rather than ethyl bromide, as an entrainment agent makes it possible to prepare the Grignard reagent of an "inert" halide free of a second, extraneous Grignard reagent.

EXPERIMENTAL

All melting points are corrected and boiling points uncorrected. Analyses were by Galbraith Laboratories, Knoxville, Tenn.

General procedure. The typical Grignard apparatus was used with condenser, stirrer and, in addition, a Hershberg dropping funnel[28] to permit the addition of the ethereal ethylene bromide over a long period of time. The assembled apparatus, together with the magnesium turnings (2.84 g., 0.116 mole), was dried by flaming the glass while dry air was drawn through. The α-chloronaphthalene (b.p. 85° at 1 mm., n_D^{25} 1.6305, 8.1 g., 0.05 mole), dissolved in 50 ml. of dry ether, was added to the flask. Gentle refluxing was maintained for the remainder of the reaction by means of a Glas-col heater. Ethylene bromide (9.3 g., 0.05 mole) in 50 ml. of dry ether was added dropwise from the Hershberg funnel over a period of 12 hr., about a drop every 15 sec. A white powdery solid formed during the initial stages but near the completion of the addition, as magnesium bromide concentration increased, the solid redissolved. At the end of the addition, two layers were noticeable, an ethereal layer on top and a sirupy brown layer on the bottom. Both layers were poured with vigorous stirring onto crushed Dry Ice.[29] A brittle, chalky mass was formed which was dissolved and dispersed by the *cautious* addition of 10% aqueous hydrochloric acid. The acidified reaction mixture was extracted with three 50-ml. portions of ether. The combined ether layers were washed with water and then extracted several times with 5% aqueous sodium bicarbonate solution. On acidification of the combined bicarbonate extracts, α-naphthoic acid precipitated as a greyish powder, m.p. 153–159°, 6.8 g., 56%; recrystallized from toluene: m.p. 160–162°, 3.0 g., 35%. The ether layer from which the acid had been removed contained 3.3 g. of a mixture of naphthalene and chloronaphthalene.

Results on variation of general procedure. Titration of the Grignard solution with acid indicated that 76% of α-chloronaphthalene was present as the Grignard reagent. No basic substance was formed from ethylene bromide and magnesium without α-chloronaphthalene present.

A 66% yield of naphthalene was obtained when the Grignard reagent was poured into cracked ice and acid rather than Dry Ice. The naphthalene was separated from all except traces of α-chloronaphthalene by sublimation at 1-mm. pressure in a short-path distillation apparatus.

The rate of addition of ethylene bromide was varied with the results shown in Table I.

The effect of excess anhydrous magnesium bromide was tested. About 0.05 mole of ethylene bromide was added to 0.164 mole of magnesium covered with ether. After magnesium bromide had formed from this addition, α-chloronaphthalene (0.05 mole) was introduced and another 0.05 mole of ethylene bromide added dropwise in the manner of the general procedure. No white precipitate formed in this experiment. The yield of crude α-naphthoic acid was 56%, m.p. 148–153° and of recrystallized acid 36%, m.p. 161–162°. The results showed no significant effect.

Two experiments using ethyl bromide rather than ethylene bromide as the entrainer were run and the results shown in Table II.

Demonstration that compound, to be added to Grignard using ethylene bromide as entrainer, may be taken as limiting reagent. α-Naphthylmagnesium chloride (0.1 mole) was prepared as in the general procedure. Benzonitrile (10.3 g., 0.1 mole) in ether was added rapidly to the Grignard solution, and the mixture allowed to stir for several hours. It was then poured on to a slurry of ice and 10% aqueous hydrochloric acid with stirring. The acid mixture was heated under reflux for several hours to insure hydrolysis of the resultant ketimine. The crude ketone was extracted with ether, and the ether extract washed with water and aqueous sodium bicarbonate and dried with anhydrous sodium sulfate. Evaporation of the ether yielded α-naphthyl phenyl ketone as a greyish solid which when recrystallized from alcohol gave slightly tan prisms, 11.4 g., 49%, m.p. 73.5–74.5°, reported m.p. 75.5–76°. A greater yield of ketone probably would have been obtained if an excess of Grignard reagent had been used.

The Grignard reagent of p-bromo-N,N-dimethylaniline. The

(27) H. O. House and J. W. Blaker, *J. Org. Chem.*, **23**, 334 (1958).

(28) L. F. Fieser, *Experiments in Organic Chemistry*, D. C. Heath, Boston (1955), 3rd Ed., p. 265.

(29) In a later experiment with the Grignard reagent of hexachlorobenzene, carbon dioxide, dried by passage through calcium chloride granules, was introduced as a gas and gave better yields of acid than the method described above.

general procedure was followed, using for each run 0.05 mole of the *p*-bromodimethylaniline, m.p. 54–55°. In place of adding the aniline to magnesium and ether in the flask, however, it was added to the dropping funnel mixed with ethylene bromide and ether in the proportions previously stated. Also, in place of adding the two-layered Grignard reagent mixture to crushed Dry Ice, dry carbon dioxide was passed over the surface until the black-green color of the mixture had been discharged and the contents had solidified. Dry ether was added during this process to replace that swept out by carbon dioxide. The salt was decomposed with saturated ammonium chloride solution, and the acid finally precipitated by addition of acetic acid. The yields of *p*-dimethylaminobenzoic acid (yellowish tan needles from alcohol, m.p. 236–239°; reported[5] m.p. 240–241°), as dependent on time of addition of the entrainer, ethylene bromide, were: 2.5 hr., 48%; 2.5 hr., 42%; 5 hr., 36%. In another run, the reagent was recovered as dimethylaniline, b.p. 46–49° at 5 mm., n_D^{25} 1.5582, 71%.

Pentachlorobenzoic acid and pentachloroacetophenone from pentachlorophenylmagnesium chloride. A small scale run of pentachlorobenzoic acid was made with the results recorded in Table III. A large scale run was also made with some modification of the general procedure. Magnesium turnings (39 g., 1.6 moles) and hexachlorobenzene (142.4 g., 0.5 mole, m.p. 228–229°) in 1 l. of dry ether was brought to gentle reflux in a 3-l., three-necked flask heated by a Glascol mantle at 20 v. Ethylene bromide (188 g., 1.0 mole) in 200 ml. of dry benzene was added through the Hershberg funnel over a period of 48 hr. (about one drop per 25 sec.). Little attention was needed provided the capillary tube of the Hershberg apparatus was properly fitted. The capillary tube was 4.5 in. long into which a B and S 24 platinum wire was inserted to fit very snugly. Efficient stirring was maintained throughout addition during which time the reaction mixture turned dark brown and formed a precipitate. The reaction mixture was allowed to cool to room temperature, and carbon dioxide, generated from Dry Ice and dried by passage through anhydrous calcium chloride, was added under the surface for at least 3 hr. and at such a rate as to minimize clogging of the entrance tube. After this addition, 10% aqueous hydrochloric acid was added slowly until the mixture was strongly acid. The ether and benzene was removed by distillation, and the crude pentachlorobenzoic acid left in the water was removed by filtration and washed free of salts with water. After solution in hot dilute ammonia water solution, filtration, and precipitation with mineral acid, 113 g., 77%, of brown-colored pentachlorobenzoic acid was obtained. Some ammonium salt was entrained with this acid if the precipitate were not digested well with hot dilute mineral acid. The color was removed by conversion of the acid to the rather insoluble sodium salt. The sodium salt was recrystallized from ethanol, m.p. 339–340°. By precipitation of the acid from a hot aqueous solution of the sodium salt, the acid was reobtained as a white powder, m.p. 202–206°, 60% over-all yield, reported[30] m.p. within the range 200 to 208°. About 8.6 g. of the acid in the form of lustrous plates, m.p. 207–211°, was obtained by recrystallization of 10 g. from 80 ml. of 50% aqueous methanol.

Pentachloroacetophenone was made also from pentachloromagnesium chloride by the method of Newman and Smith.[31] It was necessary to purify the ketone by solution in concentrated sulfuric acid and filtration through a sintered-glass funnel. The ketone in the filtrate was precipitated by dilution with water, filtered, and washed thoroughly with water. After drying, the pentachloroacetophenone was sublimed at 0.1 mm. to give colorless crystals, m.p. 89–90°, 4.5 g., 31%, reported[32] m.p. 90–92°.

Grignard reagent of p-bromoacetophenone azine. To a stirred suspension of 4.93 g., 0.0125 mole of *p*-bromoacetophenone azine (m.p. 164.5–165.5°), 1.82 g., 0.075 mole of magnesium, and 25 ml. of dry ether, a solution of 9.4 g., 0.05 mole of ethylene bromide in 25 ml. of dry ether was added dropwise over a period of 80 min. The mixture separated into a top yellow layer and a bottom reddish brown layer. Titration of aliquots indicated that 90% of the Grignard reagent was in the bottom layer. After heating the mixture an additional 3 hr. under gentle reflux, it was cooled and poured into crushed Dry Ice. The mixture was allowed to warm to room temperature and hydrolyzed after removal of the ether by stirring the residue with 150 ml. of 2*N* hydrochloric acid maintained at 75° for 30 min. The hydrolysate was cooled and extracted with 200 ml. of ether in 3 portions. The combined ether extracts were washed with 200 ml. of 5% aqueous sodium hydroxide in three portions. Acidification of the combined alkaline extracts and cooling, gave a light tan product which was removed by filtration. The tan product was recrystallized from 200 ml. of water, with a hot filtration, to yield *p*-acetobenzoic acid, 1.4 g., 34%, m.p. 206–209°. A second recrystallization from water with Norite treatment yielded white needles, m.p. 207.5–209.5°, reported[33] m.p. 208.6–209.4°; neutral equivalent 163.5, calculated 164.2.

Ethyl bromide as an entrainment reagent in place of ethylene bromide gave a 40% yield of *p*-acetobenzoic acid. In another experiment, tetrahydrofuran was used in place of ether as the solvent. Although the tetrahydrofuran was an excellent solvent for the Grignard reagent (one layer containing 83% Grignard reagent by titration), the yield of *p*-acetobenzoic acid was only 1.7%.

Phenyl-*p*-acetophenylcarbinol, m.p. 110–111.5°, needles from petroleum ether, was made in 9% yield from the addition of benzaldehyde to the Grignard reagent of *p*-bromoacetophenone azine.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.63; H, 6.24. Found: C, 79.48; H, 5.38.

The structure was confirmed by oxidation to *p*-benzoylacetophenone in 94% yield, m.p. 83–84°, reported[34] m.p. the same. The low yield in the preparation of the alcohol was attributed to the instability of a benzhydrol structure to acid hydrolysis, a step necessary to convert the azine to the ketone.

Attempts to add benzonitrile to the Grignard reagent of *p*-bromoacetophenone azine yielded only intractable, brown gums.

Grignard reagent of m-bromoacetophenone azine. The *m*-bromoketazine (m.p. 102–103°) was converted to the Grignard reagent in the same manner as the *p*-bromoketazine. The preparation differed only in that the mixture did not separate into two phases. After carbonation of the mixture in the usual manner, *m*-acetobenzoic acid, m.p. 170–173°, white needles, reported[32] m.p. 172°, was obtained in only 8% yield. The low yield was caused in part by the difficulty of purification. It was recrystallized from methylcyclohexane after recrystallization from water failed.

The Grignard reagent of *m*-chloroacetophenone azine, m.p. 86–87°, could not be made by the procedures of this paper.

Grignard reagent of the unsymmetrical dimethylhydrazone of m-bromoacetophenone. The hydrazone was made by the method of Smith and Most[35] except that azeotropic distil-

(30) E. H. Huntress, *Organic Chlorine Compounds*, John Wiley & Sons, New York, 1948.

(31) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).

(32) S. D. Ross, *J. Am. Chem. Soc.*, **70**, 4039 (1948).

(33) W. K. Detweiler and E. D. Amstutz, *J. Am. Chem. Soc.*, **72**, 2882 (1950).

(34) R. P. Zelinski, B. W. Turnquest, and E. C. Martin, *J. Am. Chem. Soc.*, **73**, 5521 (1951).

(35) P. A. S. Smith and E. E. Most, Jr., *J. Org. Chem.*, **22**, 358 (1957).

lation with toluene was used to remove the water, b.p. 105–107° at 2 mm., n_D^{25} 1.5806. The Grignard reagent was made by the general procedure and carbonated by passing dry carbon dioxide over the surface. Extraction of the ether layer with aqueous sodium hydroxide, followed by acidification of the alkaline layer gave *m*-carboxyacetophenone, m.p. 161–162°, 0.002 mole, 4%. The ether layer yielded crude acetophenone, b.p. 50° at 2 mm., 26%, n_D^{25} 1.5325, reported n_D^{25} 1.5310. A duplicate run gave 40% acetophenone of approximately the same quality.

NASHVILLE 5, TENN.

[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

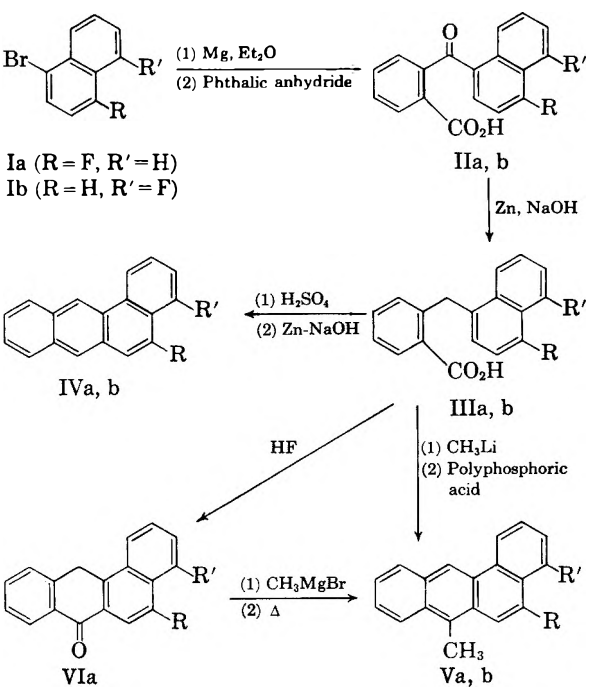
The Synthesis of Some Monofluoro-1,2-benzanthracenes[1]

MELVIN S. NEWMAN, DENIS MACDOWELL, AND SAMBASIŇA SWAMINATHAN

Received November 3, 1958

The syntheses of 3- and 4′-fluoro-1,2-benzanthracenes and of 3-fluoro- and 4′-fluoro-10-methyl-1,2-benzanthracenes are described.

Substitution of the rings in a number of aromatic carcinogens can profoundly alter their carcinogenic activity. Of the various groups available,[2] the fluoro group has several advantages, *viz*, the small size of the fluorine atom, its strong bond with carbon, and its resistance to metabolism *in situ* as contrasted with other groups. Miller, Miller, and Finger[3,4] have shown that most of the fluoro derivatives of the rat liver carcinogen 4-dimethylaminoazobenzene are as active as, or more active than, the parent dye and have further proposed that tests of the biological activity of various fluoro derivatives of biologically active molecules could be used to indicate the positions directly involved in the activity in question. If a fluoro derivative is inactive, then the position blocked may be involved in the biological activity of the nonfluorinated parent concerned. If the fluoro derivative is active, the substituted position is probably unimportant in the biological activity under study. With a view of extending this concept to a study of the carcinogenic polycyclic aromatic hydrocarbons, we have undertaken the synthesis of the various monofluoro derivatives of the carcinogens, 10-methyl-1,2-benzanthracene and 9,10-dimethyl-1,2-benzanthracene. The syntheses of the 3-fluoro- and 4′-fluoro-10-methyl-1,2-benzanthracenes as well as the corresponding parent fluoro-1,2-benzanthracenes have been carried out by the sequence of reactions outlined below:



The syntheses involved the use of 1-bromo-4-fluoronaphthalene (Ia) and 1-bromo-5-fluoronaphthalene (Ib) as starting materials. The former was obtained by standard methods involving the bromination of 1-formamidonaphthalene followed by replacement of the amino group, obtained by hydrolysis, with fluorine.[5] Ib was obtained from 1-nitronaphthalene by bromination, reduction with

---

(1) This work was supported by a grant from the National Institutes of Health.

(2) J. L. Hartwell, "Survey of Compounds Which Have Been Tested for Carcinogenic Activity," 2nd ed., 1951, U. S. Public Health Service Publication No. 149, Washington, D. C.

(3) J. A. Miller, E. C. Miller, and G. C. Finger, *Cancer Research*, **13**, 93 (1953).

(4) J. A. Miller, E. C. Miller, and G. C. Finger, *Cancer Research*, **17**, 387 (1957).

(5) A. Roe, *Org. Reactions*, V, 193 (1949).

iron and hydrochloric acid[6] and replacement of the resultant amino group with fluorine.[5]

The Grignard reagents corresponding to Ia and Ib reacted smoothly with phthalic anhydride to give the ketoacids IIa and IIb, respectively. Zinc alkali reduction of IIa and IIb afforded the acids IIIa and IIIb. IIIa was converted to the anthrone VIa with anhydrous hydrofluoric acid. This anthrone was treated with methylmagnesium bromide and crude product pyrolyzed to give a low yield (1% based on VIa) of 3-fluoro-10-methyl-1,2-benzanthracene (Va). However, a better yield (40%) of Va was obtained by reacting IIIa with excess methyllithium to give the corresponding methyl ketone and cyclizing the latter (without purification) by heating with polyphosphoric acid. The use of a mixture of hydrobromic and acetic acids, which has been employed for similar cyclizations[7] did not effect cyclization of the above methyl ketone. The acid (IIIb) was similarly converted to the corresponding methyl ketone which could be cyclized either with a mixture of hydrobromic and acetic acids (27% yield) or polyphosphoric acid (33% yield) to give 4′-fluoro-10-methyl-1,2-benzanthracene (Vb). Polyphosphoric acid does not seem to have been previously employed to cyclize the type of methyl ketones referred to above to *meso* substituted anthracenes, though other reagents have been reported.[7,8]

The acids IIIa and IIIb were treated with concentrated sulfuric acid and the resulting anthrones subsequently reduced to give 68.7% and 42.5% yields, respectively, of 3-fluoro and 4′-fluoro-1,2-benzanthracenes (IVa and IVb).

EXPERIMENTAL[9]

1-Formamidonaphthalene. Treatment of 1-naphthylamine with 90% formic acid under reflux for 2 hr. afforded the formulated amine, m.p. 135–137° (lit.[10] 138.5°) in 84% yield.

1-Bromo-4-formamidonaphthalene. Bromination of this product in glacial acetic acid and pyridine afforded the bromo compound in 93% yield, m.p. 169–172° (lit.[11] 172°).

1-Amino-4-bromonaphthalene. Saponification of the bromo compound using methanolic potassium hydroxide proceeded smoothly and gave 1-amino-4-bromonaphthalene in 81% yield, m.p. 100–103° (lit.[11] 94–95°).

1-Bromo-4-fluoronaphthalene (Ia). The above bromoamine (100 g., 0.45 mole) was diazotized in aqueous hydrochloric acid solution with sodium nitrite. Addition of 48–50% fluoboric acid caused the immediate formation of the diazonium fluoborate. The mixture was stirred at −5° for 30 min. and was then filtered, the precipitate being washed with water and cold acetone. Drying over phosphorus pentoxide crude dry diazonium fluoborate as a dark green solid, 127 g. (88%) m.p. 151–155° (dec.) (lit.[12] 151.5°).

Decomposition of a 400-g. portion of the crude diazonium fluoborate was effected by heating the solid under reflux at 160° for 10 min. The residue was then taken up in benzene and distilled, affording a yellow-brown distillate of crude bromofluoronaphthalene. This was shaken with cold concentrated sulfuric acid and redistilled to yield the desired product, 134 g. (51%), b.p. 110–115° (2 mm.), m.p. 33.9° by a time-temperature cooling curve (lit.[12] m.p. 36°).

o-(4-Fluoro-1-naphthoyl)benzoic acid (IIa). To a stirred suspension of 5.35 g. of magnesium in 50 ml. of anhydrous tetrahydrofuran and 30 ml. of anhydrous ether was added a solution of 50 g. of Ia in 60 ml. of tetrahydrofuran. Formation of the Grignard reagent proceeded steadily, and after the reaction had reached completion, it was forced by dry nitrogen into a solution of 33 g. of phthalic anhydride in 150 ml. of tetrahydrofuran. The mixture was stirred under reflux for about 2 hr. Tetrahydrofuran and ether were removed by distillation and were replaced by benzene. Decomposition of the complex was effected with cold dilute hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with ether benzene and combined with the main benzene extract. Acidic material was removed from the organic extracts by repeated extraction with aqueous potassium carbonate. These alkaline extracts afforded impure ketoacid, 61 g. m.p. 155–160°, on acidification. Recrystallization from acetonitrile gave 49.5 g. (76%) of a colorless product, m.p. 161–163°. An analytical sample obtained by several recrystallizations from acetonitrile melted at 163.0–164.9°.

Anal. Calcd. for $C_{18}H_{11}FO_3$: C, 73.5; H, 3.8. Found: C, 73.8; H, 3.6.

The alkali insoluble material obtained from the organic extracts yielded 1.8 g. of a brown oil which, on trituration with cold Skellysolve C (petroleum ether, b.p. 90–97°) gave impure 4,4′-difluoro-1,1′-binaphthyl. An analytical sample recrystallized from Skellysolve C melted at 176.0–177.0°.

Anal. Calcd. for $C_{20}H_{12}F_2$: C, 82.7; H, 4.2. Found: C, 82.7; H, 4.1.

o-(4-Fluoro-1-naphthylmethyl)benzoic acid (IIIa). A mixture of 20 g. of the ketoacid (IIa), 100 ml. of ammonium hydroxide, 50 ml. of water, and 60 g. of zinc dust activated by the addition of 3 ml. of ammoniacal copper sulfate solution, was heated under reflux for 22 hr. The mixture was cooled and filtered and the solids were extracted with an additional 100 ml. of ammonium hydroxide. After removal of neutral material from the viscous layer by extraction with ether benzene, acidification afforded 16.0 g. of impure acid (IIIa), m.p. 173.0–175.5°. Recrystallization from Skellysolve C–benzene gave 14.0 g. (74%) of IIIa, m.p. 175.0–177.0°. An analytical sample, m.p. 176.0–177.0°, was obtained as colorless needles from the same solvent.

Anal. Calcd. for $C_{18}H_{13}FO_2$: C, 77.1; H, 4.7. Found: C, 77.4; H, 4.8.

3-Fluoro-10-oxo-9,10-dihydro-1,2-benzanthracene (VIa). The acid (IIIa), (7 g.) was treated with excess anhydrous hydrofluoric acid in a polyethylene bottle. After 1 hr. the solution was poured onto ice and the yellow impure anthrone (6.0 g.) on crystallization from benzene-ethanol melted at 165–170° (4.5 g.).

Anal. Calcd. for $C_{18}H_{11}FO$: C, 82.4; H, 4.2. Found: C, 82.9; H, 4.3.

3-Fluoro-10-methyl-1,2-benzanthracene (Va). (a) To a solution of 12 g. of VIa in a solution of 300 ml. of benzene and 100 ml. of tetrahydrofuran was added excess methylmag-

(6) J. B. Shoesmith and H. Rubli, *J. Chem. Soc.*, 3104 (1927).

(7) C. K. Bradsher and S. T. Webster, *J. Am. Chem. Soc.*, **79**, 343 (1957).

(8) F. A. Vingiello and A. Borkovec, *J. Am. Chem. Soc.*, **78**, 3205 (1956).

(9) All melting points are corrected, all boiling points are uncorrected. Analyses were performed by Clark Laboratories, Urbana, Illinois, and Galbraith Laboratories, Knoxville, Tennessee. All fluorine analyses by the Huffman Microanalytical Laboratories, Denver, Colorado.

(10) G. Tobias, *Ber.*, **15**, 2447 (1882).

(11) G. T. Morgan, F. M. G. Micklethwait, and H. B. Winfield, *J. Chem. Soc.*, **85**, 750 (1904).

(12) G. Schiemann, W. Guffroy, and W. Winkelmuller, *Ann.*, **487**, 270 (1931).

nesium bromide. The mixture was heated under reflux for 16 hr., decomposed with ammonium chloride and hydrochloric acid and was then thoroughly extracted with ether benzene. Removal of the solvents afforded an oil which was heated at 190–200° for 10 min. Chromatography over alumina in benzene yielded 1.8 g. of a green solid, m.p. 125–130°. A boiling solution of this in ethanol was treated with an ethanolic solution of 1,3,5-trinitrobenzene. The red solution on cooling gave a complex which was purified by recrystallization from methanol. A benzene solution of the purified trinitrobenzene complex was passed through a column of alumina and the eluted solid was recrystallized three times from Skellysolve B to yield 130 mg. (1%) of analytically pure Va, m.p. 141.0–142.0°.

Anal. Calcd. for $C_{19}H_{13}F$: C, 87.7; H, 5.0; F, 7.3. Found: C, 87.7; H, 5.2; F, 7.2.

(b) To a stirred solution of 115 ml. of 0.8*N* methyllithium in ether, was added gradually over 15 min. a solution of 7.8 g. of IIIa in a mixture of 500 ml. of ether and 100 ml. of tetrahydrofuran. As the acid was added, a deep purple color developed. After the addition was over, the mixture was stirred for 1 hr. and then decomposed with iced water. The organic layer was separated, washed with saturated sodium chloride solution, and dried over magnesium sulfate. After removal of solvents 7.5 g. of crude oily methyl ketone was obtained as brown liquid. The alkaline aqueous layer furnished little starting material when acidified. The above liquid (6.18 g.) was added to 30 g. of polyphosphoric acid[13] at 60° and the mixture heated with frequent stirring on a steam bath for 20 min. and kept overnight at room temperature. The heated mixture was then diluted with water and the yellow solid which precipitated was collected and air-dried. Extraction of the solid with two 100-ml. portions of refluxing benzene furnished, after treatment with charcoal and concentration, two successive crops of 1.66 g. and 0.48 g. of crystals with m.p. 140–141° and m.p. 136–139°, respectively. The filtrate from the second crop was freed of benzene and the residue crystallized from Skellysolve B to give an additional 0.6 g. of crude product. By chromatography in benzene over alumina there was obtained 2.3 g. (40% yield based on the crude methyl ketone) of pale yellow Va, m.p. 141.5–142.0°, undepressed by the product obtained by method (a) above.

3-Fluoro-1,2-benzanthracene (IVa). Finely powdered IIIa (3 g.) was dissolved in 30 ml. of concd. sulfuric acid at room temperature to give a clear orange solution. After 6 hr., the solution was poured on ice and the anthrone which separated was collected and refluxed for 14 hr. with a mixture of 10 g. of zinc dust (activated with copper sulfate), 150 ml. of water, and a solution of 22 g. of sodium hydroxide in 120 ml. of water. The mixture was cooled, acidified with 60 ml. of concd. hydrochloric acid, and the solids were collected and dried. Extraction with 150 ml. of refluxing benzene followed by concentration of the extract gave 0.61 g. of pale yellow almost colorless crystals, m.p. 131–132° and a second crop of 1.04 g., m.p. 128–129°. Recrystallization of the second crop (after treatment with charcoal) afforded 0.95 g. of colorless needles, m.p. 130.5–131.0°. An additional 0.25 g. of pure product was obtained by passing the filtrate from the second crop through alumina. The total yield of pure material amounted to 1.81 g. (68.7%). The analytical sample, m.p. 131.5–132.5°, was obtained after two crystallizations from a mixture of benzene and Skellysolve B (petroleum ether, b.p. 60–70°).

Anal. Calcd. for $C_{18}H_{11}F$: C, 87.8; H, 4.5; F, 7.7. Found: C, 88.2; H, 4.5; F, 8.0.

1-Bromo-5-nitronaphthalene. To 300 g. of 1-nitronaphthalene in a 3 l. three necked flask fitted with a stirrer and condenser, was added dropwise 125 ml. of bromine. The mixture was stirred vigorously with external cooling. After 10 min., the mixture had set to a hard cake which was allowed to stand overnight at room temperature. On recrystallization from alcohol containing a little chloroform, there was obtained 336 g. (76%) of 1-bromo-5-nitronaphthalene, m.p. 118–122° (lit.[14] m.p. 121°).

1-Amino-5-bromonaphthalene. To a refluxing mixture of 1-bromo-5-nitronaphthalene (268 g., 1.06 mole), 95% ethanol (800 ml.), and hydrochloric acid (15 ml.) was added powdered iron (180 g.) in three equal portions over a period of 3 hr. The reaction was refluxed for 1 hr. after the final addition, about half of the ethanol was removed by distillation, and the residual solution was made alkaline by the addition of 20% potassium hydroxide solution. The crude oily amine solidified on cooling and was removed by filtration, powdered, and dried. The yield was 241 g. of a dark red solid m.p. 64–69° (lit.[14] 69°).

1-Bromo-5-fluoronaphthalene (Ib). The crude 1-amino-5-bromonaphthylamine (100 g., 0.45 mole) was diazotized with sodium nitrite and hydrochloric acid in a polyethylene beaker. Fluoboric acid (48–50%) (160 ml.) was added in one portion, and the thick mixture was stirred at 0–5° for 30 min. The fluoborate was removed by filtration, washed with dilute fluoboric acid, and dried over phosphorus pentoxide *in vacuo*. Yield 145 g. (100%) of a gray-green solid. This crude diazonium fluoborate (100 g.) was heated at 160° for 15 min. After evolution of boron trifluoride had ceased, the residue was repeatedly extracted with benzene and ether, the solvents were removed, and the residue was distilled under reduced pressure. The impure bromofluoronaphthalene (49 g.) b.p. 95–100° (1 mm.) thus obtained was shaken with cold concd. sulfuric acid and redistilled. Pure Ib, b.p. 85–90° at 0.5 mm., was obtained in 60% yield. A time-temperature cooling curve indicated a m.p. of 18–19°.

Anal. Calcd. for $C_{10}H_6BrF$: C, 53.4; H, 2.7. Found: C, 53.5; H, 2.7.

o-(5-Fluoro-1-naphthoyl)benzoic acid (IIb). The Grignard reagent prepared in ether from 34 g. of Ib was forced by dry nitrogen into a stirred solution of 22 g. of phthalic anhydride in 100 ml. of benzene and 100 ml. of ether. The mixture was heated under reflux for 2 hr. and was then decomposed with saturated ammonium chloride solution. The aqueous layer was thoroughly extracted with ether benzene and the combined organic extracts were extracted with aqueous potassium carbonate. The alkaline extract was boiled for a short period with decolorizing carbon and was then poured onto ice and hydrochloric acid. The precipitated acid, m.p. 174–180°, was obtained in 64% yield. An analytical sample, m.p. 181.0–182.5°, was obtained by repeated crystallization from benzene.

Anal. Calcd. for $C_{18}H_{11}FO_3$: C, 73.5; H, 3.8. Found: C, 73.5; H, 3.9.

o-(5-Fluoro-1-naphthylmethyl)benzoic acid (IIIb). A mixture of the ketoacid (IIb) (10 g., 0.034 mole), water (150 ml.), potassium hydroxide (28 g.), zinc dust (30 g.), and a few drops of ammoniacal copper sulfate was heated under reflux with stirring for 16 hr. The mixture was cooled, filtered, and extracted with an ether benzene mixture to remove any nonacidic material. Acidification of the alkaline extract afforded 8.4 g. (88%) of IIIb as a light tan solid, m.p. 173–176°. An analytical sample recrystallized from benzene–Skellysolve C melted at 176.0–177.9°.

Anal. Calcd. for $C_{18}H_{13}FO_2$: C, 77.1; H, 4.7. Found: C, 77.3; H, 4.7.

4'-Fluoro-10-methyl-1,2-benzanthracene (Vb). (a) To a stirred solution of methyllithium prepared from 3.5 g. of lithium and 23 g. of methyl iodide in ether was added dropwise a solution of 7.0 g. of IIIb in 100 ml. of ether. As the acid was added, a purple color developed. After the addition was complete, the mixture was stirred for 5 min. and then poured on ice. The methyl ketone was extracted with an ether benzene mixture and was obtained as a dark brown oil (6.4 g.) on removal of the solvents. This oil was heated

(13) Supplied by the Victor Chemical Works, Box 603, Chicago 90, Ill.

(14) G. Lock, *Monatsh.*, **81**, 850 (1950).

under reflux with 150 ml. of glacial acetic acid 20 ml. of 40% hydrobromic acid for 20 hr. and the solution was poured on ice, made alkaline with aqueous potassium hydroxide, and the hydrocarbon was extracted with ether benzene. The crude oily product was taken up in Skellysolve C and was chromatographed over alumina to yield 3.6 g. of a yellow solid which after several recrystallizations from Skellysolve B afforded 1.57 g. (27%) of pure Vb, m.p. 142.5–143.5°, as very pale yellow needles.

Anal. Calcd. for $C_{19}H_{13}F$: C, 87.7; H, 5.0; 7.3. Found: C, 87.5; H, 5.3; F, 7.1.

(b) Cyclization of 2.6 g. of the crude methyl ketone obtained in the previous experiment with 23 g. of polyphosphoric acid as described for Va, followed by chromatographic purification of the crude hydrocarbon furnished 0.80 g. (33%) of Vb, m.p. 142.2–143.0° undepressed by the product obtained above.

4'-Fluoro-1,2-benzanthracene (IVb). A solution of 8.1 g. of finely ground IIIb in 81 ml. of concd. sulfuric acid was kept at room temperature for 2 hr. and then poured on ice. The anthrone was collected and refluxed for 7.5 hr. with a mixture of 40 g. of zinc dust (activated with copper sulfate), 500 ml. of water, and a solution of 66 g. of sodium hydroxide in 200 ml. of water. After cooling and acidifying with 180 ml. of concentrated hydrochloric acid, the solids were collected, dried, and extracted with 250 ml. of refluxing benzene. The benzene extract on cooling furnished 3.85 g. of crystalline product, m.p. 169.5–172.0°. Crystallization from benzene after treatment with charcoal furnished 2.07 g. of a I crop of very pale yellow crystals m.p. 171.5–172.0° and 1.3 g. of product, m.p. 170–172°. The latter after chromatographic purification afforded 0.95 g. pure hydrocarbon, m.p. 171.5–172°, the total yield of pure hydrocarbon amounting to 3.02 g. (42.5%). The analytical sample, m.p. 171.5–172.0°, was obtained by recrystallization from a mixture of benzene and Skellysolve B.

Anal. Calcd. for $C_{18}H_{11}F$: C, 87.8; H, 4.5; F, 7.7. Found: C, 87.9; H, 4.6; F, 7.6.

COLUMBUS, OHIO

[CONTRIBUTION FROM THE TECHNICAL RESEARCH DEPARTMENT OF MATSUSHITA ELECTRIC WORKS, LTD.]

Synthetic Products from Methylolphenols, Formaldehyde, and Primary Aromatic Amines

MIYOSHI NODA, HIROSHI SHIMAOKA, AND SUSUMU NAGASE

Received October 27, 1958

Reaction of 2,6-dimethylol-*p*-cresol with aromatic primary amines resulted in the formation of *N*-(2-hydroxy-3-methylol-5-methylbenzyl)arylamines (I). Nitroso compounds (II) were obtained upon nitrosation of I, indicating that they were secondary amines Benzoxazine compounds (III) were prepared by reaction of I with formaldehyde. In the same manner *N*-(4-hydroxybenzyl)arylamines (IV) and their nitroso compounds (V) were obtained from 4-methylolphenol. Twenty-six new compounds, and two compounds obtained by two new methods were prepared and studied.

Aromatic amine-phenol-formaldehyde resins which are formed by the condensation of amine, phenol, and formaldehyde are noted for their high electric resistance.[1] However, it is rarely reported whether they are simple mixtures of aromatic amine-formaldehyde and phenol-formaldehyde resins or copolymers of the three constituents.

This work is a study of the initial condensation products of amines, phenols, and formaldehyde.

The condensation of phenols with formaldehyde and primary[2] or secondary[3] aliphatic amines has been studied in several laboratories. *o*-Alkylaminomethyl-*p*-substituted phenol, *N,N*-bis-(2-hydroxybenzyl)alkylamines and a new series of 3,4-dihydro - 3,6 - disubstituted - 1,3,2*H* - benzoxazine were obtained directly from three reactants in the presence of alcoholic potash in certain instances.[4]

The condensation of phenols with formaldehyde and primary aromatic amines has also been studied[5] by several workers, the following products being obtained: *N*-(2-hydroxybenzyl)aniline,[6,7] *N*-(2-hydroxybenzyl)-*p*-toluidine,[6] *N*-(4-hydroxybenzyl)-aniline,[6] *N*-(4-hydroxybenzyl)-*p*-toluidine[6] and *N*-nitroso-*N*-(4-hydroxybenzyl)aniline.[8] 3,4-Dihydro-3-*p*-tolyl-6-*t*-butyl-1,3,2*H*-benzoxazine and 3,4-dihydro-3-*p*-tolyl-6-bromo-1,3,2*H*-benzoxazine were also prepared by Burke and co-workers.[9]

---

(1) (a) L. Helm, Brit. Patent 25,216 (1907); (b) A. Gams and G. Widmer, U. S. Patent 2,199,155 (1940); (c) F. E. Calvert and P. A. Bury, U. S. Patent 2,449,876 (1948); (d) P. C. Schroy, J. Grabowski, and M. J. Scott, U. S. Patent 2,523,333 (1950).

(2) (a) H. A. Bruson, U. S. Patent 2,031,557 (1936); 2,114,122 (1938); (b) J. Harmon and F. M. Meigs, U. S. Patent 2,098,869 (1937); (c) H. A. Bruson, *J. Am. Chem. Soc.*, 58, 1741 (1936).

(3) (a) W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, 61, 765 (1939); (b) H. A. Bruson and C. W. MacMullen, *J. Am. Chem. Soc.*, 63, 270 (1941).

(4) (a) W. J. Burke and C. W. Stephens, *J. Am. Chem. Soc.*, 71, 609 (1949); (b) W. J. Burke, R. P. Smith, and C. Weatherbee, *J. Am. Chem. Soc.*, 74, 602 (1952); 74, 1518 (1952).

(5) (a) H. Franzen, *J. prakt. Chem.*, 72 (2), 217 (1905); (b) A. Hantzsch and E. Wechsler, *Ann.*, 325, 248–9 (1902); (c) Farbwerke Höchst AG, Ger. Patent 109,488 (1855); (d) C. A. Bischoff and E. Fröhlich, *Ber.*, 39, 3967–76 (1906).

(6) (a) O. Emmerich, *Ann.*, 241, 344–56 (1887).

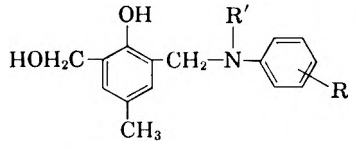
(7) (a) C. Paal and H. Senninger, *Ber.*, 27, 1802–4 (1894); (b) C. Paal, *Arch. Pharm.*, 240, 681–90 (1902).

(8) E. Bamberger and J. Müller, *Ann.*, 313, 104–16 (1900).

(9) W. J. Burke, K. C. Murdock, and Grace Ec, *J. Am. Chem. Soc.*, 76, 1677 (1954).

TABLE I

N-(2-HYDROXY-3-METHYLOL-5-METHYLBENZYL)ARYLAMINES FROM 2,6-DIMETHYLOL-*p*-CRESOL AND PRIMARY AMINES, AND THEIR NITROSO COMPOUNDS

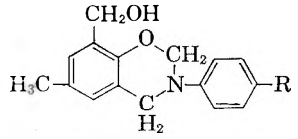


No.	R	R′	Time, (hrs.)	Yield, %	M.P., °C.	Solvent[a] for Crystal.	Molecular Formula	Mol. Wt. Calcd.	Mol. Wt. Found	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halogen Calcd.	Halogen Found	Nitrogen Calcd.	Nitrogen Found
1	*p*-CH_3O	H	8	11.6[b]	120.0	A	$C_{16}H_{19}NO_3$	273	263	70.30	70.64	7.01	7.12			5.13	5.24
2	*p*-CH_3O	N=O	2	36.2[b]	93.0	B	$C_{16}H_{18}N_2O_4$	302	295	63.49	63.25	6.01	5.95			9.28	9.26
3	*p*-Cl	H	10	10.1[b]	106.0	C	$C_{15}H_{16}ClNO_2$	277	285	64.86	65.14	5.81	5.98	11.45	11.29	5.04	5.19
4	*p*-Cl	N=O	3	30.0[c]	131.0	B	$C_{15}H_{15}ClN_2O_3$	307	302	58.73	58.77	4.93	5.29	11.56	11.75	9.13	8.99
5	*p*-CH_3	H	8	8.2[b]	119.0	A	$C_{16}H_{19}NO_2$	257	256	74.68	74.98	7.44	7.66			5.44	5.56
6	*p*-CH_3	N=O	3	27.0[b]	101.0	B	$C_{16}H_{18}N_2O_3$	286	286	67.11	67.27	6.34	6.27			9.79	9.78
7	*p*-Br	H	9	23.0[c]	109.5	F	$C_{15}H_{16}BrNO_2$	322	314	55.91	56.20	5.00	5.20	24.83	25.03	4.34	4.62
8	*p*-Br	N=O	4	9.2[d]	135.0	B	$C_{15}H_{15}BrN_2O_3$	351	352	51.30	51.14	4.30	4.32	22.75	22.40	7.98	8.15
9	H	H	2	0.92[d]	83.0	G	$C_{15}H_{17}NO_2$	243	242	74.05	74.24	7.04	6.81			5.76	5.94
10	H	N=O	3	29.7[d]	73.0	E	$C_{15}H_{16}N_2O_3$	272	280	66.16	66.42	5.92	5.81			10.29	10.07
11	*o*-CH_3O	H	6	16.4[b]	109.0	H	$C_{16}H_{19}NO_3$	273	265	70.30	70.41	7.01	7.02			5.13	5.41
12	*p*-C_2H_5O	H	8	10.4[d]	115.9	I	$C_{17}H_{21}NO_3$	287	293	71.05	71.01	7.37	7.13			4.87	5.14
13	*p*-C_2H_5O	N=O	24	59.0[d]	101.3	H	$C_{17}H_{20}N_2O_4$	316	319	64.54	64.45	6.37	6.49			8.86	8.92

[a] A, benzene-ligroin (1:1); B, methanol; C, ethylene-dichloride–ligroin (1:1); D, acetone-water (1:1); E, methanol-water (1:1); F, ethylene-dichloride–benzene (1:1); G, ligroin. H, ethanol-water (1:1); I, ethanol; J, ligroin-benzene (4:1); K, ligroin-benzene (3:1); L, ligroin-benzene (1:2); M, ligroin-benzene (2:1). [b] After double recrystallizations. [c] Crude; [d] After recrystallization. [e] After 5 recrystallizations. [f] Compound (23) and (27) did not agree in melting points with compounds previously reported by Emerich and Bischoff and Fröhlich, Hantzsch, and Wechsler, respectively.

TABLE II*

3,4-Dihydro-3-aryl-6-methyl-8-methylol-1,3,2H-benzoxazines from Formaldehyde and *N*-(2-Hydroxy-3-methylol-5-methylbenzyl)arylamines

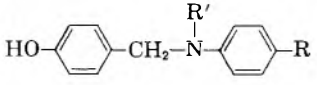


No.		Time, (hr.)	Yield, %	M.P., °C.	Solvent[a] for Crystal.	Molecular Formula	Mol. Wt. Calcd.	Mol. Wt. Found	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halogen Calcd.	Halogen Found	Nitrogen Calcd.	Nitrogen Found
14	*p*-CH_3O	2	32.0[b]	108.0	B	$C_{17}H_{19}NO_3$	285	278	71.56	71.78	6.72	6.62			4.91	4.97
15	*p*-Cl	2	35.0[b]	107.0	D	$C_{16}H_{16}ClNO_2$	290	283	66.32	66.54	5.58	5.85	12.24	11.95	4.83	5.08
16	*p*-CH_3	2	31.8[b]	83.0	E	$C_{17}H_{19}NO_2$	269	278	75.81	76.10	7.11	7.04			5.20	5.33
17	*p*-Br	2	48.2[b]	108.5	B	$C_{16}H_{16}BrNO_2$	334	326	57.50	57.78	4.83	4.77	23.91	24.20	4.19	4.24
18	*p*-C_2H_5O	0.5	96.5[i]	94.3	A	$C_{19}H_{21}NO_3$	299	302	72.21	72.09	7.07	7.18			4.68	4.59

* See Table I for key to footnotes.

TABLE III*

N-(4-Hydroxybenzyl)arylamines from 4-Methylolphenol and Primary Amines; and Their Nitroso Compounds



No.	R	R′	Time (hrs.)	Yield, %	M.P., °C.	Solvent[a] for Crystal.	Molecular Formula	Mol. Wt. Calcd.	Mol. Wt. Found	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halogen Calcd.	Halogen Found	Nitrogen Calcd.	Nitrogen Found
19	*p*-Br	H	10	19.0[e]	86.4	J	$C_{13}H_{12}BrNO$	278	274	56.13	56.10	4.31	4.20	28.73	28.47	5.03	4.99
20	*p*-Br	N=O	5	77.0[d]	131.4	A	$C_{13}H_{11}BrN_2O_2$	307	299	50.83	51.03	3.61	3.77	26.53	26.25	9.12	9.07
21	*p*-Cl	H	10	18.0[d]	70.5	K	$C_{13}H_{12}ClNO$	234	226	66.81	66.56	5.18	5.46	15.17	14.87	5.99	6.01
22	*p*-Cl	N=O	4	81.0[d]	118.6	L	$C_{13}H_{11}ClN_2O_2$	263	269	59.41	59.71	4.22	4.55	13.50	13.25	10.66	10.44
23	*p*-CH_3	H	10	21.0[d]	90.0[f]	K	$C_{14}H_{15}NO$	213	214	78.84	78.72	7.09	7.06			6.57	6.63
24	*p*-CH_3	N=O	3	59.0[d]	110.6	M	$C_{13}H_{14}N_2O_2$	242	236	69.40	69.34	5.82	6.16			11.56	11.43
25	*p*-CH_3O	H	10	57.0[d]	111.1	J	$C_{14}H_{15}NO_2$	229	224	73.34	73.29	6.59	6.84			6.11	5.89
26	*p*-CH_3O	N=O	4	88.0[d]	118.8	J	$C_{14}H_{14}N_2O_3$	258	261	65.10	64.93	5.46	5.63			10.86	11.03
27	*p*-C_2H_5O	H	8	16.0[d]	97.4[f]	K	$C_{15}H_{17}NO_2$	272	269	74.05	73.98	7.04	6.91			5.76	5.75
28	*p*-C_2H_5O	N=O	12	53.0[d]	98.8	M	$C_{15}H_{16}N_2O_3$	272	269	66.16	66.50	5.92	5.99			10.29	10.57

* See Table I for key to footnotes.

The present study deals with the condensation of primary aromatic amines (*i.e.*, *o*-anisidine, *p*-anisidine, *p*-chloroaniline, *p*-bromoaniline, *p*-toluidine, *p*-phenetidine, and aniline) with 2,6-dimethylol-*p*-cresol or 4-methylolphenol in ethanol solution by Burke's method. *N*-(2-hydroxy-3-methylol-5-methylbenzyl)arylamines (I) and *N*-(4-hydroxybenzyl)arylamines (IV) were obtained as initial condensation products respectively. The alcoholic hydroxyl of the methylol group was detected by Nessler's reagent,[10] and the phenolic hydroxyl in the product from the 2,6-dimethylol-*p*-cresol was identified with the ferric chloride test[11] and the phenolic hydroxyl in the product from the 4-methylolphenol with Linter's[12] reagent.

The amines I and IV reacted with sodium nitrite in the presence of hydrochloric acid to yield nitroso compounds whose analysis and chemical behavior revealed the presence of one nitroso group joined to the methylolphenol and showed a secondary amine property. I reacted quantitatively with formaldehyde to form 3,4-dihydro-3-aryl-6-methyl-8-methylol-1,3,2*H*-benzoxazine which was unstable when heated.

Each structural formula was established by elementary analysis, measurement of molecular weight, and behavior of each radical.

In Tables I, II, and III are listed the properties and results of chemical analyses of the new products obtained.

EXPERIMENTAL

The 2,6-dimethylol-*p*-cresol and 4-methylolphenol used herein were synthesized according to Auwers' method[13] (m.p. 129.0°) and Manasse's method[14] (m.p. 120.0°), respectively.

N-(2-Hydroxy-3-methylol-5-methylbenzyl)-p-anisidine (*1*). A mixture of 33.6 g. of 2,6-dimethylol-*p*-cresol (0.2 mole), 24.6 g. of *p*-anisidine (0.2 mole) and 300 ml. of ethanol containing 1.2 g. of potassium hydroxide was gently refluxed for 8 hr. The reaction mixture was then allowed to cool and neutralized with acetic acid. Unreacted *p*-anisidine was removed by steam distillation. The resulting solid product was dissolved in benzene and allowed to stand for one day. A white solid was obtained; crystallization from benzene-ligroin (1:1), yielded 6.3 g., m.p. 120.0°, Nessler's reagent positive, ferric chloride test positive.

Compounds 3, 5, 7, 9, 11, and 12 were synthesized in a manner similar to that described above. For their properties, see Table I.

N-Nitroso-N-(2-hydroxy-3-methylol-5-methylbenzyl)-p-anisidine (*2*). To a solution of 2.5 g. of compound 1 in dilute hydrochloric acid at a temperature below 5°, was added 0.6 g. of sodium nitrite with stirring. A light reddish resinous product was obtained. It was dissolved in ether and neutralized with sodium carbonate solution. After washing with water, a light reddish-brown, crystalline solid was obtained upon removal of ether at room temperature; recrystallization from methanol yielded 1.0 g. of tabular crystals, m.p. 93.0°, Nessler's reagent positive, Liebermann's[15] reaction positive, ferric chloride test positive.

Compounds 4, 6, 8, 10, and 13 were synthesized in a manner similar to that described above. For their properties, see Table I.

3,4-Dihydro-3-p-anisyl-6-methyl-8-methylol-1,3,2H-benzoxazine (*14*). To 3.0 g. of compound 1 dissolved in 50 ml. of methanol was added 1.6 ml. of 37% formaldehyde solution. The mixture was gently refluxed on a water bath for 2 hr. After some water was added, the reaction mixture was allowed to cool to room temperature. A white solid substance was obtained, filtered, and recrystallized from methanol to give 1.0 g. of white leaflet crystals, m.p. 108.0°, Nessler's reagent positive, ferric chloride test negative.

Compounds 15, 16, 17, and 18 were synthesized in a manner similar to that described above. For their properties, see Table II.

N-(4-Hydroxybenzyl)-p-bromoaniline (19). This compound was prepared essentially in the same manner as compound 1 except that 12.4 g. of 4-methylolphenol (0.1 mole) and 17.2 g. of *p*-bromoaniline (0.1 mole) were used: recrystallization from ligroin-benzene (4:1); white granular crystals, yield 5.2 g., m.p. 86.4°, readily soluble in acetone, alcohol, benzene, ether, and chloroform; slightly soluble in ligroin, insoluble in water, Nessler's reagent negative, Linter's reaction positive.

Compounds 21, 23, 25, and 27 were synthesized in a manner similar to that described above. For their properties, see Table III.

N-Nitroso-N-(4-hydroxybenzyl)-p-bromoaniline (*20*). This compound was prepared essentially in the same manner as compound 2 except that 3.5 g. of compound 19 was used in place of compound 1: recrystallization from ligroin-benzene (1:1) gave 3.0 g. of light yellow granular crystals, m.p. 131.4°, readily soluble in acetone, alcohol, benzene, chloroform, and ether; slightly soluble in ligroin, insoluble in water, Liebermann's reaction positive, Linter's reaction positive.

Compounds 22, 24, 26, and 28 were synthesized in a manner similar to that described above. For their properties, see Table III.

Acknowledgment. We wish to thank Prof. M. Imoto of the Osaka City University for his encouragement during this work. We are also grateful to the Matsushita Electric Works, Ltd., Technical Research Department, for the assistance which made this study possible.

KADOMACHO, KITAKAWACHIGUN
OSAKA PREFECTURE, JAPAN

(10) J. Nessler, *Arch. Pharm.*, **244**, 373 (1906).
(11) S. Soloway and S. H. Willen, *Anal. Chem.*, **24**, 979 (1952).
(12) Linter, *Z. Angew. Chem.*, **13**, 707 (1900).
(13) K. Auwers, *Ber.*, **40**, 2532 (1907).
(14) (a) O. Manasse, *Ber.*, **27**, 2409 (1894); (b) U. S. Patent **526,786** (1894).
(15) C. Liebermann, *Ber.*, **3**, 457 (1870); **7**, 247, 287, 806, 1098 (1874).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

The Synthesis of Some Alkoxy- and Alkyl-substituted Tetraphenylcyclopentadienones

ALVIN FRIEDMAN,[1] WILLIAM GUGIG,[1] LOUIS MEHR,[1] AND ERNEST I. BECKER[2]

Received July 7, 1958

The syntheses for the homologous series of ethers (alkoxytetracyclones) from C_1 to C_{11} of 2,4,5-triphenyl-3-(4′-hydroxyphenyl)cyclopentadienone are described. A number of related alkyltetraphenylcyclopentadienones are also described.

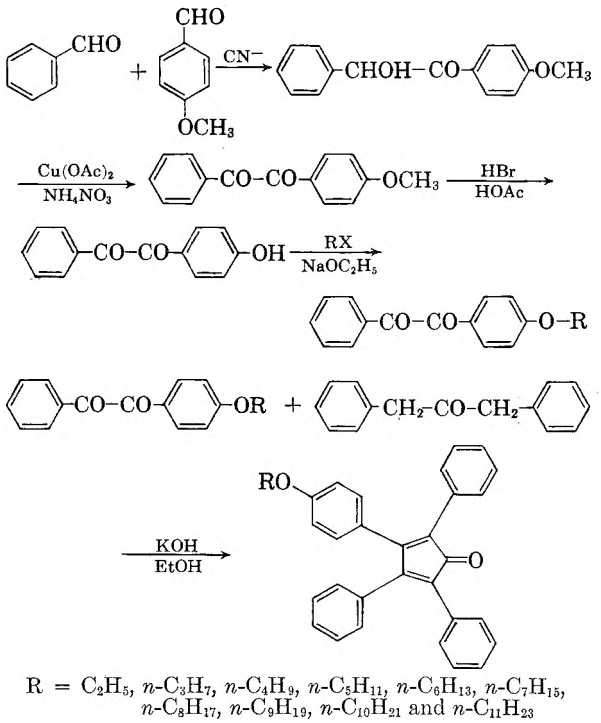
The fact that 2,4,5-triphenyl-3-(4′-octoxyphenyl)cyclopentadienone melts at 96.5–98.0° while tetracyclone (tetraphenylcyclopentadienone) melts at 219–220°[3] prompted a study of the melting point behavior of the compounds in between.

The substituted tetraphenylcyclopentadienones were arrived at by two different synthetic routes.

(1) Benzanisoin prepared by a mixed benzoin reaction between benzaldehyde and *p*-anisaldehyde was oxidized and the resulting *p*-methoxybenzil was demethylated to *p*-hydroxybenzil by means of hydrobromic acid in acetic acid. Alkylation of the hydroxybenzil with different alkyl halides gave a series of *n*-alkoxybenzils, which were condensed with benzyl ketone to give the corresponding 2,4,5-triphenyl-3-(4′-*n*-alkoxyphenyl)cyclopentadienones.

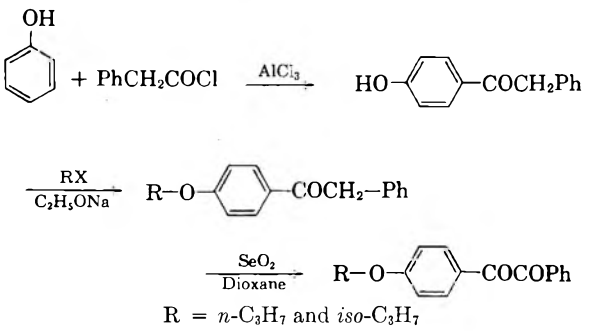
CHART I

ALKOXYTETRAPHENYLCYCLOPENTADIENONES



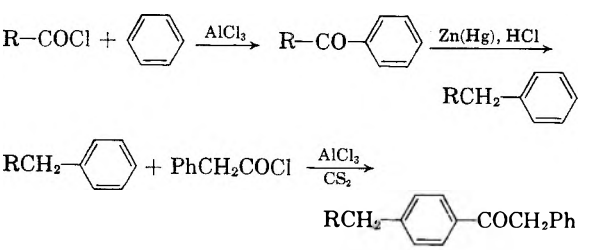
R = C_2H_5, *n*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}, *n*-C_6H_{13}, *n*-C_7H_{15}, *n*-C_8H_{17}, *n*-C_9H_{19}, *n*-$C_{10}H_{21}$ and *n*-$C_{11}H_{23}$

(2) A second route to the alkoxybenzils was *via* 4-hydroxy-α-phenylacetophenone, which was first prepared by the acylation of phenol. Alkylation gave the alkoxy-α-phenylacetophenones which were then oxidized to the corresponding benzils with selenium dioxide. This route required chromatographic purification of the benzil; the route through hydroxybenzil was preferred.



R = *n*-C_3H_7 and *iso*-C_3H_7

The 4-*n*-butyl, and 4-isobutyl-α-phenylacetophenones were prepared by the following route:



The 4-neopentyl-α-phenylacetophenone required special consideration. The literature describes the preparation of neopentylbenzene from benzylmagnesium chloride and *tert*-butyl chloride.[4,5] It was thought desirable to prepare it here by the reduction of pivalophenone. Therefore, isobutyrophenone, which had been prepared as above, was alkylated with methyl iodide and sodamide.[6] Reduction of the carbonyl group to the methylene group was carried out both by the Clemmensen[7]

(1) Taken from the M.S. theses of A.F. (1953) and W.G. (1956), and from a portion of the Ph.D. dissertation of L.M. (1953).

(2) To whom inquiries should be sent.

(3) L. Mehr, Ph.D. dissertation, Polytechnic Institute of Brooklyn (1953).

(4) E. Berliner and F. Berliner, *J. Am. Chem. Soc.*, **71**, 1195 (1949).

(5) A. Bygdén, *Ber.*, **45**, 3479 (1912).

(6) A. Haller and E. Bauer. *Compt. rend.*, **148**, 70 (1909).

(7) E. Clemmensen, *Ber.*, **46**, 1837 (1913).

reduction and Huang-Minlon modification[8] of the Wolff-Kishner reduction. Mixture melting points of the 4-alkyl-α-phenylacetophenones prepared from each of the reduction products showed no depression. This precaution ruled out the possibility that rearrangement had taken place during the Clemmensen reduction, although this conclusion was based on the reasonable, but unproved assumption that the base-catalyzed reduction would proceed without rearrangement.

The alkyl and alkoxy substituted tetraphenylcyclopentadienones were prepared by the method of Dilthey and Quint[9] as modified by Johnson and Grummitt.[10] The products obtained by cooling the reaction mixture varied from solids, which could be purified by crystallization alone, to semi-solid colored oils which required chromatography in addition. It should be noted that the 2,4,5-triphenyl-3-(4′-neopentylphenyl)cyclopentadienone was isolated in two different crystalline modifications melting at 153.5–154.0° and at 169–170°. A mixture of the two melted at 169–170°.

The variations of the melting points of the alkoxytetracyclones and of the alkoxybenzils are noteworthy. The alkoxytetracyclones show a typical alternation, with the melting point of the alkoxytetracyclone having an odd number of carbon atoms lying above those of its homologs, except for ten carbon atoms. Such changes have been associated previously with a change in crystal structure, but the necessary single crystal data were not obtained here. Among the benzils the alternation of melting points is not observed. No explanation for this is offered.

TABLE I

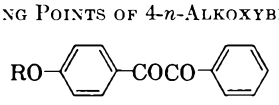
MELTING POINTS OF 2,4,5-TRIPHENYL-3-(4′-*n*-ALKOXYPHENYL)CYCLOPENTADIENONES

R	M.P., °C.
CH_3O	213–214[a]
C_2H_5O	171–172
n-C_3H_7O	182.5–183.5
n-C_4H_9O	144.5–145.5
n-$C_5H_{11}O$	184.3–185.1
n-$C_6H_{13}O$	140.8–141.5
n-$C_7H_{15}O$	142.1–143.0
n-$C_8H_{17}O$	96.5–98.0
n-$C_9H_{19}O$	115.3–115.7
n-$C_{10}H_{21}O$	134.0–134.7
n-$C_{11}H_{23}O$	125.0–125.6

[a] W. Dilthey, O. Trösken, K. Plum, and W. Schommer, *J. prakt. Chem.*, **141**, 331 (1934).

TABLE II

MELTING POINTS OF 4-*n*-ALKOXYBENZILS



R	M.P., °C.
CH_3	61.5–63.0[a]
C_2H_5	69.5–70.5[a]
C_3H_7	102.5–103.5[b]
C_4H_9	59.5–60.0[c]
C_5H_{11}	37–38[a]
C_6H_{13}	51.5–52.5[a]
C_7H_{15}	55–56[a]
C_8H_{17}	37–38[a]
C_9H_{19}	32.3–33.0
$C_{10}H_{21}$	37–38[a]
$C_{11}H_{23}$	42.0–43

[a] Footnote 25. [b] Footnote 25 reported 102–103°. [c] Footnote 25 reported 58–59°.

(8) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).
(9) W. Dilthey and F. Quint, *J. prakt. Chem.*, (2) **128**, 139 (1930).
(10) J. R. Johnson and O. Grummit, *Org. Syntheses*, Coll. Vol. III, 806 (1955).

EXPERIMENTAL

4-Hydroxybenzil. 4-Methoxybenzil (50 g., 0.208 mole) was dissolved in a mixture of 500 ml. of 48% hydrobromic acid and 250 ml. of glacial acetic acid. The mixture was refluxed for 4 hr. at which time it became homogeneous. After cooling, the reaction mixture was poured with stirring into 1 l. of cold water. The pale yellow solid which formed was filtered, washed with water, dried, and then dissolved in 200 ml. of ethyl ether. This solution was extracted with 250 ml. of 10% potassium hydroxide solution, and divided into four equal portions. The ether layer, after being dried over anhydrous sodium sulfate, was evaporated to dryness, and the residue was recrystallized from absolute ethanol to give 8 g. (0.033 mole) of unreacted 4-methoxybenzil. The aqueous phase was acidified with 1:1 hydrochloric acid and yielded, after filtration, 37.2 g. (0.165 mole, 94%) of product based on 4-methoxybenzil not recovered, m.p. 127–129° (lit.[11] m.p. 129–130°).

The purification of a number of the alkyl bromides was carried out by a modification of a procedure described by Vogel.[12]

Alkyl bromides. The commercial alkyl bromide was dissolved in previously purified petroleum ether (b.p. 68–69°) to give a 1.0:2.5 mixture. This mixture was washed successively with concentrated sulfuric acid, water, 10% sodium hydroxide, and again with water. After being dried over anhydrous sodium sulfate, the mixture was distilled to give the desired alkyl bromide. The boiling point, density, index of refraction, molar refraction, and in some cases the melting point were used as a criteria of purity.

4-Hydroxy-α-phenylacetophenone. Phenol (12.2 g., 0.13 mole) and phenylacetyl chloride (20 g., 0.13 mole) were added to 115 ml of nitrobenzene and heated for 1 hr. at 80–85°. Then aluminum chloride (22.7 g., 0.17 mole) was added slowly and the reaction mixture was kept at 80° for 1 hr. The mixture, after cooling to room temperature, was poured into 300 g. of acidified ice water and extracted with 400 ml. of ether. The ether layer was washed twice with 300 ml. of water and then extracted twice with 100 ml. portions of 10% sodium hydroxide solution. The basic solution was neutralized with hydrochloric acid, cooled, and the brown precipitate collected. This was purified by chromatographing it on an alumina column from a minimum amount of methanol. Precipitation with water and filtration gave 13 g. (0.0613 mole, 47.3%) of a white powder, m.p. 148–149° (lit. m.p. 142°,[13] 146–147°[14]).

4-Alkyl-α-phenylacetophenones. The intermediate alkylbenzenes were prepared by the Friedel and Crafts acylation

(11) J. H. Gorvin, *Nature*, **161**, 208 (1948).
(12) A. I. Vogel, *J. Chem. Soc.*, 636, 647 (1943).
(13) S. Weisl, *Monatsh*, **26**, 977 (1905).
(14) W. Dilthey and W. Schneider-Windmüller, *J. prakt. Chem.*, **159**, 273 (1943).

TABLE III

n-ALKYL BROMIDES, R—Br

R	B.P., °C. (mm. of Hg)	1 Atm.[a]	d_4^{20}	n_D^{20}	R_D Calcd.	R_D Obsd.
C_5H_{11}	33 (19)	131[b]	1.2197[c]	1.4550[d]	33.04	32.96
C_6H_{13}	56 (22)	157[e]	1.1694[f]	1.4470[g]	37.69	37.74
C_7H_{15}	49 (6)	180[h]	1.1398[i]	1.4500[j]	42.29	42.23
C_9H_{19}	69 (35)	221[k]	1.0853[l,m]	1.4524[l,n]	51.53	51.50
$C_{10}H_{21}$[o]	65 (1)	245[p]	1.0714[q]	1.4560[r]	56.15	56.12
$C_{11}H_{23}$[s]	64–71 (1)		1.0550[t]	1.4570[u]	60.76	60.72

[a] Boiling points at 1 atmosphere calculated from R. R. Driesbach, *Pressure-Volume-Temperature Relationships of Organic Compounds*, Handbook Publishers, Inc., Sandusky, Ohio, 1952. [b] N. A. Lange, *Handbook of Chemistry*, 7th ed., Handbook Publishers, Inc., Sandusky, Ohio, 1949, reported 129.7°. [c] Ref. 12 reported 1.2190. [d] Ref. 12 reported 1.44505. [e] *Handbook of Chemistry and Physics*, Chemical Rubber Publishing Co., 35th ed., 1953, reported 156.0°. [f] Ref. 12 reported 1.1705. [g] Ref. 12 reported 1.44781. [h] J. Timmermans, *Physico-Chemical Constants of Pure Organic Compounds*, Elsevier Publishing Co., 1950, reported 180.0°. [i] Footnote *h* reported 1.1398. [j] Ref. 12 reported 1.45052. [k] Ref. 12 reported 219° (745.5 mm.). [l] Value determined at 25°. [m] L. M. Ellis, Jr., and E. E. Reid [*J. Am. Chem. Soc.*, **54**, 1674 (1932)] reported 1.08490. [n] Footnote *m* reported 1.4523. [o] (1) M.p. −28° to −27°, J. D. Meyer and E. E. Reid [*J. Am. Chem. Soc.*, **55**, 1574 (1933)] reported −29.62°; (2) T. Kaneko and T. Amazaki [*Nippon Kagaku Zasshi*, **76**, 281 (1955); *Chem. Abstr.*, **51**, 17722a (1957)] report m.p. −30°. [p] Footnote 12 reported 102.5° (5.9 mm.). B.p. at 1 atm. calculated according to footnote *a* is 250°. [q] Footnote 12 reported 1.0658. [r] Footnote 12 reported 1.45527. [s] M.p. −24° to −23°. Footnote *o* (1) reported −13.15° and footnote *o* (2) reported m.p. −9°. [t] Footnote 12 reported 1.0541. [u] Footnote 12 reported 1.45697.

of benzene followed by the reduction of the resulting alkyl-aryl ketone as described below.

Pivalophenone. Isopropyl phenyl ketone (50 g., 0.337 mole) was methylated with methyl iodide and sodamide according to the method of Haller and Bauer[6] giving 47 g. (0.29 mole, 86%) of pivalophenone, b.p. 93.8–94.3° (8.5–9.0 mm.), n_D^{20} 1.5080 [lit.[15] b.p. 80–84° (3 mm.), n_D^{20} 1.5102]. The semicarbazone melted at 158–159° (lit.[16] 159°); the oxime melted at 165–166° (lit.[15] m.p. 194–195°).

Alkylbenzenes. The three ketones were reduced by the method of Clemmensen.[6] Pivalophenone was also reduced by the Huang-Minlon modification[8] of the Wolff-Kischner reaction. *n*-Butylbenzene, b.p. 180–182° (760 mm.), n_D^{20} 1.4929 [lit. b.p. 180–185° (760 mm.);[17] n_D^{20} 1.4899,[17] 1.4936[18]]. Isobutylbenzene, b.p. 170–173° (760 mm.), n_D^{20} 1.4920 [lit. b.p. 169.0–169.5° (760 mm.),[19] n_D^{20} 1.4871,[20] $n_D^{18.5}$ 1.4934[21]].

In the preparation of neopentylbenzene, zinc amalgam, made from 100 g. of mossy zinc, was covered with 50 ml. of water and 50 ml. of concentrated hydrochloric acid and then pivalophenone (10.1 g., 0.0623 mole) was added and the mixture was refluxed vigorously for 24 hr. For the first 10 hr. 20 ml. of concentrated hydrochloric acid was added each hour (10 additions). At the end of 10 hr. fresh zinc amalgam made from 125 g. of mossy zinc was added with 50 ml. of concentrated hydrochloric acid and the mixture was refluxed for the remaining 14 hr. At the end of the reaction the mixture was extracted with 150 ml. of ether and the two phases separated. The ether layer was washed twice with 100 ml. of water, dried over anhydrous magnesium sulfate and then the ether was removed on a water bath. The reaction gave 5.6 g. (0.0377 mole, 60.7%) of neopentylbenzene, b.p. 68–70° (12 mm.), n_D^{20} 1.4950.

The same substance was also prepared by the Huang-Minlon[8] modification of the Wolff-Kishner reduction. Pivalophenone (10 g., 0.0616 mole), triethylene glycol (65 ml.), potassium hydroxide (9.6 g.) and 85% hydrazine hydrate (6.5 ml.) were mixed and refluxed for 1.5 hr. Water was removed by means of a Dean-Stark trap until the temperature was brought up to 190°. After 3 hr. at this temperature, the reaction mixture was cooled to room temperature, combined with the aqueous distillate, and extracted with two 50-ml. portions of ether. The ether solution was washed with 100 ml. of water, dried over anhydrous magnesium sulfate, after which the solvent was removed on a water bath. Fractional distillation of the residue gave 5.8 g. (0.0391 mole), 63.4% of neopentylbenzene, b.p. 78–80° (21 mm.), n_D^{20} 1.4865 [lit. b.p. 185–186° (760 mm.)[22] n_D^{20} 1.4870,[4] 1.4885[22]].

4-Alkyl-α-phenylacetophenones. The three 4-alkyl-α-phenylacetophenones were made by similar procedures. The quantities given are for making 4-*n*-butyl-α-phenylacetophenone; the others used the same ratios of starting materials.

Aluminum chloride (12.9 g., 0.0969 mole) and phenylacetyl chloride (11.5 g., 0.0745 mole) were added to 100 ml. of carbon bisulfide. The alkylbenzene (0.0745 mole) was added dropwise to the reaction mixture. The mixture was refluxed for 15–20 min., cooled to room temperature, and poured into acidified ice water, which was extracted with 400 ml. of ether. The two phases were separated and the ether layer was washed twice with 400 ml. of water, once with 100 ml. of 5% sodium hydroxide solution and again with 400 ml. of water. After drying the ether solution over anhydrous magnesium sulfate, it was distilled to dryness. The residue was chromatographed in benzene solution on an alumina column. The eluant was concentrated, clarified with charcoal, and then evaporated to dryness. Crystallization of the residue from methanol gave the product. Isobutylbenzene (20 g., 0.149 mole) gave 24.5 g. (0.097 mole, 65.3%) of 4-isobutyl-α-phenylacetophenone, m.p. 52.5–53.5°. *n*-Butylbenzene (10 g., 0.0745 mole) gave 14.5 g. (0.0573 mole, 77.3%) of 4-*n*-butyl-α-phenylacetophenone, m.p. 63.5–64.0°. Neopentylbenzene (5.6 g., 0.0378 mole) gave 7.8 g. (0.0292 mole, 78%) of 4-neopentyl-α-phenylacetophenone, m.p. 80–81°.

Benzils. A mixture of 4-alkoxy-α-phenylacetophenone and selenium dioxide in acetic anhydride was heated at 144–145° in an oil bath for 4 hr. The reaction mixture was cooled and the selenium which precipitated was filtered and washed with 2–3 ml. of acetic anhydride, which was added to the filtrate. After warming the solution with 150 ml. of water, the benzil was extracted with ether. The ether layer was separated, washed once with an equal volume of water, and dried over anhydrous calcium chloride. The solvent was removed by distillation and in some cases the benzil was obtained by distilling it at reduced pressure. Some selenium remained in the product which was removed by chromatography from ethanol on an alumina column. The product was then crystallized to constant melting point from ethanol (see Table IV).

(15) J. H. Ford, C. D. Thompson, and C. S. Marvel, *J. Am. Chem. Soc.*, **57**, 2619 (1935).

(16) P. Lucas, *Compt. rend.*, **152**, 1771 (1911).

(17) A. W. Schmidt, G. Hopp, and V. Schoeller, *Ber.*, **72**, 1893 (1939).

(18) J. v. Braun and H. Deutsch, *Ber.*, **45**, 2171 (1912).

(19) W. H. Perkin, *J. Chem. Soc.*, **77**, 267 (1900).

(20) G. F. Hennion and L. A. Auspos, *J. Am. Chem. Soc.*, **65**, 1603 (1943).

(21) E. Boedtker, *Bull. soc. chim.*, [3] **31**, 965 (1904).

(22) V. N. Ipatieff and L. Schmerling, *J. Am. Chem. Soc.*, **60**, 1476 (1938).

TABLE IV

4-ALKOXYBENZILS *via* OXIDATION OF 4-ALKOXY-α-PHENYLACETOPHENONES WITH SELENIUM DIOXIDE IN ACETIC ANHYDRIDE

	Starting Materials					Product		
	Acetophenone		Selenium Dioxide		Acetic Anhydride,			Yield,
R	Grams	Mmole	Grams	Mmole	Ml.	M.P., °C.	Grams	%
C_2H_5	5.0	20.8	2.54	22.9	7.0	68–69[a]	4.1	78
n-C_4H_9	6.0	22.4	2.72	24.6	10.0	59.5[b]–60.0[c]	4.3	68
n-C_8H_{17}	9.0	27.7	3.38	30.5	18.0	37[d]–38[e]	6.2	66

[a] Footnote 23 reported 69.5–70.5°. [b] Footnote 23 reported 58–59° in 52% yield. [c] B.p. 204 (4 mm.). [d] Footnote 23 reported 37–38° in 5% yield. [e] B.p. 247–248° (3 mm.).

TABLE V

SUBSTITUTED BENZILS *via* OXIDATION OF 4-SUBSTITUTED-α-PHENYLACETOPHENONES WITH SELENIUM DIOXIDE IN DIOXANE

	Starting Materials				Products						
	4-Substituted-α-phenylaceto-phenones		Selenium dioxide (mole)	Dioxane (mole)				Analyses			
								Carbon		Hydrogen	
Y	Grams	Mole	Acetophenone (mole)	Acetophenone (mole)	M.P., °C.	Yield, %	Empirical formula	Calcd.	Found	Calcd.	Found
n-C_3H_7O	20	0.079	1.1	5.7	102.5–103.5[a]	81.5					
iso-C_3H_7O	20	0.079	1.1	5.7	30–31[b c]	76.5					
n-C_4H_9	12	0.0476	1.1	5.7	Liq[d]	95	$C_{18}H_{18}O_2$	81.17	81.09	6.81	6.90
iso-C_4H_9	12	0.0476	1.1	5.7	Liq[e]	96.3	$C_{18}H_{18}O_2$	81.17	81.43	6.81	6.96
neo-C_5H_{11}	12.8	0.048	1.1	5.7	52–53[f]	86	$C_{19}H_{20}O_2$	81.40	81.41	7.19	7.28

[a] Footnote 23 reported 102–103°. [b] Footnote 23 reported 30–31°. [c] Yield reported as liquid, b.p. 219–220° (6 mm.). [d] B.p. 147–148° (0.1 mm.), n_D^{25} 1.5773. [e] B.p. 168–169° (1 mm.), n_D^{25} 1.5762. [f] B.p. 192–194° (0.5 mm.).

TABLE VI

SYNTHESIS OF 4-ALKOXYBENZILS *via* ALKYLATION OF 4-HYDROXYBENZIL

Starting Materials[a]		Products						
					Analyses			
					Carbon		Hydrogen	
R	Alkyl bromide, *G*	Empirical formula	M.P., °C.	Yield,[c] %	Calcd.	Found	Calcd.	Found
C_2H_5	20.67[b]		68.5–70.0[d]	92				
n-C_3H_7	16.36		101.5–103.0[e]	89				
n-C_4H_9	18.08		58.0–59.5[f]	75				
n-C_5H_{11}	20.1		35.5–36.7[g]	58				
n-C_6H_{13}	21.9		50.0–51.8[h]	69				
n-C_7H_{15}	23.8		53.2–55.4[i]	78.5				
n-C_8H_{17}	25.7		36.0–38.0[j]	88				
n-C_9H_{19}	27.5	$C_{23}H_{28}O_3$	32.3–33.0	72	78.37	77.96	8.01	7.85
n-$C_{10}H_{21}$	29.4	$C_{24}H_{30}O_3$	34.7–35.4[k]	68	78.65	78.56	8.25	8.25
n-$C_{11}H_{23}$	31.3	$C_{25}H_{32}O_3$	42.0–43.0	33	78.91	78.94	8.48	8.54

[a] Alkyl bromide (0.133 mole), 4-hydroxybenzil (10.0 g., 0.0442 mole), sodium (1.02 g., 0.0442 atom), and 125 ml. of ethanol. [b] The iodide was used. [c] All yields based on 4-hydroxybenzil. [d] Footnote 23 reported 69.5–70.0°. [e] Footnote 23 reported 102.0–103.0°. [f] Footnote 23 reported 58.0–59.0°. [g] Footnote 23 reported 37–38°. [h] Footnote 23 reported 51.5–52.5°. [i] Footnote 23 reported 55–56°. [j] Footnote 23 reported 37.0–38.0°. [k] Footnote 23 reported 36–37°. There is a printing error in the empirical formula for the benzil, but our constants agree.

The remaining benzils were prepared according to Bockstahler and Wright[23] and are listed in Table V.

4-Alkyl or alkoxy-α-phenylacetophenone (0.0476 mole), dioxane 24 g., (0.272 mole), selenium dioxide (5.88 g., 0.053 mole) and water (0.054 g., 0.053 mole) were mixed and refluxed for 6–8 hr. The hot mixture was suction filtered and the selenium residue washed with 15–25 ml. of hot dioxane. The dioxane was removed by distillation under vacuum and the benzil purified by distillation, chromatography, and crystallization as needed.

4-Alkoxybenzils. 4-Hydroxybenzil (10 g., 0.0442 mole) and alkyl bromide (0.133 mole) were added to a mixture of metallic sodium (1.02 g., 0.0442 atom) in 125 ml. of absolute ethanol and refluxed until the dark brown solution formed by the hydroxybenzil and sodium ethoxide turned pale yellow.

The reaction mixture was then cooled in a Dry Ice chest and filtered with suction at about −75°. The precipitate

(23) E. R. Bockstahler and D. L. Wright, *J. Am. Chem. Soc.*, 71, 3760 (1949).

TABLE VII

SUBSTITUTED TETRAPHENYLCYCLOPENTADIENONES

Benzil[a]		Products						
					Analyses			
		Yield,		Empirical	Carbon		Hydrogen	
Y	Grams	%	M.P., °C.	formula	Calcd.	Found	Calcd.	Found
						89.89		5.95
n-C_4H_9	6.0	21.8	122.0–122.5	$C_{33}H_{28}O$	89.96	89.76	6.41	6.35
						89.90		6.41
iso-C_4H_9	6.0	27.6	132.5–133.0	$C_{33}H_{28}O$	89.96	90.12	6.41	6.59
						90.22		6.58
neo-C_5H_{11}	6.3	12.7	153.5–154.0[b]	$C_{34}H_{30}O$	89.83	89.80	6.65	6.77
		16.6	169–170[b]	$C_{34}H_{30}O$				
C_2H_3O	1.22	69	171–172	$C_{31}H_{24}O_2$	86.89	86.65	5.65	5.44
n-C_3H_7O	7.0	64.5	182.5–183.5	$C_{32}H_{26}O_2$	86.85	87.28	5.92	6.10
						87.06		5.99
iso-C_3H_7O	7.0	60	176–177	$C_{32}H_{26}O_2$	86.85	87.25	5.92	6.01
n-C_4H_9O	1.2	66	144.5–145.5	$C_{33}H_{28}O_2$	86.81	86.61	6.18	6.27
n-$C_5H_{11}O$	4.26	63.8	184.3–185.1	$C_{34}H_{30}O_2$	86.77	86.82	6.43	6.69
n-$C_6H_{13}O$	4.46	50.2	140.8–141.5	$C_{35}H_{32}O_2$	86.74	86.79	6.66	6.67
n-$C_7H_{15}O$	4.67	29.0	142.1–143.0	$C_{36}H_{34}O_2$	86.71	86.37	6.87	6.97
n-$C_8H_{17}O$	2.0	63	96.5–98.0	$C_{37}H_{36}O_2$	86.68	86.46	7.08	6.94
n-$C_9H_{19}O$	5.07	28.7	115.3–115.7	$C_{38}H_{38}O_2$	86.65	86.55	7.27	7.20
n-$C_{10}H_{21}O$	5.27	40.7	134.0–134.7	$C_{39}H_{40}O_2$	86.62	86.74	7.46	7.58
n-$C_{11}H_{23}O$	2.73	30.1	125.0–126.6	$C_{40}H_{42}O_2$	86.60	86.40	7.63	7.53

[a] An equivalent number of moles of benzyl ketone were employed. [b] Mixture melting point 169–170° with the compound immediately above.

was washed with cold water, dried in a desiccator, and then recrystallized from absolute ethanol.

2,3,4,5-Tetraphenylcyclopentadienones.[9,10] Alkyl or alkoxybenzil and an equivalent quantity of benzyl ketone in 15–25 ml. of absolute ethanol (purified by distillation from either potassium hydroxide or sodium ethoxide) was heated to boiling and a solution of potassium hydroxide in 1–2 ml. of ethanol was added and the mixture was refluxed for 15 min. The crude product was isolated by cooling the reaction mixture in a salt-ice bath. The precipitate which formed was filtered, washed with cold ethanol, and then purified by chromatography from benzene on alumina. The percolates were evaporated to dryness and the residue recrystallized from a benzene-ethanol mixture.

BROOKLYN 1, N. Y.

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY, RAMNARAIN RUIA COLLEGE, UNIVERSITY OF BOMBAY]

Effect of Substitution in the Aniline Portion on the Behavior of Semianilides of β-Arylglutaconic Acids

J. J. NERURKAR,[1] R. N. JOSHI, AND V. M. BHAVE

Received October 15, 1958

Semianilides of β-arylglutaconic acids are ordinarily found to exist in the cis form, but if the aniline portion of the semianilide is made to carry a carbomethoxy substituent in the ortho position, then the resulting *o*-carbomethoxysemianilides can be obtained as well-defined cis and trans modifications. The cis *o*-carbomethoxysemianilides are found to lose one molecule of water in two different ways, under different conditions, yielding (a) a lactonic substance and (b) the corresponding hydroxy anil.

The chemistry of substituted and unsubstituted glutaconic acids has been previously studied, principally by Thorpe *et al.*[2,3] and by other workers.[4–6] By analogy with the existence of well defined cis and trans modifications of maleic and fumaric acids, Thorpe postulated that glutaconic acids should exist in three forms namely, cis, trans, and labile.[3] The labile form was, however, found to be nonexistent. Also, attempts to isolate the simple unsubstituted glutaconic acids in cis and trans modifications failed, although Perkin *et al.*[5] were able to obtain some alkyl substituted glutaconic

(1) Present address: Laboratory of Pharmaceutical Chemistry, University of Kansas, Lawrence, Kan.

(2) F. B. Thole and J. F. Thorpe, *J. Chem. Soc.*, **99**, 2208 (1911).

(3) N. Bland and J. F. Thorpe, *J. Chem. Soc.*, **101**, 861 (1912).

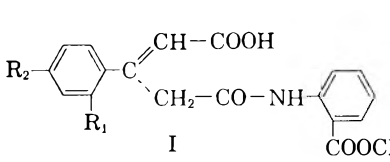
(4) W. H. Perkin, Jr., and A. E. Smith, *J. Chem. Soc.*, **83**, 8, 83 (1903).

(5) W. H. Perkin, Jr., and G. Tattersall, *J. Chem. Soc.*, **87**, 365 (1905).

(6) F. Feist, *Ann.*, **370**, 54 (1909).

acids in cis and trans modifications. Isolation of stable cis and trans forms of β-arylglutaconic acids was not found possible,[3,7] although separation of these forms in the case of the semianilides of unsubstituted and β-arylglutaconic acids has been reported.[3] This work indicates that perhaps the energy barrier between the cis and trans forms of glutaconic acid itself is too high to permit conversion of the cis to the trans isomer under ordinary conditions. Introduction of bulky groups into the molecule apparently decreases the energy barrier to the extent that conversion from cis to trans modification becomes possible. In the case of semianilides of various β-arylglutaconic acids[8-10] which were initially obtained in cis forms, though milder temperatures brought about no change, strong heating resulted in the formation of the corresponding hydroxy-anils by loss of water.

The objective of the present investigation was to prepare semianilides of β-arylglutaconic acids containing an ortho substituent on the aniline ring, which by virtue of its bulkiness might sterically hinder anil formation and thus permit cis-trans conversion. With this in mind, methyl anthranilate was used instead of aniline in the reaction with the β-arylglutaconic anhydrides as carried out previously by Limaye *et al.*[8] to give the corresponding *o*-carbomethoxy-β-aryl-*cis*-glutaconanilic acids (Ia, Ib and Ic). By analogy with the observation of

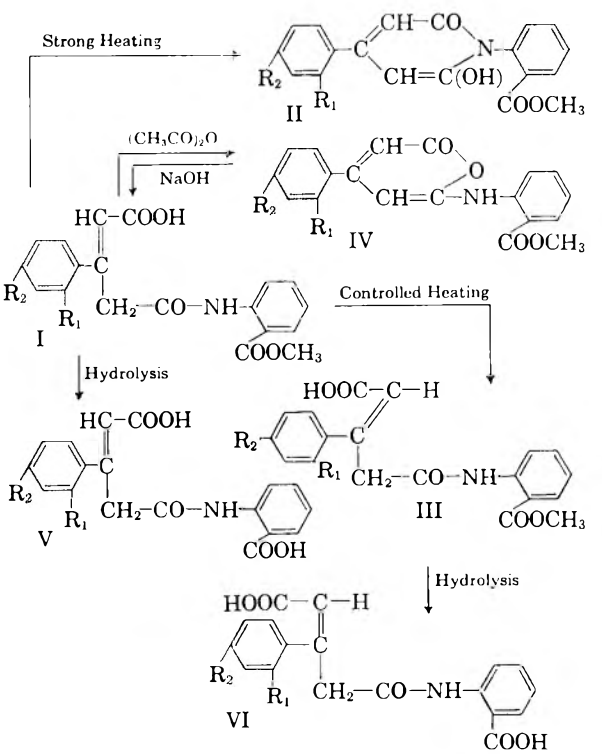


I

	R_1	R_2
a	H	OCH_3
b	OCH_3	CH_3
c	OCH_3	OCH_3

the previous workers,[2,8] these *cis*-glutaconanilic acids, on heating at elevated temperature, gave the corresponding hydroxy anils (IIa, IIb, IIc respectively).[11] When they were subjected to prolonged controlled heating at temperatures slightly above their melting points according to Thorpe's method,[3] they underwent a substantial cis to trans conversion giving IIIa, IIIb, IIIc respectively. Unlike the unsubstituted glutaconanilic acids which yield only hydroxy anils in the presence of acetic anhydride,[2] these *o* - carbomethoxy-substituted-*cis*-glutaconanilic acids (Ia, Ib, Ic) on similar treatment gave lactonic compounds, methyl *N*-[4,6-dehydro-4-β-aryl-6-oxo-2-pyranylidene]-anthranilates (IVa, IVb, IVc), which could be reconverted into the original *o*-carbomethoxy-*cis*-glutaconanilic acids (Ia, Ib, Ic) by treatment with alkali. This is apparent from the relative nucleophilicities of the carbonyl oxygen and amide nitrogen of Ia, Ib, and Ic. In the case of these carbomethoxy-*cis*-glutaconanilic acids, either of the two nucleophilic agents, *i.e.* the carbonyl oxygen or amide nitrogen is capable of attack at the carboxyl group. Without the *o*-carbomethoxy substituent, the amide nitrogen is the stronger nucleophilic atom, giving corresponding hydroxy anils by treatment with acetic anhydride. With the *o*-carbomethoxy group as in Ia, Ib, and Ic, the resonance and inductive effects become prominent, causing a decrease in electron density around the amide nitrogen atom. This decrease in nucleophilicity of the nitrogen permits the carbonyl oxygen to be more reactive, giving the corresponding lactones IVa, IVb, and IVc.

The isomeric *o*-carbomethoxy-β-aryl-*trans*-glutaconanilic acids (IIIa, IIIb, and IIIc) were found to be inert to prolonged heating at reflux temperature with acetic anhydride, thereby confirming their trans configurations. The *cis*-(Ia, Ib, and Ic) and *trans*-glutaconanilic acids (IIIa, IIIb, and IIIc), which are also methyl esters, on hydrolysis with alcoholic alkali gave the corresponding dicarboxylic acids (Va, Vb, Vc, and VIa, VIb, VIc) which may be considered respectively, as *o*-carboxy-β-aryl-*cis*-glutaconanilic acids and *o*-carboxy-β-aryl-*trans*-glutaconanilic acids. The *cis*-acids (Va, Vb, Vc) could also be obtained by the action of alcoholic alkali on the neutral lactones (IVa, IVb, and IVc).



Methyl anthranilate was also made to condense with the β-arylglutaric acids (VIIb, VIIc) or their anhydrides (VIIIb, VIIIc) to give the corresponding carbomethoxy-β-arylglutaraninilic acids (IXb,

(7) F. Feist and G. Pomme, *Ann.*, **370**, 76 (1909).

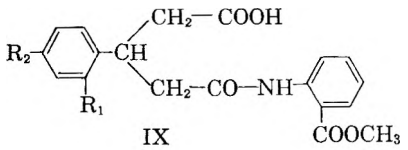
(8) D. B. Limaye and V. M. Bhave, *J. Indian Chem. Soc.*, **8**, 139 (1931).

(9) D. B. Limaye and G. R. Gogte, *J. Univ. Bombay* **3**, 135-40 (1934).

(10) G. R. Gogte, *Proc. Indian Acad. Sci.*, 1A, 48-59 (1934).

(11) To be published.

IXc). These monobasic glutaraninilic acids (IXb, IXc), on hydrolysis with alkali, gave the corresponding dibasic *o*-carboxy-β-arylglutaraninilic acids (Xb, Xc).



IX

EXPERIMENTAL

o-Carbomethoxy-β-(4-methoxyphenyl)-cis-glutaconanilic acid (Ia). A solution of 18.8 g. (0.1 mole) of β-(4-methoxyphenyl)-glutaconic anhydride[9] and 15.1 g. (0.1 mole) of methyl anthranilate in 800 ml. of warm benzene was heated at reflux temperature on a steam bath for about 30 min. Upon removal of the benzene, a pale yellow solid separated. It was collected by filtration, washed with water, and purified by dissolution in sodium bicarbonate solution and reprecipitation with dilute hydrochloric acid. Further purification by repeated recrystallizations from alcohol gave 22.6 g. (61% yield) of Ia as pinkish white needles, m.p. 146–146.5°.

Anal. Calcd. for $C_{20}H_{19}O_6N$: C, 65.03; H, 5.19; N, 3.79. Found: C, 65.24; H, 5.14; N, 3.80.

o-Carbomethoxy-β-(4-methoxyphenyl)-trans-glutaconanilic acid (IIIa). In a clean dry flask, 1 g. of Ia was heated in a paraffin bath at 150° for 0.5 hr. The resulting resinous mass was washed first with ether and then with water, giving a crystalline yellow solid. It was purified by being dissolved in dilute sodium bicarbonate solution and precipitation with dilute hydrochloric acid. Further purification by repeated recrystallizations from 50% alcohol gave 0.6 g. (60% yield) of IIIa as pale yellow needles, m.p. 185–186°.

Anal. Found: C, 65.28; H, 5.11.

Methyl N-[4,6-dehydro-4-(4-methoxyphenyl)-6-oxo-2-pyranylidene]-anthranilate (IVa). A mixture of 1 g. of Ia and 5 ml. of acetic anhydride was heated at reflux temperature for 1 hr. on a steam bath. The clear red liquid so obtained was poured into about 25 ml. of cold water, giving an orange colored solid material. This solid was collected on a filter, washed several times with water, triturated with sodium bicarbonate solution to remove any unchanged semianilide and filtered. Upon drying, the residue was recrystallized from ethyl alcohol yielding 0.4 g. (45% yield) of pale yellow crystals, m.p. 135–135.5°. This material was found to be insoluble in cold dilute sodium hydroxide solution. However, upon warming this suspension, solution was effected regenerating the semianilide (Ia) after neutralization.

Anal. Calcd. for $C_{20}H_{17}O_5N$: C, 68.36; H, 4.88. Found: C, 68.06; H, 5.08.

o-Carboxy-β-(4-methoxyphenyl)-cis-glutaconanilic acid (Va). To a solution of 1 g. of Ia in 15 ml. absolute alcohol, 2 ml. of 12.5*N* sodium hydroxide solution was added and the mixture heated at reflux temperature for about 2 hr. Removal of the solvent and neutralization of residual sodium salt with concentrated hydrochloric acid gave a pale yellow solid mass. Repeated crystallizations from alcohol gave 0.63 g. (67% yield) of faint, yellow crystals, m.p. 172° dec.

Anal. Calcd. for $C_{19}H_{17}O_6N$: C, 64.21; H, 4.82. Found: C, 64.46; H, 4.87.

o-Carbomethoxy-β-(2-methoxy-4-methylphenyl)-cis-glutaconanilic acid (Ib). The procedure used in making this compound was the same as that used for Ia. From 23 g. (0.1 mole) of β-(2-methoxy-4-methylphenyl)-glutaconic anhydride,[9] 28 g. (70% yield) of Ib, m.p. 132–132.5°, was obtained.

Anal. Calcd. for $C_{21}H_{21}O_6N$; C, 63.16; H, 5.26. Found: C, 63.30; H, 5.47.

o-Carbomethoxy-β-(2-methoxy-4-methylphenyl)-trans-glutaconanilic acid (IIIb). The procedure used in making this compound was the same as that described for IIIa. From 1 g. of Ib, 0.56 g. (56% yield) of IIIb, m.p. 162–163° was obtained.

Anal. Found: C, 63.32; H, 5.38.

Methyl N-[4,6-dehydro-4-(2-methoxy-4-methylphenyl)-6-oxo-2-pyranylidene]-anthranilate (IVb). This compound was prepared by the same procedure described for IVa. From 3.8 g. (0.01 mole) of Ib, 2 g. (57% yield) of IVb was obtained, m.p. 152–153°.

Anal. Calcd. for $C_{21}H_{19}O_5N$: C, 69.04; H, 5.2; N, 3.63. Found: C, 69.23; H, 5.36; N, 3.48.

o-Carboxy-β-(2-methoxy-4-methylphenyl)-cis-glutaconanilic acid (Vb). The procedure used in making Vb was the same as described for Va except that it was purified by crystallization from 80% acetic acid. From 4 g. (0.01 mole) of Ib, 2.8 g. (75% yield) of Vb was obtained, m.p. 200° (dec.).

Anal. Calcd. for $C_{20}H_{19}O_6N$: C, 65.03; H, 5.15; neut. equiv., 184.5. Found: C, 65.24, H, 5.30; neut. equiv., 184.7.

o-Carboxy-β-(2-methoxy-4-methylphenyl)-trans-glutaconanilic acid (VIb). To a solution of 4 g. (0.1 mole) of IIIb in 50 ml. of alcohol, 7.5 ml. of 12.5*N* NaOH was added and the whole mixture heated at reflux temperature on the water bath for 3 hr. Upon removal of the solvent, the residue was dissolved in water, filtered, and the filtrate neutralized with hydrochloric acid at 0°, giving VIb as a pale yellow mass. Crystallization from 80% alcohol gave 2 g. (52% yield) of colorless crystals VIb, m.p. 225° (dec.).

Anal. Calcd. for $C_{20}H_{19}O_6N$: C, 65.43; H, 5.15. Found: C, 64.82; H, 5.28.

o-Carbomethoxy-β-(2,4-dimethoxyphenyl)-cis-glutaconanilic acid (Ic). The same procedure as was used in making Ia was used for the preparation of this compound. From 21.6 g. (0.1 mole) of 2,4-dimethoxyphenylglutaconic anhydride,[10] 29.1 g. (73% yield) of Ic was obtained in the form of pinkish white needles, m.p. 132–134°.

Anal. Calcd. for $C_{21}H_{21}O_7N$: C, 63.16; H, 5.26. Found: C, 63.30, H, 5.47.

o-Carbomethoxy-β-(2,4-dimethoxyphenyl)-trans-glutaconanilic acid (IIIc). This compound was obtained from Ic by heating it at a temperature just above its melting point (*i.e.*, 135°) for 1 hr. From 2.0 g. of Ic, 1.2 g. (60% yield) of IIIc was obtained, m.p. 158°–159.5°.

Anal. Found: C, 63.32; H, 5.39.

Methyl N-[4,6-dehydro-4-(2,4-dimethoxyphenyl)-6-oxo-2-pyranylidene]-anthranilate (IVc). This compound was prepared by the same method described for the preparation of IVa. From 4.0 g. (0.1 mole) of Ic, 2.6 g. (70% yield) of IVc was obtained in the form of yellow plates, m.p. 146°. Upon treatment with cold dilute sodium hydroxide solution, solution was gradually effected. Acidification regenerated the semianilide Ic. Treatment of IVc with boiling dilute sodium hydroxide solution and subsequent acidification, however, gave the dibasic acid Vc, m.p. 196.5° (dec.).

Anal. Calcd. for $C_{21}H_{19}O_6N$: C, 66.15; H, 4.99. Found: C, 65.97; H, 5.21.

o-Carboxy-β-(2,4-dimethoxyphenyl)-cis-glutaconanilic acid (Vc). This dibasic acid was prepared from Ic by heating it with alcoholic alkali at reflux temperature or from IVc by boiling with decinormal sodium hydroxide solution. From 4 g. of Ic, 2 g. (55% yield) of Vc was obtained. Crystallization from 80% acetic acid gave pure Vc, m.p. 196–197° (dec.). From 3.8 g. (0.1 mole) of IVc, 1.6 g. (41% yield) of Vc was obtained.

Anal. Calcd. for $C_{21}H_{19}O_7N$: C, 62.33; H, 4.93. Found: C, 62.55; H, 4.77.

o-Carboxy-β-(2,4-dimethoxyphenyl)-trans-glutaconanilic acid (VIc). This compound was prepared from IIIc by treatment with alcoholic alkali. From 4 g. (0.1 mole) of IIIc, 1.7 g. (46% yield) of colorless VIc, m.p. 215° (dec.) was obtained.

Anal. Found: C, 62.03; H, 5.11.

β-(2-Methoxy-4-methylphenyl)-glutaric anhydride (VIIIb). A mixture of 2.5 g. (0.01 mole) of β-(2-methoxy-4-methyl-

phenyl)glutaric acid[12] VIIb, and 2 ml. of acetic anhydride was heated at reflux temperature for about an hour. The resinous mass obtained upon cooling was crystallized by the addition of ether. Crystallization from dry benzene gave 1.9 g. (72% yield), of brilliantly shining colorless plates (VIIIb), m.p. 104–105°.

o-Carbomethoxy-β-(2-methoxy-4-methylphenyl)glutaraninilic acid (IXb). This compound was prepared by the same procedure as previously described for the preparation of Ia, except that glutaric anhydride (VIIIb) was used instead of glutaconic anhydride. From 2.3 g. (0.01 mole) of VIIIb, 2.6 g. (60% yield) of IXb, m.p. 135–136°, was obtained.

Anal. Calcd. for $C_{21}H_{23}O_6N$: neut. equiv., 385.0. Found: neut. equiv., 389.1.

o-Carboxy-β-(2-methoxy-4-methylphenyl)glutaraninilic acid (Xb). This dicarboxylic acid was prepared by the alkaline hydrolysis of IXb. From 3.9 g. (0.1 mole) of IXb, 2.6 g. (71% yield) of Xb was obtained. Repeated crystallizations from dilute acetic acid and finally from alcohol gave the pure product, m.p. 165–165.5°.

Anal. Calcd. for $C_{20}H_{21}O_6N$: C, 64.69; H, 5.66; neut. equiv., 185.5. Found: C, 64.82; H, 5.51; neut. equiv., 186.5.

β-(2,4-Dimethoxyphenyl)glutaric acid (VIIc). This acid was prepared by the reduction of β-(2,4-dimethoxyphenyl)-glutaconic acid,[13] m.p. 174° (dec.) with sodium amalgum according to the method described by Chitre.[14] From 26.6 g. (0.1 mole) of β-(2,4-dimethoxyphenyl)-glutaconic acid, 21.8 g. (81% yield) of crude reduced acid was obtained, as a white mass. Crystallization from water gave 20.2 g. (76% yield) of VIIc as colorless needles, m.p. 158–159°.

Anal. Calcd. for $C_{13}H_{16}O_6$: neut. equiv., 134.0. Found: neut. equiv., 135.8.

β-(2,4-Dimethoxyphenyl)glutaric anhydride (VIIIc). This compound was prepared from VIIc by heating at reflux temperature with acetic anhydride. The yield was 82% of white crystals, m.p. 122–122.5°.

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.4; H, 5.6. Found: C, 62.5; H, 5.8.

o-Carbomethoxy-β-(2,4-dimethoxyphenyl)glutaraninilic acid (IXc). This monobasic acid was prepared from the corresponding glutaric anhydride (VIIIc) by heating it in boiling benzene solution with a molecular quantity of methyl anthranilate. Repeated crystallizations from 50% alcohol gave pure IXc, in 72% yield, m.p. 136–136.5°.

Anal. Calcd. for $C_{20}H_{23}O_7N$: neut. equiv., 401.0. Found: neut. equiv., 398.7.

o-Carboxy-β-(2,4-dimethoxyphenyl)glutaraninilic acid (Xc). This dicarboxylic acid was obtained in 61% yield from IXc by hydrolysis with alcoholic alkali. It was purified by crystallization from acetic acid giving dull crystals, m.p. 128–128.5°.

Anal. Calcd. for $C_{21}H_{21}O_7N$: neut. equiv., 193.5. Found: neut. equiv., 195.2.

BOMBAY, INDIA

(12) D. B. Limaye and R. G. Chitre, *J. Univ. Bombay*, **4**, 101 (1935).

(13) P. R. Bavdekar, M.Sc. thesis, University of Bombay, 1941.

(14) R. G. Chitre, M.Sc. thesis, University of Bombay, 1933.

[CONTRIBUTION OF THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Psoralene. II. Certain Reactions of Xanthotoxin[1]

MERVIN E. BROKKE AND BERT E. CHRISTENSEN

Received November 7, 1958

The behavior of 9-methoxypsoralene under the conditions of oxidation, chlorination, sulfonation, and ether cleavage is described. Chromium trioxide converted 9-methoxypsoralene I into psoralenequinone II. Chlorination with chlorine produced 2,3-dihydro-9-methoxy-2,3,4-trichloropsoralene VII while chlorination with sodium hypochlorite formed 4-chloro-9-methoxypsoralene VIII. Chlorosulfonic acid attacked the 4-position forming both the free sulfonic acid and the acid chloride. The conversion of 9-methoxypsoralene to 9-hydroxypsoralene was accomplished in good yield by heating with anhydrous aluminum chloride.

Xanthotoxin I (9-methoxypsoralene) is a furocoumarin that occurs in a number of plants indigenous to the Eastern Hemisphere. As its name implies xanthotoxin is a fish poison and is, in general, toxic to cold-blooded animals while it is relatively nontoxic to mammals. Current interest in this material stems from its photodynamic activity, which causes the skin to "tan" as opposed to "burn" if the drug is administered orally prior to exposure to the sunlight.

The behavior of 9-methoxypsoralene under the conditions of nitration, bromination, hydrogenation, ozonization, thionation, and various ring-opening procedures has been previously described by this laboratory.[2] This paper is concerned with the oxidation, ether cleavage, chlorination, and sulfonation of this molecule.

Schonberg has reported[3] that oxidation of 4-methoxypsoralene (bergaptene) with sodium dichromate attacked the furan double bond and formed 6-formyl-7-hydroxy-5-methoxycoumarin. His work has been confirmed in this laboratory.

It seemed unusual, therefore, that the isomer of bergaptene, 9-methoxypsoralene, was unaffected by sodium dichromate under identical conditions. Treatment with chromium trioxide in acetic acid,

(1) This work was supported in part by grants from the Division of Research Grants and Fellowships, National Institutes of Health, Public Health Service. Published with the approval of the Monographs Publications Committee, Oregon State College as Research Paper No. 351, School of Science, Department of Chemistry.

(2) M. E. Brokke and B. E. Christensen, *J. Org. Chem.*, **23**, 589 (1958).

(3) A. Schonberg, N. Badran, and N. Starkowsky, *J. Am. Chem. Soc.*, **75**, 1019 (1955).

however, did cause oxidation of 9-methoxypsoralene. Analysis of the product indicated that it might be psoralene quinone, and this was indeed shown to be the case when the product was found to be identical with the psoralene quinone obtained by the previously reported[4] oxidation of 4-amino-9-methoxypsoralene VI. The fact that the oxidation product of 9-methoxypsoralene I was psoralenequinone II was further confirmed by reduction of the quinone with sulfur dioxide to the hydroquinone III and subsequent methylation to yield isopimpinellin IV. The isopimpinellin obtained by these means was identical in melting point and infrared spectrum to the authentic sample (4). This series of reactions is shown in Fig. 1.

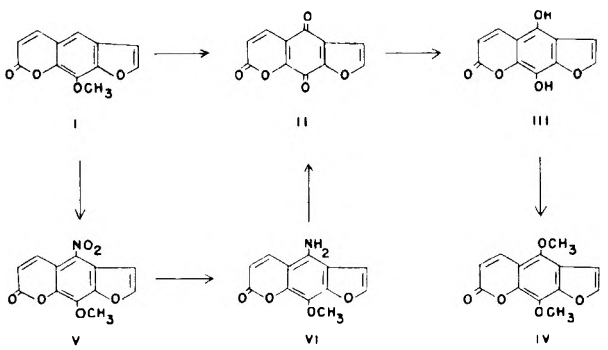


Figure 1

It has been observed that treatment of furocoumarins and chromones with aluminum chloride in benzene resulted in cleavage of the methoxyl groups in addition to the opening of the furan ring.[2,5,6] Studies of this reaction involving the use of an inactive aromatic compound to replace benzene as the solvent were undertaken. It was hoped by this means to cleave the methoxyl and leave the furan ring intact as has been reported for furochromones.[5] In no case, however, was the reaction successful. Nitrobenzene, chlorobenzene, and bromobenzene were tested at various temperatures for different periods, but in each case the product was charred, or the starting material was recovered intact.

Using a procedure of Merchant and Shah[7] for the cleavage of methoxyl groups with aluminum chloride in the absence of a solvent, the conversion of 9-methoxypsoralene to 9-hydroxypsoralene (xanthotoxol) was accomplished in yields of 40–45%. The xanthotoxol obtained by this means had an identical melting point and infrared spectrum with that of an authentic sample (4).

(4) Samples of isopimpinellin and xanthotoxol were kindly supplied by Dr. W. L. Fowlks of the University of Oregon Medical School.

(5) B. Krishnaswamy and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **15**, 437 (1942).

(6) B. Krishnaswamy and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **16**, 151 (1942).

(7) J. R. Merchant and R. C. Shah, *J. Org. Chem.*, 22, 884 (1957).

Direct chlorination of 9-methoxypsoralene with chlorine yielded, in contrast to bromination,[2] only a trichloro-derivative VII. A comparison of the ultraviolet spectrum of this compound with those of other furocoumarins as described elsewhere[2] clearly indicated that the conjugation of the lactone carbonyl to the aromatic nucleus remained intact and that addition of two of the chlorine atoms had occured in the 2,3-position. This conjugation was shown by a peak at 315 mμ.

Chlorination of 9-methoxypsoralene with sodium hypochlorite yielded a monochloro-derivative which melted at 195–196°. 4-Chloro-9-methoxypsoralene VIII has been synthesized from 4-amino-9-methoxypsoralene VI and was reported to melt at 187–188°. A mixed melting point of these two compounds was found to be 187–188°. The infrared spectra were identical between 2000–600 wave numbers with the exception of a peak at 1510 wave numbers in the sample obtained from the amine. It seemed possible that the impurity in this sample might be 4-chloro-2,3-dihydro-9-methoxypsoralene. This compound was prepared but the infrared showed no absorption at 1510 wave numbers. Sublimation of the sample of 4-chloro-9-methoxypsoralene VIII prepared from the amine left behind a small residue which had an infrared spectrum identical with that of 4-nitro-9-methoxypsoralene V and showed a strong absorbance at 1510 wave numbers. It was therefore concluded that the two monochloro-derivatives were identical with the exception that the compound from the Sandmeyer reaction was contaminated with a little of the 4-nitro-derivative.

Direct chlorination of 4-chloro-9-methoxypsoralene VIII with chlorine yielded the same trichloro-derivative VII as was obtained from chlorination of 9-methoxypsoralene. It may therefore be concluded that the three chlorine atoms in this molecule are located in the 2,3,4-positions. The above series of reactions is shown in Fig. 2.

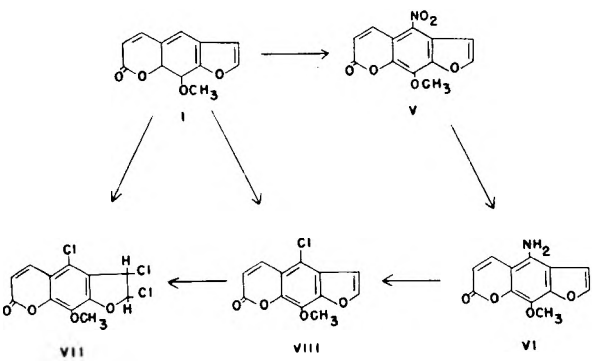


Figure 2

Sulfonation of 9-methoxypsoralene with chlorosulfonic acid yielded either the free sulfonic aid XII or the acid chloride XI; the ratio between these two products being determined by the conditions of the

reaction as described in the experimental section. The acid chloride was readily hydrolyzed to the free acid by boiling water.

That sulfonation occurred in the 4-position was established by bromination and nitration of the sulfonic acid to form the previously described[2] 4-bromo-XIII and 4-nitro-9-methoxypsoralenes V. This type of structural proof finds precedent in the work of Merchant and Shah.[7] These reactions are shown in Fig. 3.

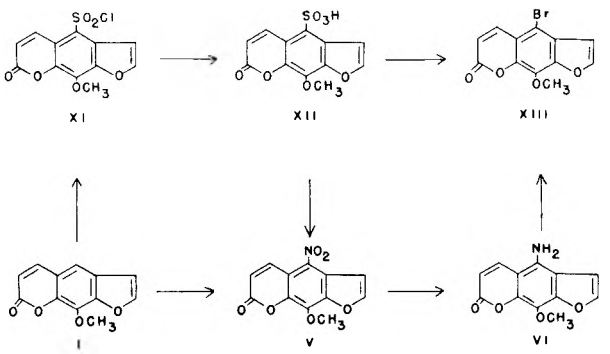


Figure 3

EXPERIMENTAL

Psoralenequinone (II). 9-Methoxypsoralene (1.0 g., 0.0046 mole) was dissolved in 30 ml. glacial acetic acid. To this solution was added 30 ml. of a 15% aqueous chromium trioxide solution. The resulting solution was brought just to boiling on the hot plate and then poured immediately into 250 ml. water and cooled. The product was filtered and crystallized from ethanol; yield 0.16–0.25 gram, 16–25%; m.p. 275–277°, dec.

The infrared spectrum of this compound was identical with that of psoralenequinone which was obtained from the previously described[8] oxidation of 4-amino-9-methoxypsoralene.

4,9-Dihydroxypsoralene (III). Psoralenequinone (0.2 g., 0.00093 mole), obtained by oxidation of 9-methoxypsoralene, was suspended in 50 ml. water and heated on the steam bath. This suspension was saturated with sulfur dioxide by bubbling the gas through the hot liquid for 10 min. At the end of this time, all of the material had dissolved giving the solution a light green color. Upon cooling, green crystals formed; yield, 0.2 g., 99%; m.p. 270° dec. The infrared spectrum of this compound was identical with that of 4,9 dihydroxypsoralene which was obtained by a similar reduction of psoralenequinone prepared from 4-amino-9-methoxypsoralene.

4,9-Dimethoxypsoralene (isopimpinellin). (IV). 4,9-Dihydroxypsoralene (0.35 g., 0.0016 mole), obtained by oxidation and subsequent reduction of xanthotoxin, was dissolved in 50 ml. acetone containing 0.5 g. potassium carbonate and 1 ml. (0.011 mole) dimethyl sulfate. This mixture was refluxed 2 hr. At the end of this time, 2 g. more of potassium carbonate were added, and heating was continued for 3 hr. The mixture was cooled, acidified with dilute hydrochloric acid, and diluted with water. The insoluble product was filtered and crystallized from ethanol using activated charcoal as a decolorizing agent; yield 0.10 g., 25%; m.p. 152–153°. A mixed melting point with an authentic sample of isopimpinellin was not depressed. The infrared spectra of the two samples were identical.

9-Hydroxypsoralene (xanthotoxol). 9-Methoxypsoralene (1.0 g., 0.0046 mole) was mixed intimately with 4.0 g. anhydrous aluminum chloride. The mixture was placed in a flask, protected with a calcium chloride drying tube, and heated 10 hr. in a bath, at a temperature of 140°. After cooling, the mixture was treated with 100 ml. 6*N* hydrochloric acid. The insoluble product was removed and washed with a small amount of water. The product was crystallized successively from dilute acetic acid and water; yield 0.4 g., 43%; m.p. 238–240°. A mixed melting point with an authentic sample of xanthotoxol (m.p. 242–244°) was found to be 239–240°. The infrared spectra of these two samples were identical.

2,3-Dihydro-3-methoxy-2,3,4-trichloropsoralene (VII). *A.* 9-Methoxypsoralene (1.0 g., 0.0046 mole) was dissolved in 50 ml. of chloroform. Chlorine was passed slowly through this solution for 15 min. at room temperature. The chloroform was then removed by means of a steam bath. At this point, it was possible to isolate the product by repeated crystallizations from ethanol. It was subsequently discovered, however, that the product was stable in the presence of sodium iodide. Furthermore, since treatment with this reagent greatly improved the isolation, the procedure was modified. The residue after evaporation of the chloroform was dissolved in 50 ml. acetone, and 0.5 g. sodium iodide was added with shaking. The resulting solution was kept at room temperature for 3 hr. and then filtered. Water was added to the point of cloudiness, and the solution was cooled in the deep freeze. Upon cooling, 1.0 g., 68%, of product was collected; m.p. 202–203°.

Anal. Calcd. for $C_{12}H_7O_4Cl_3$: C, 44.8; H, 2.17. Found: C, 44.6; H, 2.28. λ_{max} 240, 270, 315 mμ.

B. 4-Chloro-9-methoxypsoralene (0.2 g., 0.0008 mole) was chlorinated under the same conditions as above in 25 ml. chloroform. In this case, a pure product could be easily obtained by crystallization from ethanol; yield 0.1 g., 39%. The melting point and infrared spectrum were identical with those of the product from procedure *A*.

4-Chloro-9-methoxypsoralene (VIII). 9-Methoxypsoralene (0.5 g., 0.0023 mole) was suspended in 25 ml. ethanol and 25 ml. "Chlorex." One ml. 6*N* hydrochloric acid was added, and the mixture was heated gently on the steam bath for 1 hr. The reaction mixture was diluted with water and the insoluble product was collected and recrystallized from ethanol; yield 0.31 g., 54%; m.p. 194–195°.

A mixed melting point determination with 4-chloro-9-methoxypsoralene prepared from the amine,[2] m.p. 187–188°, was found to be 187–188°. The infrared spectra of these two samples were identical with the exception of a peak at 1510 wave numbers in the sample from the Sandmeyer reaction. This peak was shown to be caused by a trace of 9-methoxy-4-nitropsoralene. It was therefore concluded that these materials were identical except for this impurity.

4-Chloro-2,3-dihydro-9-methoxypsoralene (X). 4-Amino-2,3-dihydro-9-methoxypsoralene[2] (0.65 g., 0.0028 mole) was suspended in 20 ml. concentrated hydrochloric acid and cooled in an ice-salt mixture. Sodium nitrite (0.19 g., 0.0028 mole), dissolved in a little water, was added slowly. The mixture was allowed to stand in the cooling bath for 5 min. and was then poured slowly into a boiling solution containing 30 ml. 6*N* hydrochloric acid and 0.75 g. cuprous chloride. The insoluble product was filtered and recrystallized from ethanol; yield 0.36 g., 44%; m.p. 193–194°.

Anal. Calcd. for $C_{12}H_9O_4Cl$: C, 57.0; H, 3.54. Found: C, 56.6; H, 3.44.

9-Methoxypsoralene-4-sulfonyl chloride (XI) *and 9-methoxypsoralene-4-sulfonic acid* (XII). Two procedures were employed for the sulfonation of 9-methoxypsoralene. The first yielded largely the acid chloride; the second yielded predominantly the free sulfonic acid.

A. 9-Methoxypsoralene (0.5 g., 0.0023 mole) was treated slowly at room temperature with 5 ml. chlorosulfonic acid. The resulting solution was allowed to stand for 5 min. and then poured over 75 ml. ice. The insoluble acid chloride was collected and crystallized from a chloroform–petroleum ether mixture; yield 0.58–0.63 g., 80–87%; m.p. 154–155°.

(8) H. Thoms and E. Baetcke, *Ber.*, **45**, 3705 (1911).

Anal. Calcd. for $C_{12}H_7O_6SCl$: C, 46.0; H, 2.23. Found: 46.1; H, 2.43.

The filtrate yielded a trace of the free sulfonic acid upon evaporation before a hot air fan.

B. 9-Methoxypsoralene (1.0 g., 0.0046 mole) was dissolved in 15 ml. chloroform and cooled in an ice bath. Chlorosulfonic acid (3 ml.) was added dropwise with stirring. After standing for 5 min. in the ice bath, the temperature was allowed to rise to 20°. The chloroform solution was then poured over 75 ml. ice. After the ice had melted, more chloroform was added; whereupon the layers separated. The aqueous layer was extracted once more with chloroform. The combined chloroform extracts were taken to dryness and yielded from 0.15 to 0.25 g., 10–16%, 9-methoxypsoralene-4-sulfonyl chloride. This product was identical as judged by mixed melting point with that described in procedure *A*.

The aqueous layer upon evaporation yielded 1.3 g., 89%, of the sulfonic acid. This product was crystallized from acetic acid and dried by an azeotropic distillation of a benzene suspension. The melting point was 205° dec.

Anal. Calcd. for $C_{12}H_8O_7S \cdot H_2O$: C, 46.1; H, 3.18. Found: C, 46.7; H, 3.30.

9-Methoxypsoralene-4-sulfonic acid (XII). 9-Methoxypsoralene-4-sulfonyl chloride (0.2 g.) was suspended in 25 ml. water and refluxed 45 min. The resulting solution was evaporated before a hot air fan yielding 0.17 g., 85%, of product after crystallization from acetic acid. This material was shown by infrared data to be identical with the sulfonic acid obtained by the direct sulfonation described above.

4-Bromo-9-methoxypsoralene (XIII). 9-Methoxypsoralene-4-sulfonic acid (0.25 g., 0.00079 mole) was suspended in 50 ml. chloroform, and 0.09 ml., (0.019 mole) of bromine was added. This mixture was heated on the steam bath with stirring until solution was effected and most of the chloroform had evaporated. Petroleum ether was then added to precipitate the product. The product was dissolved in 50 ml. acetone and treated with 0.5 g. sodium iodide for 4 hr. at room temperature to remove any tribromo-derivative which might have been formed[2]. The acetone solution was filtered and diluted with water. The insoluble product was collected and crystallized from ethanol; yield 0.15 g., 64%. A mixed melting point determination and infrared comparison indicated that this material was identical to 4-bromo-9-methoxypsoralene obtained by direct bromination.[2]

9-Methoxy-4-nitropsoralene (V). 9-Methoxypsoralene-4-sulfonic acid (0.25 g.) was dissolved in 10 ml. glacial acetic acid and 10 ml. concentrated nitric acid. The resulting solution was heated 5 min. on the steam bath. It was then poured onto 50 g. ice, and the insoluble product was collected and crystallized from ethanol; yield 0.15 g., 72%. A mixed melting point determination and a comparison of infrared spectra showed that this product was identical to 9-methoxy-4-nitropsoralene obtained by direct nitration.[2]

Acknowledgment. The authors wish to thank the Paul B. Elder Co. of Bryan, Ohio, whose generous contribution of xanthotoxin made this investigation possible.

CORVALLIS, ORE.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

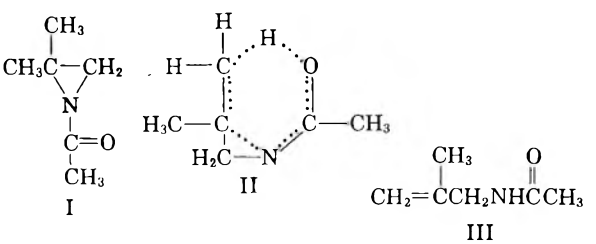
Chemistry of Ethylenimine. VI. Pyrolysis of 7-Acetyl-7-azaspiro[5.2]octane[1]

PURNENDU B. TALUKDAR[2] AND PAUL E. FANTA[3]

Received September 16, 1958

7-Acetyl-7-azaspiro[5.2]octane undergoes a pyrolytic rearrangement to give *N*-(1-cyclohexenylmethyl)acetamide. The structure of the latter compound was proven by hydrogenation, followed by hydrolysis to the known cyclohexanemethylamine. Hydrolysis of 7-azaspiro[5.2]octane in dilute sulfuric acid occurs with cleavage of the nitrogen–tertiary carbon bond.

In a previous paper in this series,[4] the pyrolytic rearrangement of 1-acetyl-2,2-dimethylethylenimine (I) to give *N*-(β-methallyl)acetamide (III) was described. Evidence was presented that the rearrangement occurs by an intramolecular mechanism similar to the Chugaev reaction, involving a cyclic transition state (II).



I II III

The present research was undertaken with the objective of further elucidating the structural and stereochemical requirements of this novel reaction. For this purpose, the structurally more rigid 7-azaspiro[5.2]octane system was investigated, as summarized in Fig. I.

7-Azaspiro[5.2]octane (V) was prepared from 1-aminocyclohexanemethanol (VIII) *via* the sulfate ester (IV) according to the conventional Wenker procedure.[5] The imine is a colorless liquid which was further characterized by the preparation of a crystalline *N*-phenylthiocarbamyl derivative.

(1) This research was aided by a grant from the Phillip Armour Foundation Cancer Fund and a grant from the American Cancer Society which provided a postdoctoral stipend for P.B.T.

(2) On study leave from the East India Pharmaceutical Works, Calcutta, India.

(3) To whom inquiries regarding this paper should be sent.

(4) P. E. Fanta and A. S. Deutsch, *J. Org. Chem.*, **23**, 72 (1958).

(5) J. S. Fruton in R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 62.

When 7-acetyl-7-azaspiro[5.2]octane (VI), obtained by the treatment of the imine with ketene, was heated at atmospheric pressure, it was rapidly converted in high yield to *N*-(1-cyclohexenylmethyl)acetamide (VII). Catalytic hydrogenation of the unsaturated amide followed by hydrolysis of the product with hydrochloric acid gave cyclohexanemethylamine (XI), which was identified by the preparation of previously reported crystalline derivatives. In concentrated sulfuric acid at room temperature, the unsaturated amide VII was cyclized to the spiro-oxazoline, 8-methyl-7-oxa-9-azaspiro[5.4]-8-decene (X).

Further evidence for the structures of VI and VII was provided by the infrared absorption spectra. The spectrum of VII had a strong band characteristic of the NH bond at 3.03 mμ which was absent in the spectrum of VI.

A concerted mechanism of the Chugaev type is acceptable for this rearrangement, since the transition state (XII) is structurally similar to the well known cholesterol 5,6-oxides (XIIIa and b)[6] and therefore is not prohibitively strained.

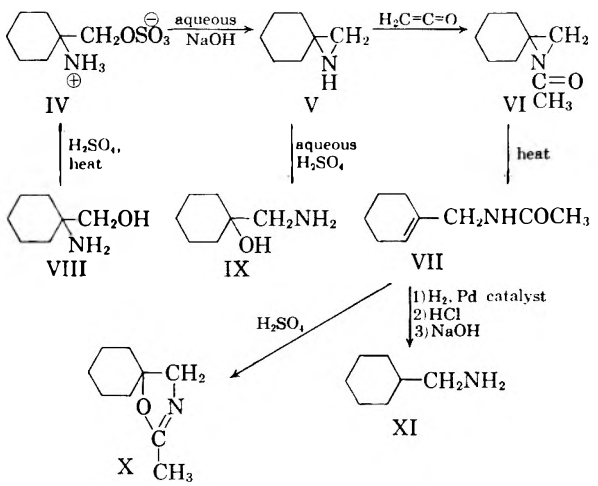
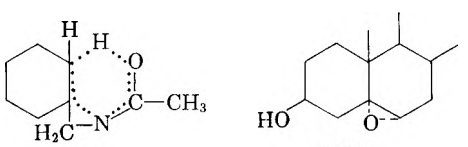
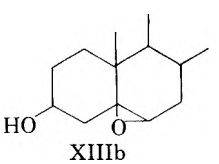


Fig. 1. Reactions in the 7-azaspiro[5.2]octane system





In view of the current interest in the application of conformational analysis to the reactions of cyclohexane derivatives, it is pertinent here to discuss the conformation of the transition state XII. The flattening of the cyclohexane ring in the spiro[5.2]octane system must be even less than in cyclohexanone,[7] therefore, the cyclohexane ring of XII may reasonably be expected to be in the chair form. The N and H atoms participating in the cyclic transition state are probably not *trans*, since this would require either an extremely strained bridging of adjacent axial substituents or the unfavorable elimination of equatorial substituents on adjacent carbon atoms. A study of the models of the two possible *cis*-conformations does not suggest which is preferred, since both conformations (axial N–equatorial H or equatorial N–axial H) would result in *cis*-elimination in accord with the well developed generalizations on the course of the Chugaev and related elimination reactions.[8]

Incidental to the main objective of this research, it was observed that hydrolysis of 7-azaspiro[5.2]-octane with dilute sulfuric acid gave 1-(aminomethyl)cyclohexanol (IX), which was isolated in the form of the crystalline *N*-phenylthiocarbamyl derivative. Under the conditions employed in the experiment, reaction was incomplete, and unreacted imine was recovered also in the form of the *N*-phenylthiocarbamyl derivative. The opening of the imine ring therefore occurred with cleavage of the nitrogen–tertiary carbon bond, as expected from the previous literature on the hydrolysis of unsymmetrical imines.[9]

EXPERIMENTAL[10]

1-Aminocyclohexanemethanol (VIII) was prepared as previously described,[11] b.p. 115–117°/25 mm., n_D^{25} 1.4963 (lit. b.p. 84°/1 mm., n_D^{25} 1.4959). Reaction of the amino alcohol with phenyl isothiocyanate gave the *N-phenylthiocarbamyl derivative*, white needles from aqueous alcohol, m.p. 141.6°.

Anal. Calcd. for $C_{14}H_{20}N_2OS$: C, 63.60; H, 7.63; N, 10.60. Found: C, 63.81; H, 7.77; N, 10.57.

1-Aminocyclohexanemethyl hydrogen sulfate (IV). A cold solution of 1.04 g. of concentrated sulfuric acid in 6 ml. of water was cautiously added to 1.29 g. of the amino alcohol, and water was slowly removed from the solution by heating it first at atmospheric pressure and finally for 15 min. at 160–170°/20 mm. A solution of the brown, solid residue in the minimum of water was treated with charcoal, filtered, and diluted with an equal volume of ethanol, giving 1.35 g. (65%) of tan solid, m.p. 256–257° dec. (uncorr.). Recrystallization from 95% ethanol gave white needles, m.p. 258–259° dec. (uncorr.).

(6) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold, New York, 1949, p. 222.

(7) W. G. Dauben and K. S. Pitzer in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, 1956, p. 39.

(8) The structural requirements for *cis* and *trans* Chugaev reactions have been discussed recently by F. G. Bordwell and P. S. Landis, *J. Am. Chem. Soc.*, **80**, 2450 (1958).

(9) V. B. Schatz and L. B. Clapp, *J. Am. Chem. Soc.*, **77**, 5113 (1955).

(10) Unless otherwise stated, melting points are corrected and boiling points are uncorrected. Analyses are by Micro-Tech Laboratories, Skokie, Ill. Infrared absorption spectra were determined in carbon tetrachloride solution between sodium chloride plates, using the Perkin-Elmer Infracord spectrophotometer.

(11) W. E. Noland, J. I. Kneller, and D. E. Rice, *J. Org. Chem.*, **22**, 695 (1957).

Anal. Calcd. for $C_7H_{15}NO_4S$: C, 40.17; H, 7.22; N, 6.69. Found: C, 40.05; H, 7.25; N, 6.60.

7-Azaspiro[5.2]octane (V).[12] A solution of sodium hydroxide (24 g.) in 30 ml. of water was added to 12 g. of the sulfate ester IV and the mixture was distilled with a small flame until the residue was nearly dry. The distillate was collected in an ice-cooled receiver containing ether and sodium hydroxide pellets. The ether solution was separated and the aqueous solution was extracted with 3 × 15 ml. portions of ether. The combined ether extracts after drying over sodium hydroxide pellets and distillation of the ether gave a pale yellow oil. Distillation of the crude product from a piece of metallic sodium gave 4.25 g. (66%) of a colorless oil with a characteristic sharp odor, b.p. 158–159°; n_D^{20} 1.4740, λ_{max} 3.07 μ (N—H band).

Anal. Calcd. for $C_7H_{13}N$: C, 75.62; H, 11.78. Found: C, 75.42; H, 11.96.

Reaction of the imine with phenyl isothiocyanate gave the *N-phenylthiocarbamyl derivative*, white lustrous plates from acetone-ligroin (30–60°) m.p. 104.7°.

Anal. Calcd. for $C_{14}H_{18}N_2S$: C, 68.25; H, 7.36; N, 11.37. Found: C, 68.36; H, 7.47; N, 11.47.

7-Acetyl-7-azaspiro[5.2]octane (VI). An excess of ketene from a modified apparatus[4] was passed through a solution of 3.7 g. of the imine V in 25 ml. of ether at room temperature. Distillation of the light yellow solution gave 3.43 g. (68%) of colorless oil, b.p. 110–112°/15 mm., $n_D^{24.5}$ 1.4760. No N—H band in the infrared absorption spectrum.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.54; H, 9.87; N, 9.14. Found: C, 70.04; H, 10.13; N, 9.27.

Further distillation of the residue from this preparation gave 700 mg. (14%) of a pale yellow liquid which was identified as the rearrangement product VII by determination of the infrared absorption spectrum.

Pyrolysis of VI to form N-(1-cyclohexenylmethyl)acetamide (VII). The acetyl imine VI (2.5 g.) was gradually heated in a Claisen flask provided with a thermometer immersed in the liquid. At about 155° an exothermic reaction occurred with a concomitant rise in temperature to 230°, where it remained for a few minutes. Further heating at 210° for 15 min., followed by a vacuum distillation yielded 2.26 g. (90%) of light yellow, viscous liquid, b.p. 166–168°/16 mm., n_D^{24} 1.5000, λ_{max} 3.03 μ (N—H band).

Anal. Calcd. for $C_9H_{15}NO$: C, 70.54; H, 9.87. Found: C, 70.14; H, 9.64.

Spiro-oxazoline, X. Concentrated sulfuric acid (5 ml.) was added slowly with cooling and swirling to 3 g. of the amide VII while the temperature was kept below 40°. After 10 min. at room temperature, crushed ice was added to the red solution, followed by an excess of sodium hydroxide. An oil separated which was extracted with 3 × 10 ml. portions of ether. The ether solution was dried over sodium hydroxide pellets and distilled, giving 1.7 g. (57%) of colorless, mobile oil, b.p. 88–89°/16 ml., $n_D^{24.5}$ 1.4690. No N—H band in the infrared.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.54; H, 9.87. Found: C, 70.34; H, 9.89.

The oxazoline formed a *picrate*, yellow needles from ethyl acetate, m.p. 188.8°.

Anal. Calcd. for $C_{15}H_{18}N_4O_8$: C, 47.12; H, 4.75. Found: C, 47.19; H, 4.80.

Hydrogenation of VII *and hydrolysis of the resulting product to cyclohexanemethylamine* XI. A solution of 1.0 g. of VII in 20 ml. of absolute ethanol was subjected to hydrogenation at atmospheric pressure with the aid of 200 mg. of 10% palladized charcoal catalyst. In the course of 40 min., the calculated amount of hydrogen (165 ml.) was absorbed and further treatment caused no more uptake of hydrogen. After removal of the catalyst, distillation gave an almost quantitative yield of colorless oil, b.p. 165–166°/17 mm., $n_D^{24.5}$ 1.4800, which was refluxed for 4 hr. with 10 ml. of 6*N* hydrochloric acid. The solution was evaporated to dryness and the white, solid residue was washed with dry ether, dissolved in a small amount of water, and made weakly alkaline by the addition of aqueous sodium hydroxide. The aqueous solution was used for the preparation of two previously reported[13] solid derivatives of cyclohexanemethylamine: the *N*-benzoyl derivative, white needles from aqueous ethanol, m.p. 106.4° (lit. 105–106°) and the *N*-phenylthiocarbamyl derivative, white plates from acetone-ligroin (30–60°), m.p. 128.4–129.4° (lit. 128–129°).

1-(Aminomethyl)cyclohexanol (IX) was prepared as previously described[14] and further characterized by the formation of the picrate, m.p. 168–169° (lit. 168–170°). Treatment of the amino alcohol with phenyl isothiocyanate gave an authentic sample of the *N-phenylthiocarbamyl derivative*, m.p. 134.5–135°, from acetone-ligroin (30–60°).

Anal. Calcd. for $C_{14}N_{20}N_2OS$: C, 63.60; H, 7.62; N, 10.59. Found: C, 63.80; H, 7.77; N, 10.57.

Hydrolysis of 7-azaspiro[5.2]octane with aqueous sulfuric acid. A solution of 500 mg. of the imine V in 10 ml. of 1*M* sulfuric acid was heated on a steam bath for 2 hr. The solution was neutralized with dilute aqueous sodium hydroxide and extracted with chloroform. The chloroform extract was dried and evaporated and the residue was treated with phenyl isothiocyanate. The product obtained was twice recrystallized from acetone-ligroin and shown by m.p. (103–104°) and mixed m.p. to be the *N*-phenylthiocarbamyl derivative of the imine V.

The aqueous solution after the chloroform extraction was made weakly alkaline and shaken with a few drops of phenyl isothiocyanate for a few minutes. Extraction with chloroform followed by evaporation of the chloroform and recrystallization of the residue from aqueous alcohol gave a crystalline solid, m.p. 133.1–134.1°, undepressed on mixing with the authentic *N*-phenylthiocarbamyl derivative of amino alcohol IX.

CHICAGO 16, ILL.

(12) C. Schuster, German Patent **871,149** (Feb. 23, 1951) claimed the preparation of this imine, b.p. 53–55°/8 mm. in 25% yield by passing the amino alcohol VIII over hot alumina.

(13) R. A. Benkeser, C. Arnold, R. F. Lambert, and O. H. Thomas, *J. Am. Chem. Soc.*, **77**, 6042 (1955).

(14) H. J. Dauben, H. J. Ringold, R. H. Wade, and A. G. Anderson, *J. Am. Chem. Soc.*, **73**, 2359 (9151).

[CONTRIBUTION FROM THE DIVISION OF PHYSICAL SCIENCES, UNIVERSITY OF CALIFORNIA AT RIVERSIDE]

Optically Active Butane-2-*d*. III. Verification of Configuration by Elimination Reactions[1]

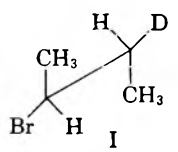
G. K. HELMKAMP AND N. SCHNAUTZ

Received September 5, 1958

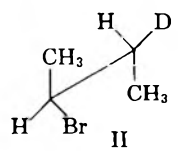
In the reaction sequence 2,3-epoxybutane → 2-butanol → 2-bromobutane → butane, a deuterium atom can be introduced stereospecifically at the first or last step by means of reduction with lithium aluminum deuteride. The anticipated inversion which should accompany these two steps has been further verified by the behavior of both *erythro*- and *threo*-2-bromobutane-3-*d* in a typical *trans*-elimination reaction. The *trans*/*cis* ratio of products from the dehydrobromination of halides were: *threo*-deuterohalide from active epoxide, 5.3; *erythro*-deuterohalide from meso epoxide, 1.2; undeuterated 2-bromobutane, 3.1. Mass spectral data are given for reaction products. Samples of monodeuterobutenes were prepared by three independent methods.

It has been demonstrated[2] that the lithium aluminum deuteride reduction of 2-bromobutane, 2,3-epoxybutane, and 2-methanesulfonoxybutane all show the same stereochemical result, namely, inversion of configuration if analogy is drawn to a comparable opening of bicyclic epoxides.[3] Each reduction can lead directly or indirectly to optically active butane-2-*d* which exhibits a sign of rotation of the plane of polarized light in agreement with that calculated for this simplest monodeuteroalkane.[4] However, further confirmation of the configuration of butane-2-*d* has been obtained here by the observation of the distribution of isomeric butenes resulting from elimination reactions of 2-bromobutane-3-*d*. Thus the levorotatory butane-2-*d* has the D configuration.

Two enantiomorphic monodeuterated 2-bromobutane derivatives were prepared from *meso*- and D-2,3-epoxybutane by reduction to 2-butanol-3-*d* with lithium aluminum deuteride followed by conversion to 2-bromobutane-3-*d* with PBr_3.[5] With inversion accompanying each reaction the products were respectively the *dl-erythro* (I) and *threo* (II) isomers. The *dl*-isomers of both I and II were obtained by Skell[6] in a study of addition reactions, and, as in this instance, the structure determination was based on elimination reactions comparable to those applied by Curtin and Kellom[7] to diastereomeric forms of 1,2-diphenylethanol-2-*d*.



I



II

Elimination reactions. The elimination of hydrogen bromide from 2-bromobutane with alcoholic potassium hydroxide under conditions favorable for an E_2 reaction leads to a mixture of 1-butene and *cis*- and *trans*-2-butene. If the halide contained a deuterium atom situated *trans* with respect to the bromine atom, as in I, an elimination reaction under identical conditions should lead to a product containing a smaller percentage of the *trans*-isomer because of the higher energy requirements in the transition state in which the C-D bond is broken. Also, in the absence of isomerization during or after the reaction, the *trans*-isomer should be free of deuterium. Conversely, the *threo*-isomer, II, should give a higher percentage of *trans*-2-butene and this should retain deuterium.

The results of elimination reactions carried out in 17.5% ethanolic potassium hydroxide at 65° are given in Table I. In each instance the distribution of isomers indicated an isotope effect which was in accord with a pattern of inversion during epoxide opening. Under the conditions of the reaction, no isomerization of butenes was found to occur.

TABLE I

PRODUCTS OF ELIMINATION REACTIONS OF 2-BROMOBUTANE AND DEUTERATED 2-BROMOBUTANES WITH 17.5% ETHANOLIC KOH

Isomer	Butene Distributions, % 1-	*cis*- 2-	*trans*- 2-	*trans*/*cis* Ratio
2-Bromobutane	23	19	58	3.1
erythro-2-Bromobutane-3-*d* (I)	35	29	36	1.2
threo-2-Bromobutane-3-*d* (II)	24	12	64	5.3

(1) This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund.

(2) G. K. Helmkamp and B. F. Rickborn, *J. Org. Chem.*, 22, 479 (1957).

(3) L. W. Trevoy and W. G. Brown, *J. Am. Chem. Soc.*, 71, 1675 (1949).

(4) W. Fickett, *J. Am. Chem. Soc.*, 74, 4204 (1952).

(5) G. K. Helmkamp, C. D. Joel, and H. Sharman, *J. Org. Chem.*, 21, 844 (1956).

(6) P. S. Skell and R. G. Allen, from abstracts of papers presented at the September 1958 meeting of the American Chemical Society at Chicago, Ill.

(7) D. Y. Curtin and D. B. Kellom, *J. Am. Chem. Soc.*, 75, 6011 (1953).

The component fractions of products of all elimination reactions were isolated by gas chromatographic methods for mass spectra determinations. In instances where deuterium should have been retained, such as the *cis*-2-butene from the *erythro*-isomer or the *trans*-2-butene from the *threo*-isomer, a major change was observed in the mass spectral pattern in the *m/e* region corresponding to 41 and 40 for undeuterated 2-butene. The 40/41 relative peak intensity for *trans*-2-butene was about 0.06 but the corresponding 41/42 ratio for deuterated analogs was never below 0.58. Several of these intensity values, along with those from the products of 2-bromobutane-2-*d*, III, are given in Table II.

TABLE II

RELATIVE PEAK INTENSITIES FOR MASS SPECTRA OF PRODUCTS OF ELIMINATION REACTIONS

Isomer and Source	Relative Peak Intensities[a]	
	41/42	40/41
cis, I	0.58	
trans, I		0.09
cis, II		0.20
trans, II	0.68	
cis, III	0.60	
trans, III	0.54	

[a] Consolidated Mass Spectrometer Model 21-620, ionizing current 20 microamperes.

The high 41/42 ratios can be accounted for by assuming isomerization, contamination with undeuterated alkene, or hydrogen migration in the mass spectrometer. The first was eliminated because neither *cis*-nor *trans*-2-butene showed measureable isomerization under the conditions of the reaction. The second and third could not be distinguished completely from one another, but deuterobutenes were prepared by independent methods for comparison of spectra.

The synthesis of a stereospecific isomer of 2-butene-2-*d* was carried out by two methods other than through the elimination reactions of deuterohalides.

The successive treatment of *cis*-2-bromo-2-butene with lithium metal (in ethyl ether) and D_2O according to the method of Curtin and Crump,[8] yielded a mixture of *cis*- and *trans*-2-butene-2-*d* (predominately *cis*) free of more than a trace of 1-butene. The 41/42 ratio of peak intensities was 0.56 for the total sample, and slightly higher for chromatographed samples.

The tiglic acid procedure for the preparation of *trans*-2-butene[9,10] applied to the synthesis of *trans*-2-butene-2-*d* yielded a product which contained no 1-butene and less than 0.5% *cis*-2-butene. The 41/42 ratio was 0.48 ,the lowest value encountered for any monodeuterobutene. Infrared analysis indicated less than 2% *trans*-2-butene was present, and the strong 960 cm.$^{-1}$ band was replaced by another strong band at about 875 cm.$^{-1}$

Although further work is being carried out on the mass and infrared spectra of deuterated butenes and precise analyses of deuterium contents will be deferred, a tentative assignment of deuterium content of isomers, based on the assumption of 98% isomeric purity of the tiglic acid butene, is given in Table III.

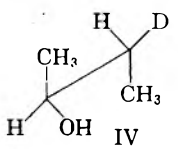
TABLE III

DEUTERIUM CONTENT OF VARIOUS ISOMERS OF 2-BUTENE FRACTION OF MOLECULES CONTAINING D

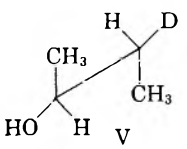
Sample Source	*cis*	*trans*
Dehydrobromination of I	0.90	0.14
Dehydrobromination of II	0.43	0.86
Dehydrobromination of III	0.90	0.95
Vinyl lithium procedure	0.94	0.93
Tiglic acid procedure		0.98[a]

[a] Determined from infrared spectrum; all others from mass spectra based on this isomer.

Since the deuteroalcohols, IV and V, showed 0.95 atom of deuterium per molecule, the lower deuterium contents of the *cis*-2-butene from I or the *trans*-2-butene from II indicate that racemization had



IV



V

taken place in the reaction sequence from epoxide to halide. In the case of the optically active series (involving deuterohalide II) this racemization could account for only a small part of the discrepancy in optical rotatory power between calculated[4] and experimental[5] values.

Vapor phase dehydrohalogenation over calcium oxide. Samples of various 2-bromobutanes were passed over calcium oxide at elevated temperatures during the search for an elimination reaction which would yield stereospecific isomers with complete loss or retention of deuterium. This reaction yielded predominately *cis*-2-butene when carried out just above the minimum temperature for reaction, and as the temperature increased the *cis-trans* ratio dropped. These ratios, given in Table IV, are due in part to an increased rate of isomerization at elevated temperatures. Also, the ratios were dependent on the length of time a packing was in use.

In the reaction of a series of compounds including 2-bromobutane, *erythro*-2-bromobutane-3-*d*, and *threo*-2-bromobutane-3-*d*, the respective ratios of 1-butene/*cis*-2-butene/*trans*-2-butene at 200° were 11/56/33, 17/51/32 and 21/40/39. Deuterium

(8) D. Y. Curtin and J. W. Crump, *J. Am. Chem. Soc.*, **80**, 1922 (1958).

(9) J. Wislicenus, H. P. Talbot, and M. Henze, *Ann.*, **313**, 228 (1900).

(10) W. G. Young, R. T. Dillon, and H. J. Lucas, *J. Am. Chem. Soc.*, **51**, 2528 (1929).

TABLE IV

EFFECT OF TEMPERATURE ON VAPOR PHASE DEHYDROHALOGENATION OF 2-BROMOBUTANE OVER CALCIUM OXIDE

T, °C.	Composition of Products, %		
	1-Butene	*cis*-2-Butene	*trans*-2-Butene
150	11	61	28
200	13	50	37
250	16	45	39
300	18	42	41

analyses on the products are given in Table V. It is of interest to note that the *threo*-isomer showed the major isotope effect and the deuterium retention was lowest. Although this might be a *cis*-elimination the equal distribution of deuterium between *cis*- and *trans*-2-butenes rules out any straightforward interpretation. Hydride shifts must be involved because the 1-butene from the *threo*, deuterohalide contained only 60% as much deuterium as that obtained through dehydrobromination with alcoholic potassium hydroxide. The 1-butene from the *erythro*-isomer contained 90% of the maximum observed deuterium.

TABLE V

DEUTERIUM CONTENTS OF PRODUCTS OF CALCIUM OXIDE DEHYDROBROMINATION REACTIONS AT 200°

Butene and Source	Deuterium Retention, %
cis, From I (*erythro*)	62
trans, From I	63
cis, From II (*threo*)	51
trans, From II	51

EXPERIMENTAL

D(−)-*2,3-Butanediol* was prepared from the fermentation of "Karo" corn syrup by *Aerobacillus polymyxa*[11] by a method adapted from that of Rose and King.[12] The observed rotation of the diol, α_D^{25} −12.90° (lit.,[13] α_D^{29} −13.08°), was somewhat lower than previous values because no attempt was made to remove the last traces of water from the compound. The criterion of optical purity was the L-2-butanol prepared according to the method of Leroux and Lucas[14]; $[\alpha]_D^{25}$ −13.50° (lit.,[14] −13.51°).

D(+)-*2,3-Epoxybutane*, D(−)-*erythro-3-butanol-2-d*, L(+)-*threo-3-bromobutane-2-d*. These compounds were products from previously reported syntheses.[5] The deuterobutanol contained 0.95 atom of deuterium per molecule.

meso-2,3-Epoxybutane, DL-*threo-3-butanol-2-d*, DL-*erythro-3-bromobutane-2-d*. This series of compounds was prepared from recrystallized *meso*-2,3-butanediol, m.p. 33.5–34.0°, by the same sequence of reactions used for the active isomers.[5]

2-Butanol-2-d. This was prepared according to the procedure given for 2-propanol-2-*d*[16]; b.p. 98–99° (740 mm.); n_D^{25} 1.3944.

2-Bromobutane-2-d. The PBr_3 method for other deuterohalide syntheses[5] was used to prepare this from the alcohol: b.p. 89.5–90.0°; n_D^{25} 1.4335.

cis-2-Butene-2-d via the organolithium reagent. With the exception of the reduction step, this reaction sequence is analogous to that used by Hoff, Greenlee, and Boord[16] for the quantitative inversion of the configuration about the carbon-carbon double bond in normal alkenes. *trans*-2-Butene was converted to the dibromide with Br_2 in CCl_4 at −5°[10] and the product was dehydrobrominated with 10 molar KOH in ethylene glycol at 150°: crude yield from butene, 93%. Fractional distillation yielded 2-bromo-2-butene: b.p. 90.6–91.6° (737 mm.); $n_D^{19.3}$ 1.4631 (lit.,[17] for *cis*-isomer: b.p. 93.9°; $n_D^{19.2}$ 1.4631). The lithium derivative was prepared from 13.5 g. (0.10 mole) of halide and 1.4 g. (0.20 g. atom) of lithium in 50 ml. of ether according to the method of Curtin and Crump.[8] The gases formed on addition of D_2O were fractionally distilled through a 25 cm. helices column; b.p. 0° ± 0.5° (735 mm.); yield 3.3 g., 58%.

Ethanol-1,1-d_2. A 3-neck, one-liter flask equipped with a mechanical stirrer, Friedrichs condenser, and dropping funnel was flame-dried and flushed with dry nitrogen. After the addition of 10 g. (0.24 mole) of lithium aluminum deuteride, about 300 ml. of ether was distilled into the apparatus from a 500-ml. flask containing lithium aluminum hydride. Over a period of 2 hr., 40 g. (0.183 mole) of triacetin in 60 ml. of dry ether was added; then the mixture was refluxed for 2 hr. and allowed to stand overnight. This was hydrolyzed with dilute sulfuric acid, dried with K_2CO_3, and distilled. The fraction boiling from 75–80° was collected. This contained 21.7 g. (0.45 mole, 82%) of ethanol-1,1-d_2, calculated from the refractive index. No further purification was made.

Ethanal-1-d. The procedure for oxidation of ethanol as described by Wertheim[18] was modified by omission of nitric acid from the oxidizing mixture. When nitric acid was present the ethanal contained a contaminant which inhibited initiation of the subsequent Reformatsky reaction. The ethanal-1-*d*-was collected in benzene then dried over $MgSO_4$. This dry solution was used directly in the Reformatsky reaction. The yields in preliminary runs using ethanol were 40–50%.

Ethyl 2-methyl-3-hydroxybutanoate-3-d and ethyl 2-methyl-3-acetoxybutanoate-3-d. Using a general Reformatsky reaction as described in "Organic Reactions,"[19] the deuteroester was prepared from 16.7 g. (0.26 g. atoms) mossy zinc, 7.3 g. (0.16 mole) ethanal-1-*d*, and 36 g. (0.20 mole) ethyl 2-bromopropanoate. The hydroxyester was not isolated but was converted directly into the acetoxyester with ketene: b.p. 84° (10 mm.); yield 20.4 g., 60% from ethanal-1-*d* (lit.[20] b.p. 97.5° at 15 mm.).

Tiglic acid-3-d. Pyrolysis of ethyl 2-methyl-3-acetoxybutanoate-3-*d* at 500°[21] yielded a mixture of methylbutenoic acids with a major portion unconjugated according to infrared spectra: b.p. 88–91° (14 mm.); yield 3.3 g., 34%. This mixture was refluxed for 5 hr. with 4 g. NaOH in 20 ml. of water-ethanol. The reaction mixture was acidified

(11) The authors are indebted to Dr. R. W. Watson of the National Research Council of Canada for a culture of N.R.C. No. 42 (3) *Bacillus polymyxa*.

(12) D. Rose and W. S. King, *Can. J. Research*, **23F**, 78 (1945).

(13) A. C. Neish, *Can. J. Research*, 23B, 10 (1945).

(14) P. J. Leroux and H. J. Lucas, *J. Am. Chem. Soc.*, **73**, 41 (1951).

(15) A. Leo and F. H. Westheimer, *J. Am. Chem. Soc.*, **74**, 4383 (1952).

(16) M. C. Hoff, K. W. Greenlee, and C. E. Boord, *J. Am. Chem. Soc.*, **73**, 3329 (1951).

(17) M. Lepingle, *Bull. soc. chim.*, **39**, 741 (1926).

(18) E. Wertheim, *J. Am. Chem. Soc.*, **44**, 2658 (1922).

(19) R. L. Shriner, "*Organic Reactions*," Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 16.

(20) E. Blaise and I. Herman, *Ann. chim. et phys.*, **20**, 190 (1910).

(21) W. J. Bailey and C. King, *J. Am. Chem. Soc.*, **77**, 75 (1955).

and the organic material was extracted with ether, dried, and distilled. This isomerization yielded some angelic acid but principally tiglic acid: b.p. 195–200°; m.p. 62–64° (lit., b.p. 198.5°[22]; m.p. 63.5–64.0°[10]).

trans-2-Butene-2-d. Tiglic acid-3-*d* was converted to the alkene by the method of Young, Dillon, and Lucas.[10] The tiglic acid hydriodide intermediate melted at 86–87.5° (lit.,[10] 86.2–86.3°). Treatment of the hydriodide with aqueous sodium carbonate at 75° yielded *trans*-2-butene-2-*d* in 67% yield. The product was at least 99.5% pure according to chromatographic analysis. The major contaminant was a trace of *cis*-2-butene-2-*d*.

(22) R. Fittig and H. Kopp, *Ann.*, 195, 81 (1879).

RIVERSIDE, CALIF.

[CONTRIBUTION FROM THE MONSANTO CHEMICAL CO., PLASTICS DIVISION]

Mechanism of the Michaelis-Arbuzov Reaction: Olefin Formation

ALBERT Y. GARNER, EARL C. CHAPIN, AND PATRICIA M. SCANLON

Received October 7, 1958

Support is given for the mechanism of the Michaelis-Arbuzov reaction in terms of the formation of a quasiphosphonium salt intermediate. The production of olefin and dialkyl phosphonate, $(RO)_2\overset{\overset{O}{\uparrow}}{P}—H$, is shown to be a general phenomenon when an *alpha*-haloalkane which has an activating group on the *beta* carbon is treated with a trialkyl phosphite. The formation of these products is explained in terms of an intramolecular *beta*-elimination involving the quasiphosphonium salt intermediate.

Introduction. During the preparation of diethyl β-bromoethylphosphonate (I) by the Michaelis-Arbuzov Reaction (1) using triethyl phosphite and 1,2-dibromoethane (2), it was found through the use of infrared spectroscopy and vapor phase chromatography that diethyl vinylphosphonate (V) and diethyl phosphonate (VI) are formed. In addition, diethyl β-bromoethylphosphonate (I), diethyl ethylphosphonate (II), ethyl bromide (III), and tetraethyl ethylenediphosphonate (IV) are found as reported previously by Ford-Moore and Williams[1a] and Kosolapoff.[1b] The most obvious explanation for the formation of these products is that the tetraethyl ethylenediphosphonate (IV) decomposes under the conditions of the reaction. This decomposition, however, has been shown not to take place. The diphosphonate (IV) is stable at 211° over a period of 5 hr., and the initial reaction was run at 150° to 170°.

$$R'X + (RO)_3P \longrightarrow R'—\overset{\overset{O}{\uparrow}}{P}—(OR)_2 + RX \quad (1)$$

$$Br—CH_2—CH_2—Br + (C_2H_5O)_3P \longrightarrow$$

$$Br—CH_2—CH_2—\overset{\overset{O}{\uparrow}}{P}—(OC_2H_5)_2 + \underset{(I)}{}$$

$$C_2H_5—\overset{\overset{O}{\uparrow}}{P}—(OC_2H_5)_2 + C_2H_5Br +$$
$$(II) \qquad (III)$$

$$(C_2H_5O)_2—\overset{\overset{O}{\uparrow}}{P}—CH_2—CH_2—\overset{\overset{O}{\uparrow}}{P}—(OC_2H_5)_2 \quad (2)$$
$$(IV)$$

$$(C_2H_5O)_2—\overset{\overset{O}{\uparrow}}{P}—CH_2—CH_2—\overset{\overset{O}{\uparrow}}{P}—(OC_2H_5)_2 \xrightarrow[211°]{} \quad (3)$$

$$(C_2H_5O)_2—\overset{\overset{O}{\uparrow}}{P}CH=CH_2 + (C_2H_5O)_2—\overset{\overset{O}{\uparrow}}{P}—H$$
$$(V) \qquad (VI)$$

The following reactions were run to determine the generality of this reaction as an olefin-forming

$$(C_2H_5O)_3P + Br—CH_2—CH_2—\overset{\overset{O}{\uparrow}}{P}—(OC_2H_5)_2 \longrightarrow$$
$$(I)$$

$$C_2H_5—\overset{\overset{O}{\uparrow}}{P}—(OC_2H_5)_2 + C_2H_5Br +$$
$$(II) \qquad (III)$$

$$(C_2H_5O)_2—\overset{\overset{O}{\uparrow}}{P}—CH_2—CH_2—\overset{\overset{O}{\uparrow}}{P}—(OC_2H_5)_2 +$$
$$(IV)$$

$$CH_2=CH—\overset{\overset{O}{\uparrow}}{P}—(OC_2H_5)_2 + H—\overset{\overset{O}{\uparrow}}{P}—(OC_2H_5)_2 \quad (4)$$
$$(V) \qquad (VI)$$

$$(C_2H_5O)_3P + Br—CH_2—CH_2—\overset{\overset{O}{\parallel}}{C}—OC_2H_5 \longrightarrow$$

$$C_2H_5—\overset{\overset{O}{\uparrow}}{P}—(OC_2H_5)_2 + C_2H_5Br +$$
$$(II) \qquad (III)$$

$$(C_2H_5O)_2—\overset{\overset{O}{\uparrow}}{P}—CH_2—CH_2—\overset{\overset{O}{\parallel}}{C}—OC_2H_5 + H—\overset{\overset{O}{\uparrow}}{P}—(OC_2H_5)_2$$
$$(VII) \qquad (VI)$$

$$+ CH_2=CH—\overset{\overset{O}{\parallel}}{C}—OC_2H_5 + \text{polyethyl acrylate} \quad (5)$$
$$(VIII)$$

(1) (a) A. H. Ford-Moore and J. W. Williams, *J. Chem. Soc.*, 1467 (1945). (b) G. M. Kosolapoff, *J. Am. Chem. Soc.*, 66, 109 (1944).

$$(C_2H_5O)_3P + Br{-}CH_2{-}CH_2{-}C_6H_5 \longrightarrow$$

$$C_2H_5{-}\overset{\uparrow}{\underset{O}{P}}{-}(OC_2H_5)_2 + C_2H_5Br +$$

(II) (III)

$$C_6H_5{-}CH_2{-}CH_2{-}\overset{\uparrow}{\underset{O}{P}}{-}(OC_2H_5)_2 +$$

(IX)

$$H{-}\overset{\uparrow}{\underset{O}{P}}{-}(OC_2H_5)_2 + C_6H_5CH{=}CH_2 \quad (6)$$

(VI) (X)

elimination reaction. In each case the products were as written. The major products were the expected Michaelis-Arbuzov products with the olefin and dialkyl phosphonate appearing to be products of a less favorable side reaction. Reaction (5) has been reported previously by McConnell and Coover,[2a] but the only products mentioned were III and VII. Likewise, Abramov and Pall[2b] do not report VI and VIII as products of this reaction. A further search of the literature yielded several references[3] to Michaelis-Arbuzov reactions involving α-haloalkanes containing an activating group on the β-carbon. These authors report olefin, dialkyl phosphonate, or both such products.

Discussion. The formation of olefin and dialkyl phosphonate can be explained through two mechanisms. The first of these mechanisms involves an ordinary base-catalyzed β-elimination with the trialkyl phosphite functioning as the base. Step

$$(RO)_3P: + X{-}CH_2{-}CH_2{-}R' \longrightarrow (RO)_3\overset{\oplus}{P}H + X{-}CH_2{-}\overset{\ominus}{C}H{-}R' \quad (1)$$

$$X{-}CH_2{-}\overset{\ominus}{C}H{-}R' \longrightarrow CH_2{=}CH{-}R' + X^{\ominus} \quad (2)$$

$$X^{\ominus} + (RO)_3\overset{\oplus}{P}H \longrightarrow (RO)_2{-}\overset{\uparrow}{\underset{O}{P}}{-}H + RX \quad (3)$$

(3) involves nucleophilic attack by halide ion on the alkyl carbon which is consistent with the last step of the Michaelis-Arbuzov reaction as pictured below. This mechanism, however, is unlikely in view of the relative weakness of trialkyl phosphites as bases compared with the bases usually used in β-eliminations, the high temperatures needed to make this reaction go and the well known nucleophilicity of phosphites.

(2) (a) R. L. McConnell and H. W. Coover, *J. Am. Chem. Soc.*, **78**, 4453 (1956). (b) V. S. Abramov and S. Pall, *Trudy Kazan. Khim. Teknol. Inst. im S. M. Kirova*, **23**, 105 (1957); *Chem. Abstr.*, **52**, 9949d (1958).

(3) (a) A. N. Podovik and N. P. Denisova, *Sbornik Statei Obshchei Khim. Akad. Nauk S.S.S.R., I*, 388 (1953); *Chem. Abstr.*, **49**, 8386 (1955). (b) B. A. Arbuzov and B. P. Lugovkin, *Zhur. Obshchei Khim.*, **21**, 99 (1951); *Chem. Abstr.*, **45**, 7002 (1951). (c) V. S. Abramov and N. A. Ilina, *Zhur. Obshchei Khim.*, **26**, 2014 (1956); *Chem. Abstr.*, **51**, 1822 (1957). (d) G. Kamai and V. A. Kukhtin, *Trudy Kazan. Khim. Tekhnol. Inst. im. S. M. Kirova*, No. 21, 147 (1956); *Chem. Abstr.*, **51**, 11983 (1957). (e) V. S. Abramov and N. A. Ilyina, *J. Gen. Chem., U.S.S.R.*, **26**, 2245 (1956).

Before discussing the second mechanism, a brief but pertinent review of the mechanism of the Michaelis-Arbuzov reaction must be given. The reaction was discovered first by Michaelis and Kähne[4] and was explored rather thoroughly later by Arbuzov.[5] These authors proposed a mechanism (4) which involves an addition reaction to form a quasiphosphonium intermediate which subsequently decomposes into the products. Myers, Preis, and Jensen[6] present the low reactivity of cyclohexyl tosylate with triethyl phosphite as being in accord with the low reactivity of cyclohexyl halides in SN_2 reactions and thus substantiating the initial stage of the Michaelis-Arbuzov reaction as an SN_2 displacement. Although Michaelis and

$$RO{-}P\!\!\left\langle \right. + R'X \longrightarrow (R'{-}\overset{\oplus}{P}{-}OR)(X^{\ominus}) \longrightarrow R'{-}\overset{\uparrow}{\underset{O}{P}}\!\!\left\langle \right. + RX \quad (4)$$

Kähne[4] isolated an intermediate from triphenyl phosphite and methyl iodide which had saltlike properties, Abramov and Pekhman[7a] and Abramov and Karp[7b,c] obtained sirups from trialkyl phosphites and α-,β-dihaloalkyl ethers. Smith and Burger[7d] conclude that no quasiphosphonium compound is involved when bulky secondary alkyl halides are used. Arbuzov and Sazonova[8a] have recently isolated several more of these intermediates using triaryl phosphites and alkyl iodides. These compounds are crystalline salts. Similarly, Razumov and Bankovskaya[8b] report the isolation of saltlike intermediates from the reaction between alkyl phosphinites, $R_2{-}P{-}OR'$, and alkyl halides, Dimroth and Nurrenback[8c] report the isolation of several quasiphosphonium salts from the reaction of carbonium ions and trialkyl phosphites. Physico chemical evidence for the existence of these intermediates is presented by Arbuzov and Fuzhenkova.[9a,b]

The over-all mechanism of the Michaelis-Arbuzov reaction has been described by Jacobsen, Harvey,

(4) A. Michaelis and R. Kähne, *Ber.*, **31**, 1048 (1898).

(5) A. E. Arbuzov, *J. Russ. Phys. Chem. Soc.*, **38**, 687 (1906).

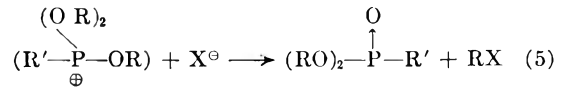
(6) T. C. Myers, S. Preis, and E. V. Jensen, *J. Am. Chem. Soc.*, **76**, 4172 (1954).

(7) V. S. Abramov and A. P. Pekhman, *J. Gen. Chem., U.S.S.R.*, **26**, #1, 171 (1956). (b) V. S. Abramov and G. A. Karp, *Doklady Akad. Nauk S.S.S.R.*, **91**, 1095 (1953); *Chem. Abstr.*, **48**, 9906g (1954). (c) V. S. Abramov and G. A. Karp, *J. Gen. Chem.*, **24**, 1823 (1954). (d) B. E. Smith and A. Burger, *J. Am. Chem. Soc.*, **75**, 5891 (1955).

(8) (a) A. E. Arbuzov and N. N. Sazonova, *Doklady Akad. Nauk S.S.S.R.*, **115**, 1119 (1957); *Chem. Abstr.*, **52**, 6239f (1958). (b) A. I. Razumov and N. N. Bankovskaya, *Doklady Akad. Nauk S.S.S.R.*, **116**, 2411 (1957); *Chem. Abstr.*, **52**, 6164i (1958). (c) K. Dimroth and A. Nurrenback, *Angew. Chem.*, **70**, 26 (1958).

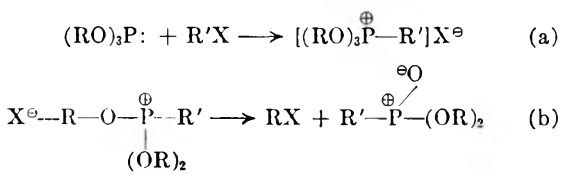
(9) (a) B. A. Arbuzov and A. V. Fuzhenkova, *Doklady Akad. Nauk. S.S.S.R.*, **113**, 1269 (1957). (b) B. A. Arbuzov and A. V. Fuzhenkova, *Doklady Akad. Nauk S.S.S.R.*, **114**, 89 (1957).

and Jensen[10a] and by Kharasch and Bengelsdorf[10b] and pictured by Saunders[11] as a displacement of halogen by phosphite to form a quasiphosphonium compound which, on attack by halide ion, eliminates RX to form the phosphonate (5). That the



(5)

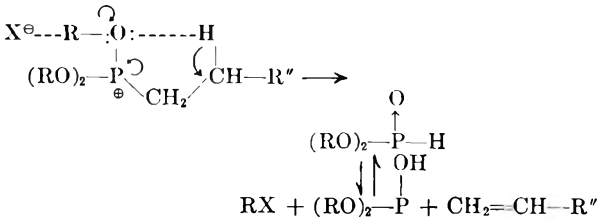
final stage of the reaction involves nucleophilic attack by halide ion on the alkyl carbon of the ester has been demonstrated experimentally. First, Landauer and Rydon[12] isolated the intermediate from methyl iodide and triphenyl phosphite and treated this material with optically active 2-octanol. The 2-iodooctane which was obtained as a product was inverted showing clearly that a bimolecular nucleophilic substitution had taken place, presumably preceded by a rapid ester interchange between the octanol and the phosphonium salt. Attacking the problem in the reverse manner, Gerrard and Jeacocke[13] reacted trioctyl phosphite containing 2-octyl residues from optically active 2-octanol with bromine and likewise obtained the inverted 2-bromooctane. On the basis of the above experimental evidence, the mechanism of the Michaelis-Arbuzov reaction can be pictured as follows:



(a)

(b)

In the case under discussion where the alkyl halide has an activating group on the β-carbon atom, the quasiphosphonium intermediate can be pictured as going through a less favorable breakdown involving a cyclic transition state which leads to an intramolecular β-elimination similar to that proposed for ester pyrolysis and Chugaev eliminations.[14]



The formation of styrene during the thermal decomposition of quarternary phosphonium hydroxides and ethoxides which contained β-phenethyl groups has been shown by Fenton and Ingold[15] and Hey and Ingold.[16] Further, the hydrogen bonding ability of the phosphoryl group has been shown clearly by Kosolapoff and McCullough[17] and Arbuzov and Razumova.[18] Baumgarten and Setterquist[19] have demonstrated recently that alkyl phosphates, like carboxylic acid esters, undergo pyrolysis to give an olefin and the acid.

To test the formation of olefin by means of an intramolecular β-elimination through the quasiphosphonium salt, triphenoxy-β-phenethylphosphonium iodide, $(C_6H_5O)_3P^{\oplus}_{I^{\ominus}}$-$CH_2$-$CH_2$-$C_6H_5$ (XI), was prepared and heated to decomposition at 210–222° and 0.15 mm. Vapor phase chromatographic analysis of the volatile products showed the presence of styrene and iodobenzene. The solid residue was identified as diphenyl β-phenethylphosphonate, $(C_6H_5O)_2$—$\overset{\overset{O}{\uparrow}}{P}$—$CH_2$—$CH_2$—$C_6H_5$ (XII), the major product and the usual Michaelis-Arbuzov product. To show that the styrene was not produced as a consequence of the pyrolysis of the ester (XII), the diphenyl β-phenethylphosphonate was heated at 240° and 0.15 mm. for 2 hr. without decomposition. The phosphonate finally decomposed at 390°. In support of the experimental evidence for the olefin formation from the quasiphosphonium salts, the models of these compounds show that the hydrogen atoms which are *alpha* to the activating group help to form a perfect five-membered ring with one of the oxygens that is attached to the phosphorus atom. In fact, these two atoms virtually touch each other.

With the positive charge on the phosphorus, the activated β-hydrogens and the close proximity of the hydrogen and oxygen in a five-membered ring, one might expect olefin formation to be more predominant. Since there are three alkoxyl groups attached to the phosphorus, the chances of the incoming negative ion attacking the same alkoxyl group which forms the ring is made even less favorable by the fact that the other alkyoxyl or aryloxyl groups are thrown outward into space where they are more susceptible to attack.

(10) (a) H. I. Jacobsen, R. G. Harvey, and E. V. Jensen, *J. Am. Chem. Soc.*, **77**, 6064 (1955). (b) M. S. Kharasch and I. S. Bengelsdorf, *J. Org. Chem.*, **20**, 1356 (1955).

(11) B. C. Saunders, *Some Aspects of the Chemistry of and Toxic Action of Organic Compounds Containing Phosphorus and Fluorine*, Cambridge University Press, Cambridge, 1957, p. 95.

(12) S. R. Landauer and H. N. Rydon, *Chem. & Ind. (London)*, 313 (1951).

(13) W. Gerrard and G. J. Jeacocke, *J. Chem. Soc.*, 3647 (1954).

(14) For a complete discussion of Intramolecular Eliminations see M. S. Newman, *Steric Effects in Organic Chemistry*, New York, John Wiley & Sons, Inc., 1956, pp. 305–14.

(15) G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 2342 (1929).

(16) L. Hey and C. K. Ingold, *J. Chem. Soc.*, 531 (1933).

(17) G. M. Kosolapoff and J. M. McCullough, *J. Am. Chem. Soc.*, **73**, 5392 (1951).

(18) A. E. Arbuzov and N. A. Razumova, *Doklady Akad. Nauk S.S.S.R.*, **97**, 445 (1954); *Chem. Abstr.*, **49**, 9538 (1955).

(19) H. E. Baumgarten and R. A. Setterquist, *J. Am. Chem. Soc.*, **79**, 2605 (1957).

Although it has no bearing on the mechanism of the Michaelis-Arbuzov reaction or olefin formation, it should be mentioned here that a large portion of the products of this reaction is a nondistillable sirup. This material is always acidic, is water soluble, and, presumably, is easily hydrolyzed. All evidence to date indicates that these materials are polypyrophosphonates which contain (P—O—P) linkages formed by olefin and alohol elimination during the long heating periods of the reaction.

EXPERIMENTAL

The β-bromoethylbenzene and the ethyl β-bromopropionate were obtained from Matheson, Coleman, and Bell, the 1,2-dibromoethane from Eastman Kodak Co., and the triethyl phosphite and diethyl phosphonate from Virginia-Carolina Chemical Corp.

β-Iodoethylbenzene. A mixture of 92.5 g. (0.5 m.) of β-bromoethylbenzene, n_D^{25} 1.5543, 74.9 g. (0.5 m.) of sodium iodide and 50 ml. of acetone was refluxed on a steam bath overnight. The resultant red liquid was separated by filtration and the solvent was stripped. Distillation of the heavy oily residue gave 92.0 g. (79.3%) of material, b.p. 71°/1.1 mm., n_D^{25} 1.5945.

Diphenyl β-phenethylphosphonate. A 5.0 g. sample (0.009 m.) of triphenoxy-β-phenethylphosphonium iodide was allowed to stand overnight in excess 10% aqueous NaOH. A white solid formed. The solid was filtered and recrystallized from *n*-hexane to give 2.5 g. (65.2%) of fine, white needles, m.p. 75–76°.

Anal. Calcd. for $C_{20}H_{19}PO_3$: C, 71.0; H, 5.62; P, 9.17. Found: C, 71.13; H, 5.44; P, 9.38.

The infrared spectrum of this material was recorded as a melt on NaCl plates.

Triphenoxy-β-phenethylphosphonium iodide. A mixture of 73.0 g. (0.3 m.) of freshly prepared β-phenethyl iodide and 146.2 g. (0.5 m.) of triphenylphosphite was heated at 128° for 5 days. The reaction mixture was protected from moisture by "Drierite" tubes. When the resultant, dark red-brown mixture was mixed with absolute ether, a dark solid fraction precipitated. The ether was decanted and a fresh portion was added and the solid became more firm. The material was mixed with an absolute ether, C.P. acetone solution, in several portions until the color became canary yellow. Then the solid was extracted in a Soxhlet extractor with a mixture of 10 ml. of C.P. acetone and 250 ml. of absolute ether until the solid was almost cream color, and the solvent no longer became yellow. Removal of the solvent and drying under vacuum left 28.3 g. of material which melted in a sealed tube at 154–157°. The solid with silver nitrate gave an immediate precipitate which was insoluble in dilute nitric acid.

Anal. Calcd. for $C_{26}H_{24}PO_3I$: C, 57.57; H, 4.43; P, 5.72; I, 23.42. Found: C, 56.86; H, 4.63; P, 5.60; I, 23.46

Reaction of triethyl phosphite with 1,2-dibromoethane. Seven hundred fifty-two g., (4.0 m.) of 1,2-dibromoethane was heated to reflux at 131°. Then 183.0 g. (1.1 m.) of freshly distilled triethyl phosphite was added dropwise under nitrogen pressure over a period of 1.5 hr. During the addition of the phosphite and subsequent heating of the mixture to a final temperature of 145° over a period of 3.5 hr., 110.8 g. (1.08 m.) of ethyl bromide was distilled from the reaction mixture through an 8-in. Vigreux and was collected in an attached cold trap. The reaction mixture was fractionated through a 15-in. Vigreux column after removal of 509.6 g. of unreacted dibromide at atmospheric pressure.

The first low boiling fractions of 33.7 g. consisted of a mixture of diethyl vinylphosphonate, diethyl phosphonate, and diethyl ethylphosphonate as shown by infrared analysis and vapor phase chromatography. Subsequently, 127.0 g. of diethyl β-bromoethylphosphonate, b.p. 90°/1 mm., n_D^{25} 1.4564 was obtained. Seven and seven-tenths grams of an intermediate fraction, n_D^{25} 1.4473, which contained some tetraethyl ethylenediphosphonate was followed by the sudden evolution of 13.4 g. of material which dropped the head temperature to 30°/2 mm. and had n_D^{25} 1.4250 which along with its infrared spectrum showed it to be pure diethyl vinylphosphonate.

Reaction of triethyl phosphite with diethyl β-bromoethylphosphonate. Diethyl β-bromoethylphosphonate, 50.7 g. (0.17 m.), was heated to 157° and 35.3 g. (0.21 m.) of distilled triethyl phosphite was added dropwise over a 3-hr. period. During the heating over a total of 6 hr., 17.9 g. (0.16 m.) of ethyl bromide distilled. The final reaction temperature was 198°. Vacuum distillation of the pale yellow, nonviscous mixture yielded 28.8 g. of a low boiling mixture of approximately 64.5% diethyl phosphonate, 25.8% diethyl vinylphosphonate, 6.9% diethyl ethylphosphonate, and 2.9% of an unknown as determined by infrared and vapor phase chromatographic analyses. A higher boiling fraction consisted of 16.2 g. of tetraethyl ethylenediphosphonate, b.p. 151–157°/1 mm., n_D^{25} 1.4397.

Reaction of ethyl β-bromopropionate with triethyl phosphite. Ninety g. (0.54 m.) of distilled triethyl phosphite was added dropwise over a period of 3 hr. to 100.0 g. (0.55 m.) ethyl β-bromopropionate at 155°. The initial addition of the phosphite caused the temperature to drop to 137° which temperature held throughout the reaction. The reaction mixture was heated for 5 hr. after the complete addition of the phosphite and 48.4 g. (0.44 m.) of ethyl bromide was distilled during the heating.

Vacuum distillation of the mixture yielded 21.9 g. of material, b.p. 66–86°/4–7 mm., which infrared showed to be diethyl phosphonate and probably diethyl ethylphosphonate, 80.0 g. of ethyl 3-diethylphosphonopropionate, b.p. 114–115°/2 mm., n_D^{25} 1.4301 and 24.1 g. of polyethylacrylate, n_D^{25} 1.4662. The distillation cold trap yielded 6.84 g. of ethyl acrylate, n_D^{25} 1.3975. The acrylate monomer and polymer were identified by their infrared spectra.

Reaction of triethyl phosphite with β-bromoethylbenzene. One hundred g. (0.54 m.) of β-bromoethylbenzene was heated to 165°, then 90.9 g. (0.54 m.) of distilled triethyl phosphite was added dropwise. The temperature rose slightly and maintained itself at 166–155° when the heat was lowered. The heat was maintained for approximately 20 hr. During this period, 33.6 g. (0.31 m.) of ethyl bromide distilled from the mixture. The reaction mixture was vacuum distilled through an 8-in. Vigreux.

The first fraction of 43.9 g. was shown by infrared to contain diethyl phosphonate, diethyl ethylphosphonate, and unreacted β-bromoethylbenzene. The second fraction was mostly diethyl ethylphosphonate, 3.9 g., and the third fraction consisted of 68.8 g. of diethyl β-phenethylphosphonate, b.p. 144–147°/2.3 mm., n_D^{25} 1.4925. The residue in the pot was dissolved in benzene and 3.2 g. of polystyrene was precipitated in methanol. The cold trap contained 10.4 g. of material which decolorized bromine in carbon tetrachloride and was shown by its infrared spectrum to be mostly styrene.

Test for thermal stability of tetraethyl ethylenediphosphonate. A sample of tetraethyl ethylenediphosphonate was heated at 211° for 5.5 hr. The material was pumped down and heated. No low boiling materials were distilled at 70°/2 mm.

Pyrolysis of diphenyl β-phenethylphosphonate. An 8.1 g. sample of diphenyl β-phenethylphosphonate was heated for 2 hr. at 240°/0.15 mm. with no decomposition. This material was heated again for 4.5 hr. at 250–305°/5 mm. still without decomposition. The material was recovered, recrystallized, and the melting point checked. Then the sample was heated at atmospheric pressure up to 390° to give a trace of water and a viscous, brown residue which was strongly acidic. The odor of styrene was strong in the attached dry ice trap, but no styrene was isolated. The infrared spectrum

of the viscous, brown residue showed polystyrene to be absent.

Pyrolysis of triphenoxy-β-phenethylphosphonium iodide. A 10.0 g. sample of triphenoxy-β-phenethylphosphonium iodide was dried overnight under vacuum and then was heated at 210–220°/0.15 mm. over a period of 4 hr. The dry ice traps which were attached to the pyrolysis apparatus contained a small amount of liquid which smelled of iodobenzene. The infrared spectrum of this material confirmed the presence of iodobenzene and hinted at the presence of styrene. Vapor phase chromatographic analysis of this material showed the presence of a small amount of styrene.

The dark solid residue in the pyrolysis tube was recrystallized from *n*-hexane as long white needles, m.p. 75.1–75.6°. A mixed melting point with authenticated diphenyl β-phenethylphosphonate of m.p. 75.0–75.3° was 75.0–75.6°.

Acknowledgment: The authors are indebted to Peter Shapras for the infrared and vapor phase chromatographic analyses.

SPRINGFIELD 2, MASS.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF MOREHOUSE COLLEGE AND THE ATLANTA UNIVERSITY]

Reactions of Methyl and Ethoxy Free Radicals in Chlorohydrocarbons: A Comparative Study of the Use of Diacetyl Peroxide and Diethylperoxydicarbonate as Agents for Linking Alpha Carbon to Alpha Carbon in Some Chloro-Substituted Aralkyls[1]

HENRY C. McBAY, OZIE TUCKER, AND PAUL T. GROVES

Received September 24, 1958

Diacetyl peroxide reacts with approximately equal facility with the chloro-substituted aralkyls, 3,4-dichlorotoluene, 2,6-dichlorotoluene, and α,α-dichlorotoluene (benzal chloride) to give the corresponding chloro-substituted bibenzyls derived from the dimerizations at the alpha positions. Diethyl peroxydicarbonate reacts with 3,4-dichlorotoluene in the same manner as does diacetyl peroxide, producing 1,2-bis(3,4-dichlorophenyl)ethane (3,4,3′,4′-tetrachlorobibenzyl), and with essentially equal yield. Diethyl peroxydicarbonate gives a poorer yield of the same dimer, 2,6,2′,6′-tetrachlorobibenzyl, as obtained from the reaction of diacetyl peroxide with 2,6-dichlorotoluene. Practically none of the dimer, tetrachlorotolane, obtained from the reaction of benzal chloride with diacetyl peroxide, is produced when diethyl peroxydicarbonate is used as the linking agent. Diacetyl peroxide links *p*-isopropylbenzal chloride unsymmetrically with itself to produce 1,1-dichloro-1-*p*-isopropylphenyl-2-methyl-2-(ω,ω-dichloro-*p*-tolyl)propane exclusively, while diethylperoxydicarbonate links *p*-isopropylbenzal chloride symmetrically with itself to produce exclusively 2,3-di-(ω,ω-dichloro-*p*-tolyl)-2,3-dimethylbutane.

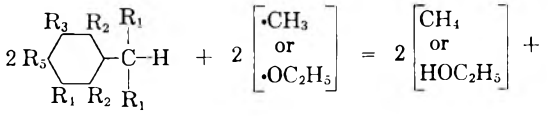
Of the several possible modes of reaction available to free radicals generated in solution, the one taken by a given free radical depends only in part upon the nature of the free radical itself. External factors of importance are temperature and the nature of the coreactant. It must be kept in mind that there is competition between solvent and parent substance, despite its low concentration in dilute solution, as coreactants for the free radical. Several factors determining the relative effectiveness of the solvent molecule in such competition have been disclosed. The relative strengths of the bonds holding the univalent atoms in the solvent molecule, which strength largely determines the ease with which the bonds holding these univalent atoms succumb to cleavage by free radicals, has been termed the *energy factor*.[2] The nature and the positions of the substituents in the solvent molecule have a pronounced effect upon the ease with which said molecule yields an univalent atom to the cleaving action of *ethoxy free radicals*, but these factors seem to have little or no effect upon the analogous action of such molecule toward *methyl free radicals*. A previous paper[3] reports that hydrogen atoms are readily cleft from solvent molecules by methyl and by ethoxy free radicals when these hydrogens are attached to the same carbon atom with methyl and/or phenyl groups. The substitution of carbomethoxy groups for the methyl and/or phenyl groups produces no noticeable effect upon the tendency of the solvent to donate a hydrogen atom to *methyl* free radical but greatly reduces its tendency to yield hydrogen to the *ethoxy* free radical. This unusual effect of the carbomethoxy group upon the course of these free radical reactions has been termed the *repulsion factor*.[3] This paper reports a continuation of these studies. It attempts to show that the introduction of chlorine atoms into positions adjacent to the "preferred" seat of attack for the cleavage reactions of these free radicals has little or no effect on the percentage of cleavage exhibited by the *methyl* free radical and no effect whatever on the site of its cleavage attack. On the other hand, the immediate proximity of these chlorine atoms to the preferred seat of attack *decreases* the percentage

(1) Presented in part before the Organic Division of the American Chemical Society at the 128th National Meeting, New York, September 1954.

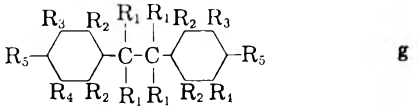
(2) H. C. McBay and O. Tucker, *J. Org. Chem.*, 19, 869 (1954).

(3) H. C. McBay, O. Tucker, and A. Milligan, *J. Org. Chem.*, 19, 1003 (1954).

cleavage exhibited by the *ethoxy* free radical, increases the extent to which this radical reacts with its parent peroxide[4] (to give the products of disproportionation Equation E); and in selected cases, even alters the site of the cleavage attack. Furthermore, with isomeric solvent molecules where the chlorines are far removed from the preferred seat of the cleavage attack and where the selected hydrogen is easily cleft there is no essential difference in the reactions of the methyl and ethoxy free radicals. The following are specific examples of the facts summarized above. Earlier studies[2]



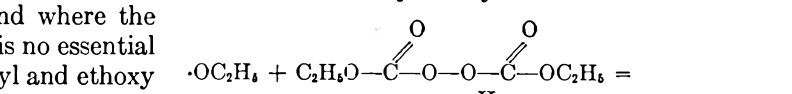
I



II

have shown that hydrocarbons such as toluene, I (all R's = H), *p*-xylene, I ($R_5=CH_3$, $R_1=R_2=R_3=R_4=H$), Cumene, I ($R_1=CH_3$, $R_2=R_3=R_4=R_5=H$), and *p*-cymene, I ($R_1=R_5=CH_3$, $R_2=R_3=R_4=H$) are all attacked by both methyl and ethoxy free radicals at the same (alpha) position to produce the indicated dimers, II, in good yields (see Equation G).

Methyl free radical attacks benzal chloride, I ($R_1=Cl$, $R_2=R_3=R_4=R_5=H$), in the alpha position to give exclusively and in 85% yield 1,1,2,2-tetrachloro-1,2-diphenylethane (tetrachlorotolane), II ($R_1=Cl$, $R_2=R_3=R_4=R_5=H$).[5] Ethoxy[6] free radical reacts with benzal chloride to give poor yields of a product as yet incompletely characterized which results presumably from attack on the ring. This product contains only a trace of tetrachlorotolane. The major portion of this product results from attack at some site which is not the alpha position, and the only remaining sites for cleavage attack yielding ethanol and leaving chlorines intact are on the ring. The contrastingly high yield of acetaldehyde resulting from this reaction together with the low yield of solvent-derived product suggests that an attack by ethoxy on the parent peroxide occurs with lower activation energy than does attack by ethoxy on this solvent molecule.



$$C_2H_5OH + CH_3C{=}O + \cdot OC_2H_5 + 2CO_2 \quad (e)$$

Moving the chlorines away from the preferred site of attack (alpha position) gives rise to identical sites of attack by both methyl and ethoxy free radicals. Methyl free radical reacts with 2,6-dichlorotoluene, I ($R_2=Cl$, $R_1=R_3=R_4=R_5=H$), by cleaving a hydrogen from the alpha position to produce the corresponding dimer, 2,6,2′,6′-tetrachlorobibenzyl,[7] II ($R_2=Cl$, $R_1=R_3=R_4=R_5=H$), in 63% yield. Ethoxy free radical attacks 2,6-dichlorotoluene at the same alpha position producing the same dimer but only in 21% yield. The ethoxy free radical disproportionates in this solvent to the extent of 27%.

The results from reactions of these free radicals in benzal chloride and in 2,6-dichlorotoluene predict that chlorines in positions still more remote from the preferred site of attack should certainly cause no difference in the reaction paths of methyl and ethoxy free radicals and should possibly give comparable yields of cleavage products from both sources. The percentage disproportionation exhibited by ethoxy free radical in 3,4-dichlorotoluene should be still less than that in the 2,6-isomer. These predictions were verified by experiment. Methyl free radical attacks 3,4-dichlorotoluene, I ($R_4=R_5=Cl$, $R_1=R_2=R_3=H$), at the alpha position producing 3,4,3′,4′-tetrachlorobibenzyl,[7] II ($R_4=R_5=Cl$, $R_1=R_2=R_3=H$), in 63% yield. Ethoxy free radical attacks 3,4-dichlorotoluene at the alpha position through cleavage of hydrogen atom to produce the same dimer in 61% yield. The ethoxy free radical disproportionates in this solvent to the extent of 11%.

All these data support the postulate of a so-called "repulsion factor"[2,3] operative in these reactions.[8] They suggest that the presence of an oxygen atom in the ethoxy free radical at that end of the radical at which the odd electron predominantly resides, and hence at that end of the radical

(4) The methyl and the ethoxy free radicals were generated in solution by the thermal decomposition of diacetyl peroxide and diethylperoxydicarbonate respectively. See ref. (2) and (10a).

(5) This reaction was first carried out in the Kharasch laboratories at the University of Chicago, Kharasch, McBay, and Urry, *Unpublished results*. The data here reported (see experimental part) have been obtained by repeating the experiment in our laboratories.

(6) Decomposition of di-*t*-butyl peroxide in benzal chloride gives good yields of tetrachlorotolane, *acetone*, and *methane*.

$$\cdot OC(CH_3)_3 = (CH_3)_2C{=}O + \cdot CH_3$$

$$2 \cdot CH_3 + 2\ C_6H_5CHCl_2 = 2\ CH_4 + C_6H_5CCl_2CCl_2C_6H_5$$

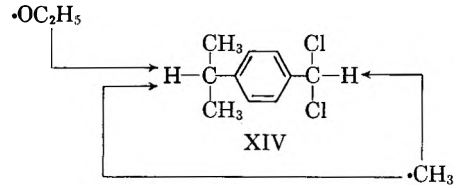
It is apparently the methyl free radical resulting from the breakdown of the *t*-butoxy free radical, and not so much the *t*-butoxy free radical itself, which attacks the alpha hydrogen of the dichloromethyl group. McBay, *Unpublished results*.

(7) Since these tetrachlorobibenzyls were heretofore unreported in the literature, it was necessary to establish their identities. This has been accomplished by synthesizing them by a different method. That different method (see experimental part) has been the Grignard coupling method.

(8) By itself and unmodified the postulate of steric hindrance of a strictly spacial type is not consistent with these facts. Note that chemically bound methyl groups are slightly *larger* than bound chlorines. See L. Pauling, *Nature of the Chemical Bond*, Cornell Univ. Press, Ithaca, New York, 1939, p. 189.

primarily involved in the cleavage mechanism, seriously affects the properties of the free radical. The oxygen atom causes the ethoxy free radical to experience repulsion by the chlorine atoms adjacent to the preferred site of attack in the coreacting solvent molecule to a much greater extent than does the purely hydrocarbon alkyl free radical, the methyl free radical. They suggest further that in extreme cases this repulsion increases the activation energy[9] associated with a given ("preferred") reaction path to the extent that this path is forbidden *when for the same coreactants there is an alternate reaction path associated with which this type of repulsion is considerably less.*

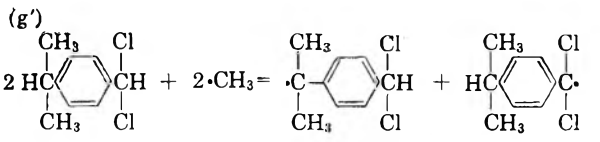
Since $\cdot CH_3$ abstracts the alpha tertiary hydrogen atom from both isopropylbenzene and benzal chloride with good facility, both giving under similar experimental conditions yields above 80%, and since $\cdot OC_2H_5$ abstracts the alpha tertiary hydrogen from isopropyobenzene but not from benzal chloride; it appeared challenging to study the reactions of each of these free radicals in *p*-isopropylbenzal chloride, XIV. The ethoxy free radical abstracts selectively and exclusively that alpha tertiary hydrogen which is not flanked by, but is remote from, the chlorine atoms. This selective attack gives the symmetrical dimer, 2,3-dimethyl-2,3-di(*p*-dichloromethylphenyl)butane (Dimer B) without admixture of any of its isomers [see Reaction (b)]. The methyl free radical reacts



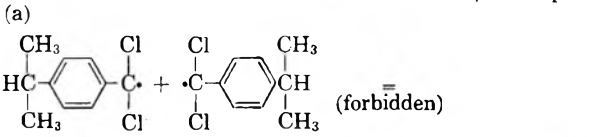
with *p*-isopropylbenzal chloride, XIV, in the manner predicted by the results cited above. It is *not* selective in its cleavage attack on this molecule. It abstracts with equal distribution the alpha tertiary hydrogens from each end of this molecule thus producing in solution an equimolar mixture of two isomeric residual radicals. This study discloses an heretofore unreported selectivity [Reaction (c)] involving the dimerization of an equimolar mixture of two such free radicals.

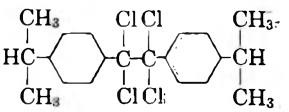
A purely random process statistically controlled should produce from this mixture of residual free radicals the Wurtz-type distribution of these dimers: 25% A, 25% B, and 50% C. Actually, the product isolated is 1-*p*-isopropylphenyl-1,1-dichloro-2-methyl-2-*p*-(ω,ω-dichlorotolyl)propane (Dimer C), with no detectable quantities of any of its isomers. This selectivity in the dimerization process is here attributed to a chlorine-to-chlorine

(g′)

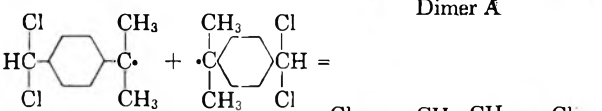


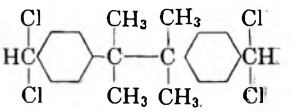
(a)



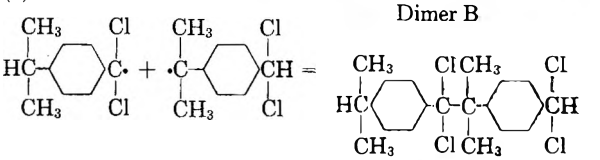


(b)





(c)



type of repulsion similar to the chlorine-to-ethoxy repulsion discussed above and to the carboxy-to-ethoxy and carbomethoxy-to-ethoxy repulsion postulated in earlier reports.[2,3] Note that an equimolar mixture of two isomeric residual free radicals could dimerize to produce *in addition to Dimer C* the symmetrical isomer (Dimer B) *only if* an equal number of these radicals dimerized to produce the other symmetrical isomer (Dimer A). If chlorine-to-chlorine repulsion prohibits the formation of Dimer A, there must be the concomitant but secondary consequence that the formation of Dimer B is also forbidden. This does not imply that dimerizations of the type represented by Equation (a) are categorically forbidden. Note that tetrachlorotolane, II (R_1=Cl, R_2=R_3=R_4=R_5=H), is formed in good yield despite the possible existence of any such chlorine-to-chlorine repulsion. Indeed, the synthesis of tetrachlorosuccinyl chloride and of dimethyl tetrachlorosuccinate has thus far been accomplished[10] only through dimerizations of residual free radicals across carbon atoms which are completely surrounded by these supposedly self-repelling groups. This does imply, however, that such dimerizations occur only when there is no other alternative path available involving less "repulsion." These results are related to, and this postulate is consistent with, the data obtained from

(9) S. Glasstone, K. Laidler, and H. Eyring, *The Theory of Rate Processes*, McGraw-Hill Book Co., New York, 1941, p. 141.

(10) (a) M. S. Kharasch, H. C. McBay, and W. H. Urry, *J. Org. Chem.*, **10**, 394 (1945). (b) H. W. Doughty and B. Freeman, *J. Am. Chem. Soc.*, **44**, 638 (1922).

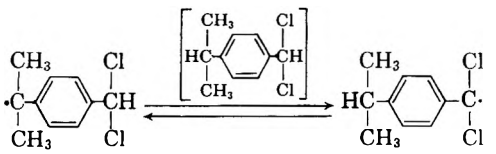
studies[11] on directive effects in aliphatic chlorination.

An alternate interpretation of these results is that:

(i) Methyl and ethoxy free radicals have exhibited no difference with respect to the positions from which they have extracted a hydrogen atom from *p*-isopropylbenzal chloride, but that

(ii) A subsequent tautomeric shift[12] of H-atom within the residual free radical of first order or

(ii$_a$) A subsequent attack of either isomeric residual free radical on solvent to produce the other



is responsible for the distribution of isomeric residual free radicals which ultimately dimerize to produce the final products observed.

If, however, one embraces this theory he is immediately faced with the more difficult task of accounting for the occurrence of the shift in one direction when ethoxy free radical is used to generate this/these residual free radical and, either the absence of the shift or, shift in opposite direction when methyl free radical is used. Since the experimental conditions are the same for both reactions it is thermodynamically unsound to assume that a residual free radical of first order should exhibit a property thus dependent upon its past history (whether it was generated by action of a methyl or an ethoxy free radical). The authors have therefore rejected this latter interpretation of the results reported in this paper.

The possibility has been suggested that only one of these two isomeric residual free radicals becomes solvated and that the dimerization of two such solvated radicals might be sterically retarded, while the dimerization of the solvated with the unsolvated radical might not be sterically retarded. While such selective solvation might be plausible when two such isomeric residual free radicals are dissolved in some foreign solvent, different in structure from either of these radicals, it is not very likely in this particular case. The one solvent in which such selective solvation is least likely to occur is the *parent molecule* from which each of these isomeric radicals has been derived. In this work the isomeric radicals which have exhibited selective dimerization have done so in just that solvent, their parent molecule. This suggestion seems therefore unsatisfactory as an explanation of the reported selectivity in the dimerization process.

TABLE I

ATTACK OF METHYL AND ETHOXY RADICALS UPON SOLVENT

Molecules Subjected to Free Radical Attack	Methyl Free Radical		Ethoxy Free Radical		
	Position of attack	% Cleavage	Position of attack	% Cleavage	% Disproportionation
Cumene[a]	Alpha	100	Alpha	70.	19.
3,4-Dichlorotoluene	Alpha	63.	Alpha	61.	11.
2,6-Dichlorotoluene	Alpha	63.	Alpha	21.	27.
Benzal chloride	Alpha	85.	Ring[b]	35.[c]	37.
			Alpha	<03.	
p-Isopropylbenzal chloride	Alpha	47.			
	Alpha'[d]	47.	Alpha'[d]	50.	9.

This table makes no reference to radical capture by the benzene ring which in all probability occurs to a small extent in all these reactions.

[a] Data on this molecule taken from Kharasch, McBay, and Urry, *J. Org. Chem.*, **10**, 406 (1945) and McBay and Tucker, *J. Org. Chem.*, **19**, 869 (1954). [b] Attack at some undetermined position/s on the benzene ring. [c] Calculated as dimer. [d] Alpha' indicates alpha position at methylated (unchlorinated) end of this molecule.

Characterization of the Dimers. Several of these dimers (2,6,2′,6′-tetrachlorobibenzyl, 3,4,3′,4′-tetrachlorobibenzyl, Dimer B, and Dimer C) are unreported in the literature, and it has been therefore necessary to characterize them. The identity of 2,6,2′,6′-tetrachlorobibenzyl and of 3,4,3′,4′-tetrachlorobibenzyl has been established through the synthesis of these compounds by a different route. The Grignard coupling technique in each case gives rise to products which do not depress the melting points of these respective dimers prepared by the free radical coupling technique outlined above. The purity of the products obtained by the free radical method has in these two cases been repeatedly observed to be of a higher degree than when the Grignard coupling technique was used. 3,4,3′,4′-Tetrachlorobibenzyl was quantitatively converted by oxidative degradation to 3,4-dichlorobenzoic acid.

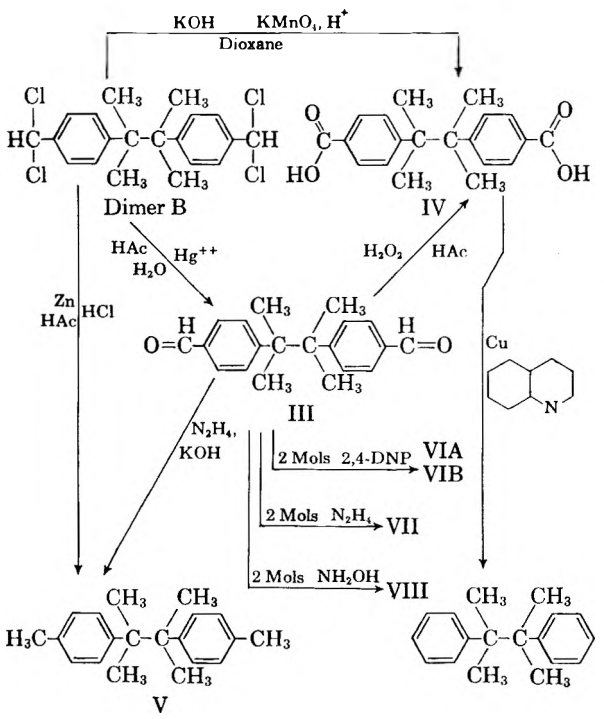
(11) A. B. Ash and H. C. Brown, *Record of Chemical Progress*, 9, 81 (1948). R. J. Breazeale, H. W. Davis, and A. M. Whaley, paper presented before Georgia Section, ACS, Atlanta, October 1950. G. M. Buffett, Ph.D. thesis, Univ. of Wisconsin, 1933. H. M. Waddle and H. Adkins, *J. Am. Chem. Soc.*, 61, 3361 (1939). M. S. Kharasch and H. C. Brown, *J. Am. Chem. Soc.*, 62, 925 (1940). C. W. Gayler and H. M. Waddle, *J. Am. Chem. Soc.*, 63, 3358 (1941). Observations which appear to be analogous to those reported in this paper have repeatedly been made by workers in the field of free radical copolymerization. Here cross termination is found to occur more frequently than coupling of like radicals. For a detailed discussion of these results see C. Walling, *Free Radicals in Solution*, John Wiley & Sons, New York, 1957, pp. 132–140, p. 146.

(12) Tautomeric shifts involving H-atoms (a, b) and Cl-atoms (c) have been reported to occur within residual free radicals of first order. (a) M. W. Gladstone, *J. Am. Chem. Soc.*, 76, 1581 (1954). (b) M. S. Kharasch and R. L. Dannley, *J. Org. Chem.*, 10, 406 (1945). (c) W. H. Urry and J. R. Eizner, *J. Am. Chem. Soc.*, 74, 5822 (1952).

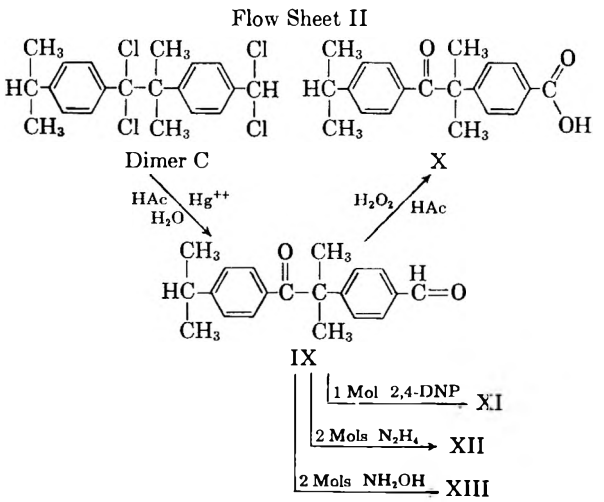
The 2,6,2′,6′-tetrachlorobibenzyl, where the chlorines are in close proximity to the ethylenic hydrogens, was not oxidized to an aromatic acid by methods involving use of $K_2Cr_2O_7$, CrO_3, of $KMnO_4$ as oxidizing agents.[13] This dimer, the 2,6,2′,6′-isomer, so resistful to oxidation, was converted by orthodox methods to a tetranitro derivative whose analysis agreed with the theoretical value. The procedures followed in attempting to elucidate the structures of Dimer B and Dimer C are represented schematically by Flow Sheet I and Flow Sheet II. All compounds here represented have been analyzed, and the results are presented in Table II.

Both Dimer B and its carbonyl derivative have been successfully reduced to the parent hydrocarbon, but the methods used have not converted Dimer C or its carbonyl derivative into their parent hydrocarbon. These unsymmetrical compounds related to Dimer C seem to be more sensitive to reductive cleavage. For comparison this latter hydrocarbon has been synthesized by Grignard technique.

Flow Sheet I



Flow Sheet II



EXPERIMENTAL

Reagents. The diacetyl peroxide and the diethyl peroxydicarbonate have been prepared, purified, and analyzed by methods previously described.[5,(10a)] The chlorotoluenes were Eastman products redistilled through a column of approximately 40 plates: 2,6-dichlorotoluene, b.p. 72.5°/10 mm., n_D^{20} 1.5517, lit.[14] b.p. 54–56°/8 mm., n_D^{20} 1.5510; 3,4-dichlorotoluene, b.p. 85.5°/14 mm., n_D^{20} 1.5490, lit.[15] b.p. 207–208°/760 mm., n_D^{20} 1.5490; benzal chloride, b.p. 45.5°/4.5 mm., n_D^{20} 1.5509, lit.[16] b.p. 104–105°/30 mm., n_D^{20} 1.5503. *p*-Isopropylbenzal chloride was obtained from Eastman's white-label *p*-isopropyl benzaldehyde by treating with phosphorus pentachloride.[17] The product was triply distilled through a 20-plate column, b.p. 104–106°/2 mm., n_D^{20} 1.5340.

Thermal decomposition of diacetyl peroxide in benzal chloride,[5] preparation of 1,2-diphenyl-1,1,2,2-tetrachloroethane. Diacetyl peroxide (45.9 g., 0.38 mole) dissolved in benzal chloride (296.7 g., 1.83 moles) was introduced slowly beneath the surface of benzal chloride (152.1 g., 0.94 mole) held at 115°. From the thermal decomposition of the peroxide in this solvent were obtained the following volatile products: carbon dioxide (27.5 g., 0.61 mole); hydrogen chloride (0.45 g., 0.01 mole); methyl acetate (0.2 g., 0.003 mole); and methane (12.2 l., STP, 0.54 mole). Distillation of the nonvolatile contents of the reaction vessel gave unreacted benzal chloride (366.1 g., 2.38 moles), b.p. 38.5°/1 mm. Remaining in the stillpot was a mass of straw-colored crystals (74.9 g., 0.23 mole). Trituration with Norit in hot ligroin (b.p.60°) and recrystallization from ligroin gave white crystals melting at 161–162°. The melting point recorded in the literature[18] for 1,2-diphenyl-1,1,2,2-tetrachloroethane is 162°. A mixture of these crystals with authentic 1,2-diphenyl-1,1,2,2-tetrachloroethane melted at 162°.

Anal. Calcd. for $C_{14}H_{10}Cl_4$: C, 52.54; H, 3.15; Cl, 44.31. Found: C, 52.51; H, 3.11; Cl, 43.91.

Thermal decomposition of diethyl peroxydicarbonate in benzal chloride. A solution containing diethyl peroxydicarbonate (0.49 mole), dissolved in benzal chloride (283.2 g., 1.76 moles), was slowly added in single drops beneath the surface of benzal chloride (97.3 g., 0.64 mole) held at 92–95°. The following volatile products were obtained: carbon

(13) Other workers have experienced great difficulty in obtaining 2,6-dichlorobenzoic acid through the oxidation of the side chain in 2,6-dichloro-alkyl benzenes. (a) J. B. Cohen and H. D. Dakin, *J. Chem. Soc.*, **79**, 1132 (1901). (b) E. H. Huntress, *Organic Chlorine Compounds*, John Wiley & Sons, New York, 1948, p. 848.

(14) P. R. Austin and J. R. Johnson, *J. Am. Chem. Soc.* **54**, 657 (1932).

(15) H. Wahl, *Compt. rend.*, **203**, 2161 (1936).

(16) M. S. Kharasch and H. C. Brown, *J. Am. Chem. Soc.*, **61**, 2146 (1939).

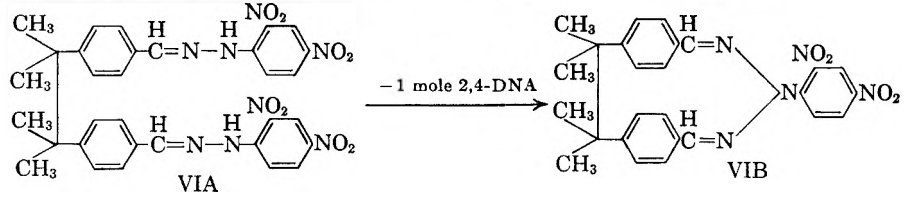
(17) V. Cahours, *Ann.*, **70**, 44 (1849). P. Sieveking, *Ann.*, **106**, 258 (1858).

(18) E. H. Huntress, *Organic Chlorine Compounds*, John Wiley & Sons, New York, 1948, p. 408.

TABLE II[a]

		Isomeric Chlorohydrocarbons		Isomeric Carbonyl Compounds		Derived Carboxylic Acids		Isomeric Dihydrazones[b]		Isomeric Dioximes		2,4-Dinitro Phenylhydrazones	
		Sym.	Unsym.	Sym.	Unsym.	Sym.	Unsym.	Sym.	Unsym.	Sym.	Unsym.	Sym.	Unsym.
Reference		Dimer B	Dimer C	III	IX	IV	X	VII	XII	VIII	XIII	VI[c]	XI[d]
Formula		$C_{20}H_{12}Cl_4$	$C_{20}H_{22}Cl_4$	$C_{20}H_{22}O_2$	$C_{20}H_{24}O_2$	$C_{20}H_{22}O_4$	$C_{20}H_{22}O_3$	$C_{20}H_{26}N_4$	$C_{20}H_{26}N_4$	$C_{20}H_{24}N_2O_2$	$C_{20}H_{24}N_2O_2$	$C_{32}H_{30}N_8O_8$	$C_{26}H_{26}N_4O_5$
M.P., °C.		207–208	138	207–208	104	285[e]	196–198	275–276[e]	284–285[e]	215–217	194–196	319[e,f]	205–206
Calcd. for:	C	59.43	59.43	81.59	81.59	73.62	77.39						65.81
	H	5.48	5.48	7.53	7.53	6.79	7.14						5.52
	N							17.37	17.37	8.63	8.63	17.12	11.80
	Cl	35.09	35.09										
	N.E.					163	310						
Found:	C	59.14	59.16	81.77	81.40	73.71	77.00						65.74
	H	5.63	5.48	7.61	7.48	6.93	7.30						5.56
	N							16.84[b]	16.68[b]	8.82	8.63	14.70[c]	11.81
	Cl	35.03	34.92										
	N.E.					164	295						

[a] All melting points are uncorrected. [b] The dihydrazones of both isomers have given consistently low nitrogen analyses. The authors have no explanation for this discrepancy. [c] Repeated preparations of this derivative gave a product analyzing consistently at 14.70 20% N. This suggests strongly that the di-2,4-DNP derivative has formed but loses intramolecularly one mole of 2,4-DNA in following manner to form VIB. Calcd. for $C_{26}H_{26}N_8O_4$: N = 14.85. Found: N = 14.70. [d] This is the mono-2,4-DNP derivative. Steric hindrance about the keto group prevents the formation of the di-2,4-DNP derivative. [e] Melts with decomposition. [f] Melting point taken on a hot stage.



While evidence here presented is certainly inconclusive, this tentative structure VIB is of interest because of its heterocyclic relationship to the newly discovered paracyclophanes. See a series of papers by D. J. Cram and co-workers, *J. Am. Chem. Soc.* (beginning with) **73,** 5691 (1951).

dioxide (36.5 g., 0.83 mole); hydrogen chloride[19] (1.0 g., 0.027 mole); ethanol (29.8 g., 0.65 mole); and acetaldehyde (6.6 g., 0.15 mole). From the materials remaining in the reaction vessel was obtained, by distillation at reduced pressure, unreacted benzal chloride (295.2 g., 1.83 moles, b.p. 45°/2 mm.). Remaining in the distillation flask was an oil residue (55.8 g.) which deposited yellow crystals on standing. These crystals (45.0 g.) were separated on a fritted disk by suction filtering, washed with petroleum ether (b.p. 30–60°), triturated with methyl ethyl ketone, and dried. This product had no sharp melting point and exhibited an average chlorine content of *ca.* 39%. Heating these crystals caused a decrease in chlorine content, and recrystallization from pyridine has reduced the chlorine content through dehydrochlorination to 27.2%. By fractional crystallization (also by selective oxidation) there was obtained from this sample 2.5 g., 0.008 mole, of pure tetrachlorotolane, m.p. 162–163°. The remainder of the crystalline material/s obtained from this reaction is the subject of further investigation.

Preparation of 2,6,2′,6′-tetrachlorobibenzyl. (i) *By thermal decomposition of diacetyl peroxide in 2,6-dichlorotoluene.* A solution containing diacetyl peroxide (34.0 g., 0.289 mole), dissolved in 2,6-dichlorotoluene (175 g., 1.08 moles), was added one drop at a time beneath the surface of 2,6-dichlorotoluene (30.2 g., 0.18 mole) held at 130–140°. From the thermal decomposition of the peroxide and using techniques elsewhere[2,10(a)] described, the following volatile products were obtained and identified: carbon dioxide (20.2 g., 0.45 mole); hydrogen chloride (0.2 g., 0.006 mole); methyl acetate (3.7 g., 0.05 mole); and methane (8.5 l., STP, 0.38 mole). From the material remaining in the reacton vessel was obtained, by distillation at reduced pressure, unreacted 2,6-dichlorotoluene (158.2 g., 1.0 mole), b.p. 76°/12 mm. The residue remaining in the flask was a straw-colored oil which deposited white crystals (38.2 g., 0.119 mole). These crystals were recrystallized from ligroin (b.p. 60–90°) and melted at 155°.

Anal. Calcd. for $C_{14}H_{10}Cl_4$: C, 52.54; H, 3.15; Cl, 44.31; mol. wt., 320. Found: C, 52.69; H, 3.18; Cl, 43.78; mol. wt., (cyoscopically in benzene), 318.3.

All attempts to oxidize this compound to 2,6-dichlorobenzoic acid failed. $KMnO_4$, CrO_3, and $K_2Cr_2O_7$ have been used as oxidizing agents, and in no case was there produced an aromatic acid. The original compound was reclaimed unchanged or burned completely to a mixture of aliphatic acids. Other workers[13] have reported such resistance to oxidation exhibited by aralkyls with chlorines in the 2,6-positions. Prolonged refluxing (92 hr.) of 1 g. of 2,6,2′,6′-tetrachlorobibenzyl in 50 ml. of a mixture of (50% by volume) of concentrated nitric and sulfuric acids gave a solution which upon dilution with water deposited crystals. After repeated washing in hot water these pale yellow crystals melted at 295°.

Anal. Calcd. for $C_{14}H_6N_4O_8Cl_4$: N, 11.46. Found: N, 11.54.

No attempt was made to determine the positions of the nitro groups in this tetranitro derivative.

(ii) *By thermal decomposition of diethyl peroxydicarbonate in 2,6-dichlorotoluene.* A solution containing diethyl peroxydicarbonate (0.38 mole), dissolved in 2,6-dichlorotoluene (249.0 g., 1.55 moles), was added drop by drop beneath the surface of 2,6-dichlorotoluene (132.2 g., 0.82 mole) held at 110°. The following volatile products were obtained and identified: carbon dioxide (32.9 g., 0.75 mole); ethanol (29.9 g., 0.65 mole); and acetaldehyde (4.2 g., 0.1 mole). From the materials remaining in the reaction vessel was obtained, by distillation at reduced pressure, unreacted 2,6-dichlorotoluene (347.0 g., 2.17 moles, b.p. 72–73°/13 mm.). The straw-colored oily residue deposited pale yellow crystals (25.8 g., 0.08 mole), which were recrystallized from an ethanol-butanone mixture (50% by volume), m.p. 154.5°. These crystals did not depress the m.p. of the dimer obtained from the reaction described in the foregoing paragraph.

Anal. Calcd. for $C_{14}H_{10}Cl_4$: C, 52.54; H, 3.15; Cl, 44.31. Found: C, 52.62; H, 3.05; Cl, 43.62. Mol. wt. Calcd. for: 320. Found: 318.2.

(iii) *By Grignard coupling technique. The preparation of 2,6-dichlorobenzyl chloride.* 2,6-Dichlorotoluene was chlorinated with sulfuryl chloride and benzoyl peroxide according to the method of Kharasch and Brown.[20] A trichloro derivative was obtained in 60% yield, b.p. 85–88°/3 mm. This material crystallized in the condenser, m.p. 49–50°; lit.[13(b)] value, 49–50°.

Anal. Calcd. for $C_7H_5Cl_3$: Cl, 54.45. Found: Cl, 54.62.

This compound was converted to the corresponding 2,6-dichlorophenylacetic acid derivative as follows. An ethereal solution containing 2,6-dichlorobenzyl chloride (20.0 g., 0.1 mole) was added to 2.5 g. of magnesium turnings in sodium-dried ether. After complete reaction dry carbon dioxide gas in excess was passed into the system just above the surface of the ethereal solution of the Grignard reagent. By the usual procedure[21] the carbonated product was isolated in 60% yield. White crystals (12.0 g., 0.06 mole) of crude 2,6-dichlorophenylacetic acid were obtained. Recrystallization from aqueous ethanol gave a product melting at 156°.

Anal. Calcd. for $C_8H_6O_2Cl_2$: C, 46.86; H, 2.95; Cl, 34.58; neut. equiv., 205. Found: C, 47.11; H, 3.20; Cl, 34.18; neut. equiv., 201.

This acid was converted to its phenacyl ester by the usual procedure.[22] The ester was recrystallized from 95% ethanol and melted at 60–62°.

Anal. Calcd. for $C_{16}H_{12}O_3Cl_2$: Cl, 21.95. Found: Cl, 22.12.

Its structure thus established,[23] 2,6-dichlorobenzyl chloride was converted in following manner to the corresponding dimeric bibenzyl derivative. 2,6-Dichlorobenzyl chloride (20.0 g., 0.10 mole) dissolved in dry ether was added slowly with stirring to magnesium turnings (2.5 g.) covered with dry ether in a system equipped with a reflux condenser and protected from atmospheric moisture. To the Grignard reagent thus prepared was added 20.0 g., 0.10 mole, of 2,6-dichlorobenzyl chloride and the system refluxed on a water bath with stirring for 10 hr. The ether solution was poured off and the salt in the bottom of the vessel was extracted with more ether. Evaporation of these combined ethereal solutions gave a yellow-brown oil which deposited white crystals. These crystals were boiled with Norit in 60–90° ligroin and finally recrystallized from ligroin. In 30% yield was obtained pure 2,6,2′,6′-tetrachlorobibenzyl, m.p. 156.5°. This compound does not depress the melting points of the 2,6,2′,6′-tetrachlorobibenzyls prepared by the methods pre-

(19) The ratio of moles of HCl obtained to moles of peroxide used increases with an increase in reaction temperature above 95°. In each repetition of this experiment the Michler's ketone in the HCl-absorption tubes did not change its color until near the end of the reaction period (3 hr.). Since at these temperatures neither benzal chloride nor tetrachlorotolane produces HCl, these facts indicate that product or products different from these are formed during the reaction, and that at temperatures above 95° these products begin to decompose producing HCl as their concentrations are built up in solution during the course of the reaction.

(20) M. S. Kharasch and H. C. Brown, *J. Am. Chem. Soc.*, 61, 2146 (1939).

(21) S. V. Putnambeker and E. A. Zoellner in H. Gilman and A. H. Blatt, *Org. Syntheses*, 2nd ed., Coll. **Vol. I**, 524 (1941).

(22) R. L. Shriner and R. C. Fuson, *Systematic Identification of Organic Compounds*, 3rd ed., John Wiley & Sons, New York, 1948, p. 157.

(23) While the chlorination of 2,6-dichlorotoluene and of 3,4-dichlorotoluene have been reported in the literature, we found no report of their chlorination using sulfuryl chloride and thus felt obliged to establish the structures of the chloro derivatives thus obtained.

viously described. Despite the failure to oxidize this compound to known degradation products, the structure seems well established through the synthesis of the same compound by the well established Grignard coupling method.

Anal. Calcd. for $C_{14}H_{10}Cl_4$: C, 52.54; H, 3.15; Cl, 44.31; mol. wt. 320. Found: C, 53.02; H, 3.09; Cl, 44.37; mol. wt. (cryoscopically in benzene) 318.2.

Preparation of 3,4,3',4'-tetrachlorobibenzyl. (i) *By thermal decomposition of diacetyl peroxide in 3,4-dichlorotoluene.* A solution containing diacetyl peroxide (32.5 g., 0.27 mole), dissolved in 3,4-dichlorotoluene (347.5 g., 2.15 moles), was added one drop at a time beneath the surface of 3,4-dichlorotoluene (105.7 g., 0.65 mole) held at 130°. From the thermal decomposition of the peroxide and using techniques already described[10(a)] the following volatile products were obtained and identified: carbon dioxide (17.9 g., 0.407 mole); methyl acetate (4.7 g., 0.063 mole); and methane (6.01 l., STP, 0.267 mole). From the residue remaining in the reaction vessel was obtained, by fractional distillation at reduced pressure (b.p. 80°/10 mm.), unreacted 3,4-dichlorotoluene (420.0 g., 2.60 moles). The viscous oil (33.0 g.), which did not distill under these conditions, deposited upon standing for two days pale yellow crystals (28.9 g.). These crystals were separated from the oil by suction filtering on a fritted disk. Upon recrystallization from 95% ethanol these crystals melted at 111°.

Anal. Calcd. for $C_{14}H_{10}Cl_4$: C, 52.54; H, 3.15; Cl, 44.31; mol. wt., 320. Found: C, 52.18; H, 3.30; Cl, 43.67; mol. wt. (cryoscopically in benzene) 317.3.

(ii) *By thermal decomposition of diethyl peroxydicarbonate in 3,4-dichlorotoluene.* A solution containing diethyl peroxydicarbonate (0.36 moles), dissolved in 3,4-dichlorotoluene (516.0 g., 3.20 moles), was introduced one drop at a time beneath the surface of 3,4-dichlorotoluene (70.5 g., 0.43 mole) held at 120°. Resulting from the thermal decomposition of the peroxide in this solvent the following volatile products were obtained and identified[2]: carbon dioxide (26.5 g., 0.60 mole); ethanol (28.8 g., 0.62 mole); and acetaldehyde (1.6 g., 0.036 mole). From the material remaining in the reaction chamber was obtained, by distillation at reduced pressure, unreacted 3,4-dichlorotoluene (501.0 g., 3.10 moles), b.p. 80°/10 mm., n_D^{25} 1.5470. The residue (63.2 g., 0.20 mole) crystallized on cooling and was digested in hot ligroin (b.p. 60–90°) solution with Norit. These crystals are white in color and melted at 111–112°.

Anal. Calcd. for $C_{14}H_{10}Cl_4$: C, 52.54; H, 3.15; Cl, 44.31; mol. wt., 320. Found: C, 52.51; H, 3.16; Cl, 44.07; mol. wt., 318.6.

When mixed in equal quantity with 3,4,3',4'-tetrachlorobibenzyl obtained from the reaction with diacetyl peroxide described in preceding paragraph this material melted at 111°. This material (2.0 g.) was oxidized quantitatively by the orthodox method[24] to an aromatic acid (m.p. 205.5–206°) which does not depress the m.p. of an authentic sample of 3,4-dichlorobenzoic acid. Literature[25] value for this m.p. is 206°.

(iii) *By Grignard coupling technique. The preparation of 3,4-dichlorobenzyl chloride.* 3,4-Dichlorotoluene was chlorinated with sulfuryl chloride and benzoyl peroxide according to the method of Kharasch and Brown.[20] A trichloro derivative was obtained in 60% yield, b.p. 84°/1.5 mm., 104°/5 mm., $n_D^{22.5}$ 1.5763, lit. value,[26] b.p. 241°.

Anal. Calcd. for $C_7H_5Cl_3$: Cl, 54.45. Found: Cl, 54.55.

This compound was converted to the corresponding ethyl benzyl ether to demonstrate that the third chlorine had replaced a hydrogen in the aliphatic portion of the molecule.[23]

Ethyl 3,4-dichlorobenzyl ether. 3,4-Dichlorobenzyl chloride (87.6 g., 0.45 mole) was refluxed for 90 min. in 300 ml. of 60% aqueous ethanol containing 22.5 g. of sodium hydroxide. Upon cooling the mixture separated into two layers. The top layer contained very little of the reaction products. The bottom layer was distilled after drying over anhydrous potassium carbonate. The fraction boiling at 73–75°/1 mm. (65.2 g., n_D^{22} 1.5312) was ethyl 3,4-dichlorobenzyl ether.

Anal. Calcd. for $C_9H_{10}OCl_2$: C, 52.71; H, 4.91; Cl, 34.59; mol. wt., 205. Found: C, 52.51; H, 4.67; Cl, 34.52; mol. wt. (cryoscopically in benzene) 209.5.

A solid residue (8.0 g., 0.04 mole) was recrystallized from ethanol and shown by its m.p. (50–53°) to be the expected 3,4-dichlorobenzyl alcohol. The ether in predominance over the alcohol has been obtained by other workers under similar conditions.[27] 3,4-Dichlorobenzyl ethyl ether has been prepared in quantitative yield from this 3,4-dichlorobenzyl chloride and sodium ethoxide in absolute ethanol by warming to reflux temperature for 10 min. The ether prepared in this way was distilled at reduced pressure, b.p. 83°/2 mm., n_D^{24} 1.5303. It is identical with the one just described.

Using the same procedure and the same quantities of reagents as described for the synthesis of 2,6,2',6'-tetrachlorobibenzyl, the 3,4-dichlorobenzyl chloride was converted to the corresponding dimer, 3,4,3',4'-tetrachlorobibenzyl. It has been repeatedly observed that the 3,4-dichlorobenzyl chloride is more reactive toward magnesium in forming the Grignard reagent than is 2,6-dichlorobenzyl chloride. The 3,4,3',4'-dimer was obtained in 25% yield, m.p. 112°. This product does not depress the m.p. of dimer obtained from the reaction of either diacetyl peroxide or diethylperoxydicarbonate on 3,4-dichlorotoluene.

Mol. wt. calcd. for $C_{14}H_{10}Cl_4$: 320. Found: (cryoscopically in benzene) 317.3.

It has been oxidized in glacial acetic acid to give 83.3% yield of an acid melting at 205–206.5°. When mixed with authentic 3,4-dichlorobenzoic acid this product melted at 206–207°. The melting point recorded in the lit.[25] for 3,4-dichlorobenzoic acid is 206°.

The thermal decomposition of diethyl peroxydicarbonate in p-isopropylbenzal chloride, the preparation of 2,3-di-(p-ω,ω-dichlorotolyl)-2,3-dimethyl-n-butane (Dimer B). A solution containing diethylperoxydicarbonate (1.02 moles[28]), dissolved in *p*-isopropylbenzal chloride (391.5 g., 1.90 moles), was introduced in single drops beneath the surface of *p*-isopropylbenzal chloride (157.6 g., 0.77 mole) held at 110°. From the thermal decomposition of the peroxide the following volatile products were obtained and identified: carbon dioxide (83.0 g., 1.90 moles); ethanol (85.7 g., 1.86 moles); acetaldehyde (3.5 g., 0.08 mole); and hydrogen chloride (2.5 g., 0.069 mole). From the material remaining in the reaction vessel there was deposited, upon cooling to room temperature and standing overnight, a light tan powder (87.1 g.). This solid, which is much less soluble in the parent monomeric solvent than is Dimer C, was collected by suction filtering on a fritted disk, and the filtrate was distilled at reduced pressure. Unreacted *p*-isopropylbenzal chloride (360.1 g., 1.78 moles), b.p., 92°/1 mm., was collected leaving a residue (101.0 g.) of additional dimer which solidified on cooling. The total mass (188.1 g., 0.464 mole) of the powder, Dimer B, was triturated with boiling ligroin and melted at 207–208°. There was obtained along with this amount of solid about 10 g. of an unidentified dark brown oil. Attempts to determine the molecular weight of

(24) R. L. Shriner and R. C. Fuson, *Systematic Identification of Organic Compounds*, 3rd ed., John Wiley & Sons, New York, 1948, p. 198.

(25) W. P. Wynne, *J. Chem. Soc.*, **114**, 705 (1936).

(26) F. Beilstein and A. Kuhlenberg, *Ann.*, **146**, 326 (1868); **152**, 224 (1869).

(27) J. Yasumura, *Scientific Papers of Faculty of Engineering, Univ. of Tokyo*, **3**, 14 (1951); *Chem. Abstr.*, **40**, 1464 (1952).

(28) The method generally used for the analysis of the peroxide [V. R. Kokatnur and M. Jelling, *J. Am. Chem. Soc.*, **63**, 1432 (1941)] is not entirely satisfactory when the peroxide is dissolved in a solvent like isopropyl benzal chloride containing a high percentage of allylic chlorines.

this Dimer B using the Rast camphor method have given results which were meaningless except as to indicate that the dimer is only partially miscible with camphor.

Anal. of Dimer B. (See Table II.)

Reduction of Dimer B, preparation of 2,3-di(p-tolyl)-2,3-dimethylbutane (Di-*p*-cymene). In nearly quantitative yields this dimer (Dimer B), m.p. 207–208° (13.5 g., 0.003 mole) was reduced by the Clemmensen technique[29] using hydrogen chloride in acetic acid. The hydrocarbon obtained was recrystallized from 95% ethanol and melted at 155.5°. This was mixed with an equal quantity of an authentic sample of 2,3-di(*p*-tolyl)-2,3-dimethylbutane (di-*p*-cymene), and the mixture melted at 155°. Lit.[30] value, 156°.

Hydrolysis of Dimer B, preparation of 2,3-di(p-methanalphenyl)-2,3-dimethylbutane (III). Dimer B, 2,3-di-(*p*-ω,ω-dichlorotolyl)-2,3-dimethylbutane (5.5 g.) was dissolved in a mixture of 500 ml. of glacial acetic acid, 500 ml. of water, and 2.5 g. of mercuric chloride. This mixture was digested at reflux temperature for 3 days with a water trap attached to the condenser to protect the system from atmospheric oxygen after which the water and acetic acid were removed by distillation under reduced pressure of the water pump. Some crystals were volatile with steam and were collected with the distillate. These were added to the crystalline residue, and the whole (1.80 g.) was taken up in peroxide-free ether and extracted with aqueous 5% sodium carbonate. The neutral ethereal extract was dried over calcium chloride and distilled. The crystals remaining were recrystallized from 95% ethanol and appeared as pale yellow very hard platelets, m.p. 207–208°. They gave a positive test with Schiff's aldehyde reagent.

Anal. of III. (See Table II.)

This dialdehyde (III) has also been obtained by hydrolysis of Dimer B in presence of mercuric chloride using aqueous acetone as the solvent. It was converted by the Wolff-Kishner technique[31] to the corresponding hydrocarbon, *2,3-di-p-tolyl-2,3-dimethylbutane*, m.p. 153–154°. This hydrocarbon did not depress the m.p. of an authentic sample of 2,3-di-*p*-tolyl-2,3-dimethylbutane.

The preparation of 2,3-di-p-carboxyphenyl-2,3-dimethylbutane (IV). Permanganate in acid solution oxidized the Dimer B in poor yield to the corresponding dicarboxylic acid (IV), but produced some terephthalic acid. Better yields (50%) were obtained by digesting small samples (10–12 g.) of Dimer B in aqueous dioxane with sodium hydroxide and adding hydrogen peroxide at intervals over a period of 16 hr. The finely powdered crystalline acid, sparingly soluble in water, was obtained by evaporating part of this solvent at reduced pressure and acidifying the mixture with dilute hydrochloric acid. Upon redissolving in dilute sodium hydroxide, reacidifying, and washing repeatedly in hot water these crystals were dried in vacuo at 110°. They melted with decomposition over the range 280–285°. The neutral equivalent was determined in aqueous ethanol (see Table II). This acid (IV) has also been obtained by oxidizing with hydrogen peroxide in glacial acetic acid the dialdehyde (III) described in the preceding paragraph. This dicarboxylic acid (IV) does not depress the m.p. of authentic 2,3-di-*p*-carboxyphenyl-2,3-dimethylbutane. Lit.[32] value 275–280° with decomposition. The acid (IV) obtained as here described has also been decarboxylated to produce 2,3-dimethyl-2,3-diphenyl-*n*-butane by a method described elsewhere.[32]

Condensation derivatives of 2,3-di-(p-methanalphenyl)-2,3-dimethylbutane (III). The dialdehyde (III) has, by conventional methods,[33] been converted into the dihydrazone derivative (VII), the dioxime (VIII), and the di-2,4-dinitrophenylhydrazone (VI). The melting points and the analyses for these derivatives are given in Table II.

The thermal decomposition of diacetyl peroxide in p-isopropylbenzal chloride, the preparation of 1-p-isopropylphenyl-1,1-dichloro-2-methyl-2-p-(ω,ω-dichlorotolyl)propane (Dimer C). A solution[34] containing diacetyl peroxide (66.5 g., 0.563 mole[28]), dissolved in *p*-isopropylbenzal chloride (460 g., 2.26 moles), was introduced in single drops beneath the surface of *p*-isopropylbenzal chloride (94.7 g., 0.47 mole) held at 130°. From the thermal decomposition of the peroxide in this solvent the following volatile products were isolated and identified: carbon dioxide (39.7 g., 0.90 mole), methyl acetate (14.8 g., 0.2 mole), and methane (16.0 l., STP, 0.71 mole). From the material remaining in the reaction vessel, unreacted *p*-isopropylbenzal chloride (314.6 g., 1.90 moles, b.p. 75°/0.5 mm., n_D^{26} 1.5313) was obtained by distillation at reduced pressure. Upon cooling, the remaining oil crystallized to a yellow-brown solid mass (134.2 g., 0.332 mole), which was triturated with hot ligroin and melted at 138°. These crystals (Dimer C) were identified as 1-*p*-isopropylphenyl-1,1-dichloro-2-methyl-2-*p*-(ω,ω-dichlorotolyl)propane by methods described in the following paragraphs.

Anal. of Dimer C. (See Table II.)

Hydrolysis of Dimer C, preparation of p-(p-isopropyl-ω,ω-dimethylphenacyl)benzaldehyde (IX). Hydrolysis of this Dimer C in basic medium (KOH in aqueous dioxane) gives largely resin. In neutral solution (aqueous acetone) the yield of the keto-aldehyde is slightly better, but it does not approximate that obtained from hydrolysis in acidic (aqueous acetic acid) medium. Dimer C (18.2 g.) was dissolved in a mixture of 800 ml. of water and 800 ml. of glacial acetic acid to which was added 2.5 g. of mercuric chloride. While protected with a water trap against atmospheric oxygen, this mixture was digested at reflux temperature for 96 hr. The water and acetic acid were removed by distillation under reduced pressure of the water pump. The hydrolysis product was not volatile with steam. There remained a red-brown oil which formed on cooling a yellow-brown crystalline mass (14.9 g.) and some resin (0.51 g.). These crystals were distinctly more soluble in acetic acid than their precursor, Dimer C. They were taken up in peroxide-free ether and extracted with aqueous 5% sodium carbonate. Evaporation of the ether from the dried ($CaCl_2$) neutral fraction deposited white, somewhat iridescent platelets, m.p. 104°. These crystals gave negative Beilstein test for halogen and a positive Schiff's aldehyde test. These crystals (IX) were characterized as the keto-aldehyde, *p*-(*p*-isopropyl-ω,ω-dimethylphenacyl)benzaldehyde, by the reactions described in the following paragraphs.

Anal. of IX. (See Table II.)

Preparation of p-(p-isopropyl-ω,ω-dimethylphenacyl)benzoic acid (X). The ether-insoluble sodium salt (which is also

(29) C. H. F. Allen and R. H. Kimball in A. H. Blatt, *Org. Syntheses*, **Coll. Vol. II**, 499 (1943). While this method works well with Dimer B, we have been unsuccessful in attempting to reduce Dimer C to the corresponding hydrocarbon by this method.

(30) E. Boedtker and R. Kerlor, *Compt. rend.*, **188**, 1681 (1929).

(31) D. Todd in R. Adams, *Organic Reactions*, **4**, 378 (1948).

(32) H. C. McBay and P. T. Groves, *J. Org. Chem.*, **21**, 691 (1956).

(33) R. L. Shriner and R. C. Fuson, *Systematic Identification of Organic Compounds*, 3rd ed., John Wiley & Sons, New York, 1948, pp. 167–172.

(34) Diacetyl peroxide dissolves extremely slowly in this solvent at room temperature. The process is highly endothermic, but *it is, to be sure, not advisable* to warm this material containing the entire 0.56 mole of diacetyl peroxide to hasten process of dissolving. Note that during the course of the thermal decomposition reaction, the entire 0.56 mole of peroxide is heated, but it is introduced *one drop* at a time *beneath the surface* of the hot (130°) *p*-isopropyl benzal chloride where it is thus decomposed in small lots over a period of 3–5 hr. All these reactions are carried out behind plexiglas explosion screens one half to one inch thick (2, 10a).

sparingly soluble in water) obtained through sodium-carbonate extraction mentioned in the preceding paragraph was acidified with dilute hydrochloric acid to produce the free acid, X. This glistening white crystalline substance was recrystallized from 50% aqueous ethanol and dried in vacuo at room temperature, m.p. 198°. This keto-acid, X, has also been obtained by oxidizing the parent keto-aldehyde, IX, described in the preceding paragraph, with hydrogen peroxide in dilute acetic acid.

Anal. of X. (See Table II.)

In order to demonstrate that this acid, X, contains a keto group it was treated in the conventional manner[33] with hydroxylamine hydrochloride, and a white crystalline material was obtained with an m.p. 211–212°. Nitrogen analysis on this material corresponds to the derived ketoximino-hydroxamic acid.

Anal. Calcd. for $C_{20}H_{24}N_2O_3$: N, 8.23. Found: N, 8.32.

Condensation derivatives of p-(p-isopropyl-ω,ω-dimethylphenacyl)benzaldehyde (IX). The keto-aldehyde (IX) has by conventional methods[33] been converted into the dihydrazone derivative (XII), the dioxime (XIII), and the mono-2,4-dinitrophenylhydrazone (XI). The melting points and the analyses for these derivatives are given in Table II.

Acknowledgments. This work has been supported in part by a Frederick Gardner Cottrell Grant-in-Aid from the research Corporation. We are grateful for financial assistance from the Atlanta University Carnegie Corporation Grant-in-Aid Committee.

Some of the microanalyses reported in this paper were done at the Clark Microanalytical Laboratory, Urbana, Ill. Analyses reported in this paper of compounds containing relatively high N/C ratio have been performed in our own laboratories by Mr. Ratio Jones using a specially prepared combustion train, Huggins and Jones, *Unpublished results;* Ratio Jones, Master's thesis, Atlanta University, June 1954.

ATLANTA, GA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WAYNE STATE UNIVERSITY]

Polymers II. Polydimethyleneacetylene[1,2]

WILLIAM J. BAILEY[3] AND EDWARD J. FUJIWARA[4]

Received June 28, 1957

Condensation of 1-chloro-4-bromo-2-butyne with magnesium produced a mixture of soluble and insoluble polymers. Extraction of this mixture produced a low yield of soluble polydimethyleneacetylene, m.p. above 400°, with a molecular weight of 1000 to 2000. The structure of the polymer was proved by analysis, oxidation to succinic acid, and hydrogenation to polymethylene. This result emphasizes the fact that symmetry greatly promotes crystallinity of polymers and strongly increases their melting points.

In order to determine the correlation between the chemical structure and the physical properties of hydrocarbon polymers the synthesis of a series of polymers of unusual but known chemical structure has been undertaken. Hydrocarbon polymers were chosen for this study since complicating factors, such as hydrogen bonding and strong dipole interactions, would be absent. In a previous paper the synthesis of an all-*cis* diene polymer, poly-1,2-dimethylenecyclohexane, related in structure to natural rubber, was reported. In contrast to natural rubber, the polydimethylenecyclohexane was a high melting crystalline solid. This result emphasized the fact that small changes in structure often have a very marked effect on the physical properties of polymers.

Since the phenomenon of *cis-trans* isomerism in diene polymers introduces several complications, it was of interest to study the effect of a symmetrical triple bond on the properties of a hydrocarbon polymer, particularly a polymer in which the triple bond essentially replaces a double bond. The simplest case would be polydimethyleneacetylene (I), an analog of an all-1,4 polybutadiene. This polymer I was of special interest since it had been predicted to be a good low temperature rubber on the basis that the polymer chain would be free to rotate at low temperatures. One might expect that the acetylene group, which has no substituents and is symmetrical, would offer no steric hindrance to rotation about the adjacent single bonds. The acetylene polymer I was of further interest in that it might serve as a starting material for the synthesis of an all-*cis* or an all-*trans* polybutadiene.

The starting material for the preparation of polydimethyleneacetylene was 1-chloro-4-bromo-2-butyne (II).[5] When the mixed dihalide II was vigorously stirred with a large excess of magnesium, a Grignard reagent easily formed. When it was allowed to stand, this Grignard coupled with itself to form an insoluble polymer mixture III. The untreated mixture contained a Grignard as an end group or some adsorbed Grignard reagent. When the polymerization was carried out in the usual

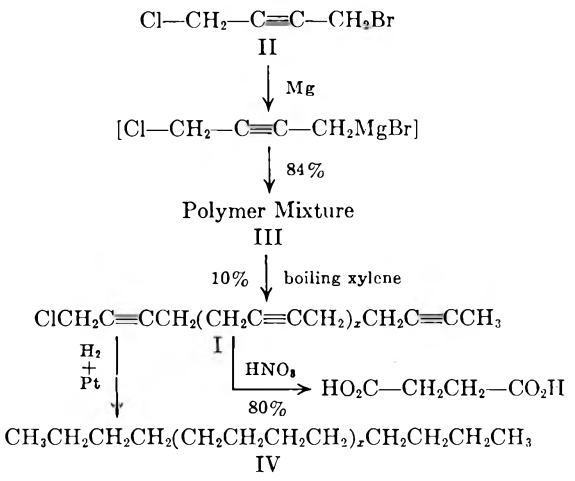
(1) Previous paper in this series, *J. Am. Chem. Soc.*, **76**, 5418 (1954).

(2) Presented before the Division of Polymer Chemistry at the 118th National Meeting of the American Chemical Society, Chicago, Ill., September 1950.

(3) Present address, Department of Chemistry, University of Maryland, College Park, Md.

(4) Office of Naval Research Fellow, 1949–50; Ethyl Corporation Fellow, 1950–51.

(5) W. J. Bailey and E. J. Fujiwara, *J. Am. Chem. Soc.*, **77**, 165 (1955).



way, the formation of this insoluble precipitate began when about one third of the dihalide II had been added. The final products appeared to be identical, even if the addition of halide was stopped at this point. Titration of an aliqout of the reaction mixture indicated that, when all of the halide had been added, an 18% yield of soluble Grignard reagent was present. The powdery polymeric III was infusible and not completely soluble in any solvent tested, even at very high temperatures. The polymer was stable for indefinite periods when it was stored under nitrogen but it absorbed oxygen from the air quite rapidly.

In order to characterize the polymer mixture III, a separation was made into an insoluble fraction IIIa and a soluble fraction I. Thus when the polymer III was extracted with hot solvents, such as cumene, methylnaphthalene or biphenyl, approximately 10% of the polymer III dissolved. Boiling xylene, however, proved to be the most convenient solvent. When the hot solution was cooled, almost all of the dissolved polymer reprecipitated, but, for convenience in filtering, methanol was added to the cold solution. The product, soluble polydimethyleneacetylene (I), was a light-cream-colored powder. Although the polymer I was completely soluble in boiling xylene, 100 ml. of the hot solvent was required to dissolve 0.1 g. When a melting point determination was performed in a sealed tube in an atmosphere of carbon dioxide, no visible change occurred below 400° and the sample of I could be recovered unchanged. At temperatures above 400° the sample darkened somewhat but did not appear to soften or to melt even at 550°.

The structure of the soluble polydimethyleneacetylene (I) was indicated by a series of chemical and physical tests. If the chlorine atoms, which occur as end groups, are neglected, the polymer has the correct carbon-hydrogen analysis. Oxidation of the soluble I with nitric acid produced an 80% yield of succinic acid. (Oxidation with potassium permanganate gave only a 48% yield of succinic acid.) Catalytic hydrogenation in xylene at 200° produced a linear polymethylene (IV). Although hydrogenation also occurred in biphenyl, the mechanical difficulties with this solvent were much greater. The structure of the polymethylene (IV) was indicated by the fact that it had the correct carbon-hydrogen analysis and softened at 65–90°. Viscosity measurements, followed by calculations according to Kemp and Peters[6] for the normal hydrocarbons, indicated an approximate value of 1500 while cryoscopic measurements in camphor indicated a molecular weight of about 1300. In addition a polymethylene with a molecular weight of about 1500 might be expected to soften in the range of 65–90°.

A further check on the molecular weight of the original soluble polydimethyleneacetylene (I) was obtained from the chlorine end groups. If it is assumed that there is one chlorine atom at the end of each polymer chain, a molecular weight of approximately 2500 can be calculated. Because the polymer I underwent a smooth catalytic hydrogenation, one must conclude that the polymer formed a true solution and not an extremely fine dispersion of an insoluble polymer. In a cross-linked polymer some of the unsaturated groups could not be absorbed directly on the catalyst surface. It is also unlikely that any extensive degradation of the original polymer I took place during hydrogenation under a variety of experimental conditions.

The properties of the soluble polydimethyleneacetylene (I) can be rationalized by assuming that the triple bonds produce a rigid, symmetrical structure in which each dimethyleneacetylene unit is completely linear. The structure would look like a series of sticks joined at the ends. Such an arrangement would permit the polymer chains to align themselves very close together and to form strong crystallites in which the rigid nature of the molecules would make it very difficult for the molecules to move. Actually, the high degree of symmetry in this polymer would greatly enhance the crystallinity. The large effect of symmetry on the melting point of hydrocarbon polymers was emphasized by the high melting point and high crystallinity of poly-1,2-dimethylenecyclohexane.[1] The fact that this polydimethyleneacetylene (I) was crystalline was confirmed by an x-ray diffraction study[7] on the powder. Unfortunately, the material could not be fused and drawn into a fiber for more exact structure determination.

The properties of the polydimethylenacetylene (I) are quite similar to those reported by Jacobson[8] and by Szwarc[9] for poly-*p*-xylylene. Jacobson prepared his polymer by a Grignard coupling with

(6) A. R. Kemp and H. Peters, *Ind. Eng. Chem.*, **35**, 1108 (1943).

(7) The authors are grateful to Dr. H. N. Campbell, General Laboratories, United States Rubber Co., Passaic, N. J., for the x-ray diffraction studies.

(8) R. A. Jacobson, *J. Am. Chem. Soc.*, **54**, 1514 (1932).

(9) M. Szwarc, *Discussions Faraday Soc.*, 46 (1947).

α,α'-dibromo-*p*-xylene. Szwarc, on the other hand, prepared his polymer by the pyrolysis of *p*-xylene, presumably through polymerization of the intermediate 3,6-dimethylene-1,4-cyclohexadiene. In both cases the products were high melting and relatively insoluble. One can assume that the benzene ring introduced rigidity and linearity into the polymer chain in the same way that the triple bond does in the present polymer.

Further evidence concerning the structure of the soluble polydimethyleneacetylene (I) was obtained from studies of its partial reduction. It was hoped that the acetylene polymer I would serve as a starting material for the syntheses of an all-*cis* and an all-*trans* polybutadiene. Previous workers have indicated that chemical reduction of a triple bond gives almost entirely the *trans* olefin,[10] whereas catalytic hydrogenation gives primarily the *cis* isomer.[11] Preliminary chemical reductions of I were carried out with a variety of reducing agents, including sodium in liquid ammonia, sodium plus methyl or ethyl alcohol and disodionaphthalene. Because of the limited solubility of the polydimethyleneacetylene (I), only reductions with sodium plus a xylene solution of *n*-amyl alcohol were at all satisfactory. Results of several preliminary runs are listed in Table I. It is interesting that, as the percentage of triple bonds reduced to *trans* double bonds increases to about 50%, the softening point falls to 160–165° and the solubility in xylene increases markedly. That no other major transformation in the polymer structure occurred during this chemical reduction was indicated by the fact that complete hydrogenation of these partially reduced polymers produced a linear polymethylene identical with that obtained from the original soluble polydimethyleneacetylene (I). Since the properties of the partially reduced polymers do vary with the triple bond content, one may conclude that the decreased symmetry has a very large effect and that the properties of the original polymer I are not completely unexpected. Initial attempts at partial catalytic hydrogenation of the polymer I to produce an all-*cis* polymer were not successful because the products were invariably a mixture of starting material and the completely reduced polymer. Apparently the polymer is adsorbed on the surface of the catalyst and is essentially completely reduced before it is desorbed.

TABLE I

Run	Sodium, G.	Reaction Temperature, °C.	Carbon-Hydrogen Ratio of Product	Softening Point, °C.	Solubility, Mg./100 Ml. of Benzene
1	1.2	90	1/1.12	215–220	20
2	2.4	120	1/1.18	180–190	80
3	4.8	140	1/1.25	160–165	310
4	6.0	140	1/1.25	160–165	300

(10) K. N. Campbell and L. T. Eby, *J. Am. Chem. Soc.*, **63**, 216 (1941).

(11) R. A. Raphael, *Acetylene Compounds in Organic Synthesis*, Academic Press, Inc., New York, N. Y., 1955.

The structure of the insoluble fraction (IIIa) of the original polymer mixture was not determined. Whether the insoluble polymer IIIa was cross linked or was just a high molecular weight polydimethyleneacetylene was not easy to establish. Oxidation of IIIa with nitric acid produced a 60% yield of succinic acid, but the lower yield may be due to the more vigorous conditions that were required for complete oxidation compared to those for the soluble I.

The mechanism of the polymerization of chlorobromobutyne may be quite complex. Johnson[12] found that the reaction of 1,4-dichloro- or 1,4-dibromo-2-butyne with ethyl- or methylmagnesium iodides gave good yields of the corresponding substituted acetylene. However, propargyl Grignard reagents have been shown to produce a mixture of products, including allenes,[13a] when carbonated. However, alkylation reactions of these propargyl Grignard reagents have been reported to give the unrearranged product.[13b,c]

One might speculate that an occasional allenic group could be formed during the polymerization and that these reactive groups could dimerize to form a cross-linked network as the main product. However, in view of the high melting point and relatively low molecular weight of the soluble polydimethyleneacetylene (I), it appears unlikely that it could contain any appreciable amount of allenes or branches resulting from their dimerization. It also is possible that some 1,2,3-butatriene could have been formed during the formation of the Grignard and subsequently polymerized to produce a complex structure.[14] Actually, considerably more vigorous conditions are required for the preparation of butatriene from 1,4-dibromo-2-butyne than those used for the present condensation. Of course, a 1,4-addition of 1,2,3-butatriene would produce linear polydimethyleneacetylene identical with that produced by a coupling reaction.

EXPERIMENTAL[15]

Materials. Magnesium was freshly prepared by turning a bar of 99.9% pure magnesium on a lathe and storing the turnings under nitrogen. The *1-chloro-4-bromo-2-butyne (II)*,[5] b.p. 45° (2 mm.), n_D^{25} 1.5470, was freshly distilled before use.

Polymerization of 1-chloro-4-bromo-2-butyne (II). Magnesium turnings (28.8 g.; 1.2 moles) and 800 ml. of anhydrous ether were placed in a 2-liter, three-necked creased flask equipped with an efficient stirrer. To this mixture was added 67 g. (0.4 mole) of 1-chloro-4-bromo-2-butyne

(12) A. W. Johnson, *J. Chem. Soc.*, 1009 (1946).

(13) (a) J. H. Wotiz, *J. Am. Chem. Soc.*, **72**, 1639 (1950); (b) M. S. Newman and J. H. Wotiz, *J. Am. Chem. Soc.*, **71**, 1292 (1949); (c) T. Y. Lai, *Bull. soc. chim.*, **53**, 1543 (1933).

(14) W. M. Schubert, T. H. Liddicoet, and W. A. Lanks, *J. Am. Chem. Soc.*, **75**, 1929 (1954).

(15) The authors are indebted to Vivian Kapusinski for the microanalyses. All melting points are corrected.

(II) at a rate sufficient to maintain gentle reflux of the solvent. When approximately one third of the halide II had been added, a precipitate of a fine, light tan, flocculent powder formed in the reaction mixture and, as the addition and reaction progressed, the mixture became quite thick. After all of the halide II had been added, the reaction mixture was stirred for an additional hour until all evidence of reaction had subsided. (Since the chlorobromo compound II is an extremely potent vesicant and lachrymator, low concentrations can be detected by anyone who is sensitive to it.) Little or no unreacted dihalide remained after this period of stirring. The reaction mixture was diluted with anhydrous ether until the excess magnesium settled cleanly to the bottom. After the ether slurry of the polymeric precipitate was decanted from the magnesium, the slurry was centrifuged to collect the polymer. The precipitate was washed 3 times with ether and then suspended in a liter of 80% methanol containing 5% sulfuric acid and allowed to stand with frequent shaking for 10 hr. The polymer was removed by filtration, washed with water until free of acid, and then washed with acetone until all color was removed. The wet precipitate was treated with an acetone solution of an antioxidant (Neozone D) and dried in a vacuum desiccator at a pressure of 0.2 mm. to produce 17.5 g. (84%) of a light tan powdery polymer (III). When a sample of this powder was exposed to air for 2 days, it turned brown and increased in weight by 15%.

Isolation of a soluble fraction of polydimethyleneacetylene (I). A suspension of 17.5 g. of the light tan crude polydimethyleneacetylene (III) described above in 2 l. of anhydrous xylene was maintained under reflux for 48 hr. under an atmosphere of carbon dioxide. The hot solution was then quickly filtered through a fritted glass funnel of medium porosity, and the filtrate was concentrated under reduced pressure to about 200 ml. After the concentrate was added to approximately 600 ml. of methanol, the precipitated polymer was removed by means of a centrifuge. The solid was washed with acetone and dried under reduced pressure as described previously to yield 1.75 g. of light-cream-colored powder of soluble polydimethyleneacetylene (I).

Anal. Calcd. for C_4H_4: C, 92.35; H, 7.65. Found: C, 91.30; H, 7.30; Cl, 1.19.

(When samples of this polymer I were analyzed in the usual way for carbon and hydrogen, they invariably ignited in an explosive manner; however, with proper wrapping of the sample with platinum foil satisfactory results were obtained.)

Oxidation of soluble polydimethyleneacetylene (I). To a mixture of 0.52 g. of soluble polydimethyleneacetylene (I) and 50 ml. of 10% nitric acid heated on a steam bath was added dropwise concentrated nitric acid until the oxidation became fairly vigorous. After the oxidation had subsided, the reaction mixture was evaporated to dryness on the steam bath. The thick pasty residue was mixed with 50 ml. of water and the mixture was exhaustively extracted with ether for 48 hr. The ether was removed from the extract by evaporation to produce 1.20 g. of crude succinic acid. This residue was dissolved in 5 ml. of boiling water and this solution was decolorized with charcoal. This solution was cooled and the resulting succinic acid was removed by filtration. The filtrate was concentrated to produce an additional quantity of acid and the process was repeated to produce a third crop of crystals. The total yield of succinic acid, m.p. 185–186° (reported[16] m.p. 185°), was 0.95 g (80%). A mixed melting point determination with an authentic sample of succinic acid showed no depression.

Catalytic reduction of soluble polydimethyleneacetylene (I). A mixture of 0.26 g. of soluble polydimethyleneacetylene (I), 200 ml. of xylene, and 0.05 g. of freshly prepared Adams catalyst (PtO_2) was hydrogenated at 200° and 90 atm. for 6 hr. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to approximately 20 ml. This concentrated polymer solution was added dropwise to 100 ml. of methanol. The resulting precipitate was removed by filtration, washed with methanol, and dried under reduced pressure to produce 0.24 g. (85%) of a waxy linear polymethylene (IV), softening point 65–90°.

Anal. Calcd. for $(CH_2)_x$: C, 85.73; H, 14.27. Found: C, 85.50; H, 14.01.

Molecular weight determinations of the hydrogenated polydimethyleneacetylene (IV). Viscosity measurements at 25° of 1, 0.5, and 0.25% solutions of linear polymethylene (IV) in benzene indicated an intrinsic viscosity[17] of 0.36. By the use of the equation of Kemp and Peters[6] for normal hydrocarbons with a K_m of 2.4×10^{-4} a molecular weight in the range of 1500 is calculated.

A solution of 2.612 mg. of polymer IV in 39.175 mg. of camphor showed a melting point depression of 2.2°. Calculations[18] with this cryoscopic data indicated a molecular weight of approximately 1300.

X-ray study of soluble polydimethyleneacetylene (I). Since this polymer I could not be drawn into a fiber, only a powder pattern was obtained. Crystallinity of the polymer was indicated by the powder pattern[7] which possessed a very strong line corresponding to an interplanar spacing of 3.8 Å and a very weak line corresponding to a spacing of 4.2 Å.

Partial reduction of soluble polydimethyleneacetylene (I). To a solution of 52 mg. of soluble polydimethyleneacetylene (I) in 150 ml. of xylene was added 1.2 g. of sodium sand. While this mixture was vigorously stirred at 90°, 10 ml. of *n*-amyl alcohol was added dropwise over a period of 30 min. This reaction mixture was stirred at 90° until all the sodium had disappeared and the mixture was extracted with water until it was free of base. The xylene layer plus a small amount of a precipitate were dried by means of azeotropic distillation with a Dean-Stark trap under an atmosphere of carbon dioxide. The mixture was cooled to room temperature and the undesired precipitate was removed by filtration. The filtrate was concentrated under reduced pressure to approximately 25 ml. and this concentrate was added dropwise to 125 ml. of methanol. The precipitate was removed by filtration and dried under partial vacuum to produce 0.43 mg. of partially hydrogenated polydimethyleneacetylene, softening point 215–220°. The results of several reductions under a variety of conditions are listed in Table I.

DETROIT 1, MICH.

(16) H. Marshall and A. T. Cameron, *J. Chem. Soc.*, 1522 (1907).

(17) A. Weissberger, *Physical Methods of Organic Chemistry*, Vol. I, Interscience Publishers, Inc., New York, N. Y., 1950, p. 350.

(18) J. B. Niederl and V. Niederl, *Organic Quantitative Microanalyses*, John Wiley and Sons, Inc., New York, N. Y., 1938, p. 217.

[FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, HEBREW UNIVERSITY]

p-Vinylbenzoic and p-Vinylphenylacetic Acids

ERNST D. BERGMANN AND JOCHANAN BLUM

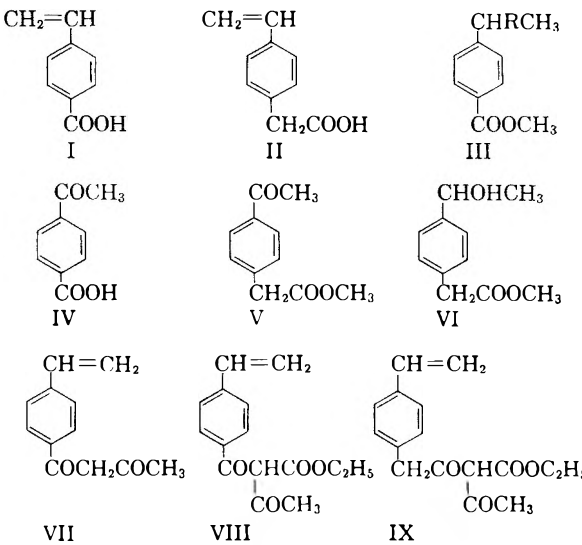
Received August 11, 1958

Preparative methods for p-vinylbenzoic and p-vinylphenylacetic acids have been worked out. (p-Vinylbenzoyl)acetone (VII) and ethyl α-(p-vinylphenylacetyl)acetoacetate (IX) have been synthesized. In orienting experiments, it has been found that the two compounds polymerize very quickly and that the polymers obtained have no chelating properties. Further experiments in this direction have, therefore, been abandoned.

The purpose of this study was to prepare polystyrenes substituted in the benzene rings by 1,3-diketone groupings which would be capable of forming chelates with heavy metal ions and thus represent exchange resins endowed with a specific affinity. The starting materials were p-vinylbenzoic and p-vinylphenylacetic acid. p-Vinylbenzoic acid (I) has been prepared before by Marvel and Overberger,[1] but in over-all yields of only 1.8 to 4.1%, and by Emerson[2] in better yield, but by a method not easily applied to the preparation of larger quantities. p-Vinylphenylacetic acid (II) has not been synthesized before.

When methyl p-ethylbenzoate (III, R = H) was brominated with *N*-bromosuccinimide, the expected bromo-compound (III, R = Br) was obtained in 82% yield, but the bromine atom was unexpectedly refractory towards pyridine or collidine. Alcoholic alkali gave p-(α-ethoxyethyl)-benzoic acid, and silver hydroxide methyl p-(α-hydroxyethyl)benzoate (III, R = OH), in 43 and 20% yield, respectively. The latter could be smoothly (85%) dehydrated to the methyl ester of (I) by the usual method employing potassium hydrogen sulfate; however, the over-all yield, calculated on (III, R = H), was only 14%. An over-all yield of 37% was obtained from the easily available p-methylacetophenone. It was oxidized with permanganate to p-acetylbenzoic acid (IV), the methyl ester of which was reduced to (III, R = OH) smoothly by means of sodium borohydride.

The reaction of methyl phenylacetate with acetyl chloride in the presence of aluminum chloride gave 66% of a monoacetyl derivative; its structure (V) was proven by oxidation to terephthalic acid. Whilst with aluminum isopropoxide instead of the expected carbinol VI its isopropyl ether was obtained,[3] sodium borohydride effected the reduction smoothly, and VI could be dehydrated by means of potassium hydrogen sulfate to the methyl ester of II.



Methyl p-vinylbenzoate condensed with acetone in the presence of sodium hydride to give p-vinylbenzoylacetone (VII) in 16% yield. The condensation, on the other hand, of p-vinylbenzoyl chloride —which was prepared from the sodium salt of I and oxalyl chloride—with the magnesium enolate of ethyl acetoacetate gave directly the polymer of the expected ketoester VIII in 81% yield. This may well be due to the presence of a p-divinylbenzene system in the enol form of VIII. The methyl ester of II, on the other hand, gave in this reaction in 30% yield the desired keto ester IX, together with some polymeric material, whilst the condensation with acetone led practically only to polymeric material.[3a]

Preliminary experiments have shown that the tendency to polymerization of the two vinyl-monomers VII and IX is so great that their transformation into the copper and uranium chelates is accompanied by polymerization. On the other hand, judging from the intensity of the color reaction, the complex formed from the two monomers with ferric chloride in methanol appears to be quite stable in solution. Further attempts to

(1) C. S. Marvel and C. G. Overberger, *J. Am. Chem. Soc.*, **67**, 2250 (1945).

(2) W. S. Emerson, J. W. Heyd, H. E. Lucas, E. C. Chapin, G. R. Owen, and R. W. Shortridge, *J. Am. Chem. Soc.*, **68**, 674 (1946). *Cf.* the recent papers by J. Cazes, *Compt. Rend. Acad. Sciences*, **247**, 1874 (1958) and G. S. Kolesnikov and T. A. Soboleva, *Izvest. Akad. Nauk S.S.S.R., otdel Khim. Nauk*, 762 (1958); *Chem. Abstr.*, **52**, 20025 (1958).

(3) Such cases have been observed before. See A. L. Wilds, *Org. Reactions*, II, 190 (1944).

(3a) The polymer of methacroylacetone has been described recently by R. Teyssié and G. Smets, *Makromol. Chem.*, **26**, 245 (1958).

prepare polymers that exhibit specific chelating properties have been abandoned.

In the course of this study, we have tried in vain to replace—by means of metallic lithium or butyl lithium—the bromine atom in methyl *p*-bromophenylacetate and *p*-bromobenzoate and in *p*-bromophenylmethylcarbinol.[4]

EXPERIMENTAL

p-Ethylbenzoic acid. From 400 g. of sodium hydroxide in 3.4 l. of water and 290 g. of bromine a solution of sodium hypobromite was prepared at a temperature not exceeding 5°, and 195 g. of *p*-ethylacetophenone[5] was added within 1 hr. and at a temperature of 0 to 5°. The stirring was continued for 1 hr. at 35° and the solution gently heated to 90°, so that the bromoform formed could evaporate (2 hr.). The solution was cooled, treated with a solution of 30 g. of sodium bisulfite in 200 ml. of water, freed from colored impurities by extraction with ligroin (60–90°), and acidified. After recrystallization from alcohol or cyclohexane, the compound melted at 112°; its yield was 153 g. (79%). The *methyl ester*[6] boiled at 121–123° (20 mm.) [lit.[2] 127–130° (24 mm.)]; it was obtained in 91% yield.

Methyl p-(α-bromoethyl)benzoate (III, R = Br). A mixture of 148 g. of the foregoing ester, 160 g. of *N*-bromosuccinimide, 0.1 g. of benzoyl peroxide, and 600 ml. of carbon tetrachloride was refluxed for 45 min., filtered, and distilled. The compound boiled at 135–138° (1 mm.) with slight decomposition; yield, 180 g. (82%).

p-(α-Ethoxyethyl)benzoic acid. To a cold solution of 24 g. of potassium hydroxide in 40 ml. of ethanol, 24 g. of the foregoing ester was added. The mixture was refluxed for 2 hr., filtered, and acidified with an excess of 10% hydrochloric acid. The acid (14 g.; 43%) crystallized nicely from aqueous alcohol and melted at 105°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.2. Found: C, 67.8; H, 6.8.

p-Acetylbenzoic acid (IV). A mixture of 288 g. of *p*-methylacetophenone, prepared in analogy to the *p*-ethyl compound[5] in 95% yield, 60 g. of magnesium sulfate, and 3 l. of water was heated at 60° and 158 g. of potassium permanganate (less than the theoretical quantity!) added in portions of about 30 g. with stirring, so that a new portion was only added when the preceding one had been completely reduced. (The reaction is strongly exothermic and has to be checked with cold water from time to time.) The reaction mixture was acidified with dilute sulfuric acid, the manganese dioxide reduced with a saturated solution of sodium bisulfite, the solution cooled to 5°, and the solid filtered and washed with petroleum ether (100–120°). Recrystallization from water gave 72 g. of IV, m.p. 200–201°.

From the filtrate (two phases), 180 g. of *p*-methylacetophenone was recovered by extraction with petroleum ether. It is not advisable to increase the conversion by using an excess of the oxidant or more stringent conditions; this only leads to the formation of terephthalic acid. The *methyl ester* was prepared by the method of Clinton and Laskowski[6] in 89% yield. It formed, after recrystallization from carbon tetrachloride or hexane, colorless plates of m.p. 93–94°.[2]

Methyl p-(α-hydroxyethyl)benzoate (III, R = OH). To a suspension of 87 g. of the methyl ester of (IV) in 300 ml. of ether, a solution of 5 g. of sodium borohydride in 28 ml. of anhydrous methanol was added slowly (20 min.) with agitation and cooling with ice water. The reaction was continued for 4 hr. and the mixture acidified with 10% hydrochloric acid. The layers were separated and the aqueous phase extracted with ether. The product (yield, 64 g., 73%) boiled at 134° (3 mm.) [lit.[2]: 134° (4 mm.)].

Methyl p-vinylbenzoate. The following conditions, if strictly adhered to, give optimum yields. A Claisen flask of 25-ml. capacity (for the distillation of solids) was half filled with anhydrous potassium hydrogen sulfate and in a vacuum of 1–2 mm. heated at 200–215° for 15 min. Through a dropping funnel (tip inside the salt layer!) 18.5 g. of (III, R = OH) was added within about 2 hr., so that the temperature of the distilling vapors did not exceed 90° (at 1 mm.) and the potassium salt remained dry all the time. The distillate was redistilled; it boiled at 87° (1 mm.) and showed a m.p. of 36° (lit.[2]: m.p. 35–36.5°). The yield was 14 g. (84%).

p-Vinyl-benzoylacetone (VII). Following the method of Swamer and Hauser,[7] a solution of 16 g. of methyl *p*-vinylbenzoate and 9 g. of acetone in 50 ml. of ether was added to a suspension of 2.4 g. of sodium hydride in 250 ml. of ether at 0° and in an atmosphere of nitrogen. When the reaction had subsided, the stirring was continued for 4 hr. at 0° and 15 hr. at room temperature. The product was decomposed with 5 ml. of methanol at −10° and acidified with 7 ml. of glacial acetic acid at 0°. The ethereal solution was filtered, washed with sodium bicarbonate solution and water, dried, and distilled. The product (yield, 3 g., 16%) boiled at 123–125° (1.5 mm.). 35% of the starting material was recovered.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.6; H, 6.4. Found: C, 76.0; H, 6.4.

Polymeric ethyl α-(p-vinylbenzoyl)-acetoacetate (VIII). (*a*) The hydrolysis of 16 g. of methyl *p*-vinylbenzoate was carried out at room temperature with a solution of 8 g. of sodium hydroxide in 80 ml. of anhydrous ethanol and in the presence of 0.1 g. of copper powder. After 24 hr., the sodium salt was filtered, dried, dissolved in 20 ml. of water, and acidified. *p*-Vinylbenzoic acid (I), recrystallized from aqueous alcohol, melted at 142°[1]; its yield was 12 g. (81%).

(*b*) *p-Vinylbenzoyl chloride* was prepared in benzene solution from 17 g. of sodium *p*-vinylbenzoate and 15 g. of oxalyl chloride in 100 ml. of benzene in the presence of 0.1 g. of copper powder. After 3 hr., the benzene was evaporated *in vacuo*, replaced twice by fresh benzene, and the operation repeated. The benzene solution was used eventually for the next step.

(*c*) Following the method of Viscontini and Merckling,[8] the magnesium enolate was prepared from 13 g. of ethyl acetoacetate, and at 0–10° the chloride prepared from 17 g. of sodium *p*-vinylbenzoate added. After 12 hr., the product was decomposed with 10% sulfuric acid and the ethereal solution washed with water, sodium bicarbonate solution, and again water, and dried, and the solvent distilled. A viscous polymer was obtained which initially gave the color reaction with ferric chloride and a green copper complex; after a short time it became hard, and the color reactions were negative. Analysis showed that the product had the expected composition. Yield was 81%.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.2; H, 6.2. Found: C, 69.8; H, 6.8.

Methyl p-acetylphenylacetate (V). At 0° and with agitation, 150 g. of methyl phenylacetate, prepared by the method of Clinton and Laskowski[6] (b.p. 119°/25 mm.; 94%) was added slowly to a suspension of 293 g. of aluminum chloride in 600 ml. of carbon disulfide. To the product, which consisted of 2 liquid layers, 94 g. of acetyl chloride was added within about 90 min. and the mixture refluxed for 10 hr. and decomposed with 2 kg. of ice and 1 l. of concentrated hydrochloric acid. The organic layer was washed with 10% hydro-

(4) Successful experiments of this kind, though not in very good yield, have been reported by R. G. Jones and H. Gilman, *Org. Reactions*, **VI**, 339 (1951).

(5) D. T. Mowry, M. Renoll, and W. F. Huber, *J. Am. Chem. Soc.*, **68**, 1105 (1946).

(6) Prepared by the method of R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).

(7) F. W. Swamer and C. R. Hauser, *J. Am. Chem. Soc.*, **72**, 1352 (1950).

(8) M. Viscontini and N. Merckling, *Helv. Chim. Acta*, **35**, 2280 (1952).

chloric acid, water, 10% sodium carbonate solution, and again water, dried, and distilled. The product, which was obtained in 66% yield (128 g.), boiled at 136° (0.5 mm.).

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.7; H, 6.3. Found: C, 69.0; H, 6.4.

Oxidation to terephthalic acid. A mixture of 2 g. of (V), 1 g. of sodium carbonate, 8 g. of potassium permanganate, and 100 ml. of water was refluxed for 30 min. The solution was filtered and acidified; yield of terephthalic acid, 1.2 g. (76%). The product was identified by the mixed m.p. of its dimethyl ester with an authentic specimen.

Methyl p-(α-isopropoxyethyl)-phenylacetate. A mixture of 192 g. of V, 224 g. of aluminum isopropoxide, and 1500 ml. of isopropyl alcohol was heated in a column in the usual manner, until no more acetone appeared in the distillate. Then the excess isopropyl alcohol was distilled off and the residue treated with 700 ml. of water, 400 ml. of concentrated hydrochloric acid, and 50 ml. of benzene. The product was extracted with ether; it boiled at 140–160° (0.05 mm.) and, on redistillation, at 148° (0.05 mm.). Its yield was 135 g. (57%).

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.2; H, 8.5. Found: C, 71.4; H, 8.3.

Methyl p-(α-hydroxyethyl)-phenylacetate (VI). In the manner described for the preparation of III (R = OH), 192 g. of V in 600 ml. of ether was reduced with 10 g. of sodium borohydride in 50 ml. of methanol. The product (153 g., 79%) boiled at 144° (2 mm.).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.2. Found: C, 68.2; H, 7.6.

Methyl p-vinylphenylacetate (as II). In the manner described above, 19.5 g. of VI was dehydrated over potassium hydrogen sulfate. The unsaturated ester, of which 16 g. (91%) was obtained, boiled at 107° (2 mm.).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.0; H, 6.8. Found: C, 75.1; H, 6.5.

p-Vinylphenylacetic acid (V). A mixture of 39 g. of the foregoing ester, 17 g. of potassium hydroxide in 100 ml. of anhydrous ethanol, and 0.2 g. of copper powder was kept at room temperature for 24 hr. The alcohol was distilled *in vacuo* and the residue acidified with cold dilute sulfuric acid. Successive recrystallization from aqueous ethanol and petroleum ether gave 30 g. (92%) of the desired acid, which melted at 101°.

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.1; H, 6.2. Found: C 74.1; H, 6.1.

Ethyl α-(p-vinylphenylacetyl)acetoacetate (IX). In the manner described for the synthesis of VIII, the chloride of (II) was prepared from 20 g. of potassium *p*-vinylphenylacetate and 15 g. of oxalyl chloride in 100 ml. of benzene and the solution added to the magnesium enolate of 13 g. of ethyl acetoacetate. After 12 hr. at room temperature, the product was worked up. Two distillations gave the pure ester IX, b.p. 144° (0.4 mm.) in a yield of 9 g. (30%); the residue was polymeric.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.1; H, 6.6. Found: C, 69.9; H, 6.8.

An attempt to prepare the copper chelate from the crude product gave a dark green solution which, however, polymerized almost instantaneously. Also in the condensation of methyl *p*-vinylphenylacetate and acetone, in the presence of sodium hydride, most of the ester that reacted was converted into a polymer, and only a very small fraction boiling at 143–149° (1.5 mm.) was obtained, which gave the ferric chloride reaction expected of (*p*-vinylphenylacetyl)-acetone.

p-Bromophenylacetic acid, purified by sublimation and then melting at 114°, was prepared from *p*-bromoacetophenone[9] by the method of Schwenk and Bloch[10]; the yield was 20%, when the time of the hydrolysis of the thiomorpholide was extended to 25 hr.

Ethyl p-Bromophenylacetate was prepared as usual and boiled at 152° (22 mm.).

Methyl p-Bromobenzoate was obtained from the acid by the method of Clinton and Laskowski[6] in 92% yield (after recrystallization from ligroin it melted at 79–80°), and *p-bromophenyl-methyl-carbinol* according to Ziegler and Tiemann.[11] None of these substances exchanged the bromine atom for lithium, when treated with lithium metal or butyl lithium in ethereal solution.

JERUSALEM, ISRAEL

(9) R. Adams and C. R. Noller, *Org. Syntheses,* **Coll. Vol. I,** 109 (1941).

(10) E. Schwenk and E. Bloch, *J. Am. Chem. Soc.,* **64,** 3051 (1942).

(11) K. Ziegler and P. Tiemann, *Ber.,* **55,** 3406 (1922).

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

Friedel-Crafts Acylations of 1-Phenyl-2,5-dimethylpyrrole and 1,2-Diphenyl-5-methylpyrrole

RICHARD RIPS AND N. P. BUU-HOÏ

Received October 7, 1958

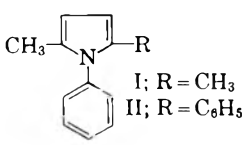
Friedel-Crafts acylations of 1-phenyl-2,5-dimethylpyrrole yield diketones when acetyl and propionyl chloride are used, and both mono- and di-ketones with benzoyl and anisoyl chloride. On the other hand, 1,2-diphenyl-5-methylpyrrole gives predominantly monoketones with both types of acid chlorides, substitution occurring at the 4-position. Condensation of 3,4-diacylpyrroles with hydrazine hydrate leads to derivatives of 5,6-diazaisoindole, a new heterocyclic nucleus analogous to purine.

Although the pharmacological potentialities of the pyrrole nucleus have not yet been thoroughly investigated, several compounds in this series have already shown promising activity as possible antispasmodics and sedatives.[1] For further work in this field, pyrrole ketones represent convenient intermediates, and Friedel-Crafts acylations of some 1,2,5-trisubstituted pyrroles have therefore been investigated. 1-Phenyl-2,5-dimethylpyrrole (I) and 1,2-diphenyl-5-methylpyrrole (II), readily prepared by Knorr-Paal condensation of aniline with

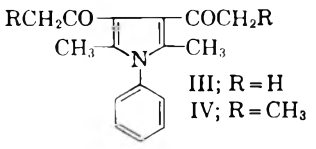
(1) *Cf.* N. P. Buu-Hoï, R. Rips, and R. Cavier, *J. Med. Pharm. Chem.,* in press; E. Cionga, *Compt. rend.,* 200, 780 (1935).

hexane-2,5-dione and phenacylacetone, respectively,[2] were chosen for the present study.

1-Phenyl-2,5-dimethylpyrrole underwent stannic chloride–catalyzed acylation with acetyl and propionyl chloride to give good yields of 3,4-diacetyl- (III) and 3,4-dipropionyl-1-phenyl-2,5-dimethylpyrrole (IV). Aluminum chloride has also been found useful as a catalyst, although the

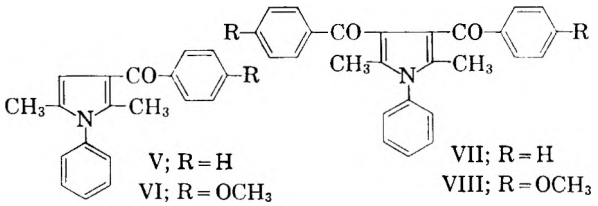


I; R = CH_3
II; R = C_6H_5



III; R = H
IV; R = CH_3

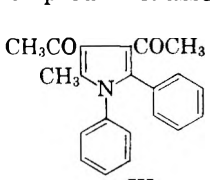
yields of diketones recorded were substantially lower; a study of the effect of temperature on the yields showed the optimum temperature of the reaction to be about 50° for stannic chloride and about 40° for aluminum chloride. When aromatic acid chlorides such as benzoyl and anisoyl chloride were used, both the monoketones (V and VI) and the diketones (VII and VIII) expected were obtained in practically equal amounts.



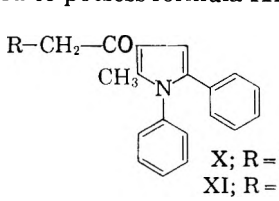
V; R = H
VI; R = OCH_3

VII; R = H
VIII; R = OCH_3

The ready diacetylation and dipropionylation of 1-phenyl-2,5-dimethylpyrrole is in sharp contrast with the behavior of 1,2-diphenyl-5-methylpyrrole. This latter gave with acetyl chloride predominantly a monoketone, with very little of the expected diketone (IX); with propionyl chloride, only a monoketone could be isolated. The monoacetylation product was shown to be 4-acetyl-1,2-diphenyl-5-methylpyrrole (X), as it was identical with the compound previously synthesized by Aggarwal, Qureshi, and Ray[3] by means of a Knorr-Paal condensation of aniline with 1,1-diacetyl-2-benzoylethane; by analogy, the monopropionylation product is assumed to possess formula XI.

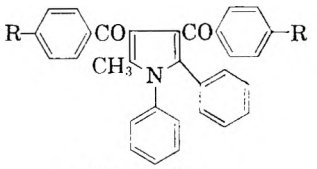


IX

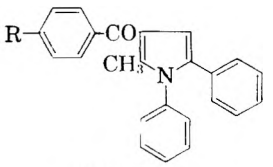


X; R = H
XI; R = CH_3

The fact that the 4-position in the molecule of 1,2-diphenyl-5-methylpyrrole is attacked preferentially to the 3-position is remarkable in view of the strong *ortho*-activation in the analogous molecule of biphenyl.[4] This anomaly cannot be accounted for entirely by the steric hindrance exerted at the 3-position by the phenyl radical, as benzoylation and anisoylation of II resulted in considerable amounts of the diketones XII and XIII along with the corresponding monosubstitution products XIV and XV.

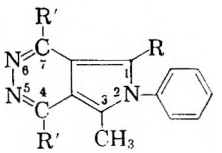


XII; R = H
XIII; R = OCH_3



XIV; R = H
XV; R = OCH_3

All the diketones reported above readily underwent condensation with hydrazine hydrate to give cyclic azines of general formula XVI, which are



XVI

derivatives of 5,6-diazaisoindole, a new nitrogen heterocycle analogous to purine. This reaction not only proves the structure of the diketones used, but also provides a convenient route to compounds of biological interest as potential antipurines. An alternative method already reported[5] for the preparation of pyrrole diketones of type III is the Knorr-Paal condensation of primary amines with *sym*-tetraacetylenethane.

EXPERIMENTAL

Acetylation of 1-phenyl-2,5-dimethylpyrrole. (a) *With aluminum chloride.* To a water cooled solution of 15 g. of pyrrole I and 14 g. of finely powdered aluminum chloride in 200 ml. of dry carbon disulfide, 7.5 g. of acetyl chloride was added in small portions with stirring, and the mixture heated at 40° for 2 hr. on a warm water bath. After cooling, water was added, the organic layer washed with 5% aqueous sodium hydroxide, then with water, and dried over sodium sulfate, the solvent was distilled off, and the residue vacuum-fractionated. Yield: 9 g. (40%) of *3,4-diacetyl-1-phenyl-2,5-dimethylpyrrole*, b.p. 235–240°/15 mm., which crystallized from methanol in colorless prisms, m.p. 98°, giving a yellow coloration with sulfuric acid.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7; N, 5.5; O, 12.5. Found: C, 75.1; H, 6.8; N, 5.6; O, 12.8.

In an experiment in which aluminum chloride was added at 0° and the reaction mixture then kept overnight at 15°, an 18% yield of the same compound was recorded.

(b) *With stannic chloride.* To a solution of 20 g. of pyrrole I and 10 g. of acetyl chloride in 100 ml. of dry thiophene-free benzene, 36.5 g. of stannic chloride was added in small portions with stirring, and the mixture was then heated for 2 hr. at 50° on a water bath. After the usual treatment, 16 g. (52% yield) of diketone III was obtained.

(2) L. Knorr, *Ann.*, **236**, 313 (1886); C. Paal, *Ber.*, **18**, 2254 (1885).

(3) J. S. Aggarwal, A. V. Qureshi, and J. N. Ray, *J. Am. Chem. Soc.*, **54**, 3988 (1932).

(4) *Cf.* N. P. Buu-Hoï, C. A. Coulson, P. Daudel, R. Daudel, M. Martin, A. Pullman, and B. Pullman, *Rev. sci.*, **85**, 1041 (1947).

(5) M. Dennstedt and J. Zimmerman, *Ber.*, 20, 1760 (1887); D. B. Bright, *J. Am. Chem. Soc.*, **79**, 3202 (1957).

1,3,4,7-Tetramethyl-2-phenyl-5,6-diazaisoindole (XVI; R = R′ = CH_3). To a solution of 2.5 g. of the foregoing diketone in 10 ml. of ethanol, 1 g. of 95% hydrazine hydrate was added. An immediate exothermic reaction set up, with formation of a precipitate, which was collected and recrystallized twice from methanol. Yield: 2.2 g. (87.6%) of colorless needles, m.p. 318°, giving a yellow coloration with sulfuric acid.

Anal. Calcd. for $C_{16}H_{17}N_3$: C, 76.5; H, 6.8; N, 16.7. Found: C, 76.2; H, 7.1; N, 16.8.

Propionylation of 1-phenyl-2,5-dimethylpyrrole. A solution of 10 g. of this pyrrole and 12 g. of propionyl chloride in 100 ml. of benzene was treated with 18.2 g. of stannic chloride, and the mixture treated in the same manner as for the preparation of ketone III. The yield was 14 g. (84%) of a diketone, b.p. 252°/20 mm., crystallizing from aqueous methanol in silky colorless needles, m.p. 66°.

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.3; H, 7.5; O, 11.3. Found: C, 76.2; H, 7.4; O, 11.2.

The same product was obtained in 23% yield when aluminum chloride was used as catalyst, the reaction being performed at room temperature and in carbon disulfide.

1,3-Dimethyl-2-phenyl-4,7-diethyl-5,6-diazaisoindole (XVI; R = CH_3, R′ = C_2H_5). Prepared from 1.4 g. of the foregoing diketone and 0.5 g. of hydrazine hydrate in 5 ml. of ethanol (3 hr. refluxing), this compound crystallized from aqueous methanol in silky colorless needles, m.p. 190°.

Anal. Calcd. for $C_{18}H_{21}N_3$: C, 77.5; H, 7.6. Found: C, 77.2; H, 7.6.

Benzoylation of 1-phenyl-2,5-dimethylpyrrole. The reaction, performed in the usual way with 20 g. of this pyrrole, 18 g. of benzoyl chloride, and 37 g. of stannic chloride in benzene, yielded on vacuum-fractionation, two ketonic portions. The lower boiling portion (15 g., b.p. 260°/15 mm.) consisted of *3-benzoyl-1-phenyl-2,5-dimethylpyrrole* (V), crystallizing from methanol in colorless leaflets, m.p. 126°.

Anal. Calcd. for $C_{19}H_{17}NO$: C, 82.9; H, 6.2; N, 5.8. Found: C, 82.6; H, 6.5; N, 5.5.

The higher boiling fraction (10 g., b.p. 320–330°/17 mm.) consisted of *3,4-dibenzoyl-1-phenyl-2,5-dimethylpyrrole* (VII), crystallizing from ethanol in colorless plates, m.p. 186°.

Anal. Calcd. for $C_{26}H_{21}NO_2$: C, 82.9; H, 5.6; O, 8.4. Found: C, 82.6; H, 5.6; O, 8.5.

A similar reaction, using the same quantities of starting materials, and performed with aluminum chloride at 40° in carbon disulfide, gave 17 g. of the diketone (VII).

1,3-Dimethyl-1,4,7-triphenyl-5,6-diazaisoindole (XVI; R = CH_3, R′ = C_6H_5). Prepared by refluxing for 5 hr. a solution of 0.5 g. of diketone VII and 0.4 g. of hydrazine hydrate in 5 ml. of ethanol, this compound (0.4 g.) crystallized from ethanol in shiny pale yellow needles, m.p. 294°.

Anal. Calcd. for $C_{26}H_{21}N_3$: N, 11.2. Found: N, 11.0.

Anisoylation of 1-phenyl-2,5-dimethylpyrrole. The reaction-product from 20 g. of this pyrrole, 22 g. of anisoyl chloride, and 16.5 g. of aluminum chloride in carbon disulfide at 40°, likewise yielded two portions on vacuum-fractionation. The portion boiling at 275–290°/14 mm. (5.5 g.) crystallized from methanol to give *3-anisoyl-1-phenyl-2,5-dimethylpyrrole* (VI), lustrous colorless leaflets, m.p. 116°.

Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.6; H, 6.3; O, 10.5. Found: C, 78.3; H, 6.3; O, 10.8.

The portion b.p. *circa* 300°/2 mm. (15 g.) consisted of *3,4-dianisoyl-1-phenyl-2,5-dimethylpyrrole* (VIII), crystallizing from methanol in colorless leaflets, m.p. 183°.

Anal. Calcd. for $C_{28}H_{25}NO_4$: C, 76.5; H, 5.7; O, 14.6. Found: C, 76.4; H, 5.8; O, 14.7.

A stannic chloride–catalyzed acylation, using the same amounts of starting materials, and performed at 50°, yielded 10 g. of the monoketone and 10 g. of the diketone.

1,3-Dimethyl-1-phenyl-4,7-di(p-methoxyphenyl)-5,6-diazaisoindole (XVI; R = CH_3, R′ = C_6H_4—OCH_3). Crystallized from ethanol as lemon yellow plates, m.p. 295°.

Anal. Calcd. for $C_{28}H_{25}N_3O_2$: N, 9.7. Found: N, 9.8.

Acetylation of 1,2-diphenyl-5-methylpyrrole. All the acylations of pyrrole II were effected with equimolar amounts of the pyrrole and of the acid chlorides. The acetylation, performed at various temperatures and with aluminum chloride as well as stannic chloride, always yielded predominantly *4-acetyl-1,2-diphenyl-5-methylpyrrole* (X), b.p. 240–242°/11 mm., crystallizing from methanol in fine colorless needles, m.p. 101–102°; the literature[3] gave m.p. 101°. The corresponding *oxime* crystallized from ethanol in colorless prisms, m.p. 176°.

Anal. Calcd. for $C_{19}H_{18}N_2O$: N, 9.7. Found: N, 9.7.

Repeated fractional crystallization from methanol of the higher boiling fractions yielded small amounts (less than 10% of the weight of the monoketone obtained) of *3,4-diacetyl-1,2-diphenyl-5-methylpyrrole* (IX), fine colorless needles, m.p. 161°, giving a yellow coloration with sulfuric acid.

Anal. Calcd. for $C_{21}H_{19}NO_2$: C, 79.5; H, 6.0; N, 4.4; O, 10.1. Found: C, 79.4; H, 6.2; N, 4.7; O, 10.1.

The yields of monoketone plus diketone recorded were as follows:

Catalyst	Temperature, °C.	Yield, %
$AlCl_3$	0–5	15
$AlCl_3$	18	38
$AlCl_3$	40	52
$SnCl_4$	18	48
$SnCl_4$	60	59

1,2-Diphenyl-3,4,7-trimethyl-5,6-diazaisoindole (XVI; R = C_6H_5, R′ = CH_3). Crystallized from aqueous ethanol in silky colorless needles, m.p. 239°.

Anal. Calcd. for $C_{21}H_{19}N_3$: N, 13.4. Found: N, 13.3.

Propionylation of 1,2-diphenyl-5-methylpyrrole. With stannic chloride at 50° (3 hr. heating), a 60% yield of *4-propionyl-1,2-diphenyl-5-methylpyrrole*, b.p. 254–255°/15 mm., was obtained; recrystallization from ethanol gave lustrous colorless leaflets, m.p. 126°. No diketone could be isolated from the higher boiling portions.

Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.0; H, 6.6. Found: C, 82.9; H, 6.5.

With aluminum chloride as catalyst at 40°, the same monoketone wos obtained in 40% yield.

Tne corresponding *semicarbazone* crystallized from ethanol in lustrous colorless leaflets, m.p. 260°.

Anal. Calcd. for $C_{21}H_{22}N_4O$: N, 16.2. Found: N, 16.2.

Benzoylation of 1,2-diphenyl-5-methylpyrrole. With stannic chloride at 50° as catalyst as above, two products were obtained. (a) A 49% yield of *4-benzoyl-1,2-diphenyl-5-methylpyrrole* (XIV), b.p. 244°/0.3 mm., crystallizing from methanol in colorless prisms, m.p. 131–132°.

Anal. Calcd. for $C_{24}H_{19}NO$: C, 85.4; II, 5.7. Found: C, 85.3; H, 5.7.

The corresponding *2,4-dinitrophenylhydrazone* crystallized from aqueous dioxane in fine violet-brown prisms, m.p. 190°.

Anal. Calcd. for $C_{30}H_{23}N_6O_4$: N, 13.5. Found: N, 13.4.

(b) A 32% yield of *3,4-dibenzoyl-1,2-diphenyl-5-methylpyrrole* (XII), b.p. >260°/0.5 mm., crystallizing from ethanol in fine colorless prisms, m.p. 200°.

Anal. Calcd. for $C_{31}H_{23}NO_2$: C, 84.3; H, 5.3. Found: C, 84.2; H, 5.2.

With aluminum chloride at 40°, a 39% yield of diketone XII was recorded.

1,2,4,7-Tetraphenyl-3-methyl-5,6-diazaisoindole (XVI; R = R′ = C_6H_5). Crystallized from ethanol in lemon yellow plates, m.p. 277°, giving a golden-yellow coloration with sulfuric acid.

Anal. Calcd. for $C_{31}H_{23}N_3$: N, 9.6. Found: N, 9.5.

Anisoylation of 1,2-diphenyl-5-methylpyrrole. With stannic chloride at 50°, two products were also obtained in this case.

(a) A 51% yield of a portion b.p. 310–312°/11 mm., consisting of *4-anisoyl-1,2-diphenyl-5-methylpyrrole* (XV), crystallizing from ethanol in fine colorless prisms, m.p. 179–180°.

Anal. Calcd. for $C_{25}H_{21}NO_2$: C, 81.7; H, 5.8. Found: C, 81.4; H, 5.7.

The corresponding *semicarbazone* crystallized from ethanol in colorless needles, m.p. 241°.

Anal. Calcd. for $C_{26}H_{24}N_4O_2$: N, 13.2. Found: N, 13.5.

(b) A 40% yield of *3,4-dianisoyl-1,2-diphenyl-5-methylpyrrole* (XIII), b.p. 300–305°/0.5 mm., crystallizing from ethanol in colorless prisms, m.p. 208°.

Anal. Calcd. for $C_{33}H_{27}NO_4$: C, 79.0; H, 5.4; N, 2.8. Found: C, 78.7; H, 5.4; N, 2.8.

With aluminum chloride, a 29% yield of diketone XIII was obtained at 40°, and a 9% yield when the reaction was performed at room temperature.

1,2-Diphenyl-3-methyl-4,7-di(p-methoxyphenyl)-5,6-diazaisoindole (XVI; R = C_6H_5, R′ = C_6H_5—OCH_3). Crystallized from ethanol in yellow plates, m.p. 301°, giving a deep yellow coloration with sulfuric acid.

Anal. Calcd. for $C_{33}H_{27}N_3O_2$: C, 79.7; H, 5.5; N, 8.7. Found: C, 79.7; H, 5.5; N, 8.7.

PARIS V^e^, FRANCE

Notes

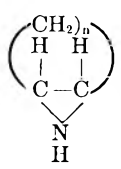
A department for short papers of immediate interest.

Chemistry of Ethylenimine. V. Cycloheptenimine or 8-Azabicyclo[5.1.0]octane[1]

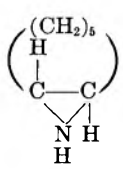
PURNENDU B. TALUKDAR[2] AND PAUL E. FANTA[3]

Received July 29, 1958

Previous papers in this series have described the preparation and hydrolysis of cyclopentenimine[4] (I) and cyclohexenimine (II).[5] These observations have now been extended to the next member of the homologous series, cycloheptenimine (III).



I. n = 3
II. n = 4
III. n = 5



IV

Cycloheptenimine was prepared from (±)-*trans*-2-aminocycloheptanol *via* the sulfate ester according to the conventional Wenker procedure. The imine is a colorless liquid which was further characterized by the preparation of a crystalline *N*-phenylthiocarbamyl derivative. Hydrolysis of the imine in aqueous perchloric acid gave (±)-*trans*-2-aminocycloheptanol. Since opening and closing of the aziridine ring occurs with inversion at the substituted carbon atom, the three- and seven-membered rings of cycloheptenimine must be fused in the *cis*-configuration.

Furthermore, in view of the unsuccessful attempt to prepare *trans*-cycloheptene oxide,[6] it is unlikely that the analogous *trans*-imine (IV) is capable of existence. However, both *cis* and *trans* imines of higher homologs in this series, analogous to the known oxides, should be possible, and this problem will be the subject of future investigation.

(1) This research was aided by a grant from the Phillip Armour Foundation Cancer Fund and a grant from the American Cancer Society which provided a postdoctoral stipend for P. B. Talukdar.

(2) On study leave from the East India Pharmaceutical Works, Calcutta, India.

(3) To whom inquiries regarding this paper should be sent.

(4) P. E. Fanta, *J. Chem. Soc.*, 1441 (1957).

(5) O. E. Paris and P. E. Fanta, *J. Am. Chem. Soc.*, 74, 3007 (1951).

(6) L. N. Owen and G. S. Saharia, *J. Chem. Soc.*, 2582 (1953).

EXPERIMENTAL[7]

Cycloheptene oxide. Although this oxide has been prepared in acceptable yield by the reaction of cycloheptene with perbenzoic[6] or peracetic[8] acid, we found it more convenient to use a procedure similar to that recently described for the preparation of cyclopentene oxide.[9] A suspension of *N*-bromosuccinimide (140.6 g., 1% excess) in 310 ml. of water was stirred at 10–12° while 76.5 g. of cycloheptene was added dropwise. After 1.5 hr. of stirring at room temperature, the heavy layer of bromohydrin was separated and the aqueous solution was extracted with three 50 ml. portions of ether. The combined extract and oil was dried over anhydrous sodium sulfate and the ether was distilled, leaving crude bromohydrin in the form of a pale yellow, viscous oil.

The crude bromohydrin was added dropwise with stirring to 250 ml. of 20% aqueous sodium hydroxide at 5–7°. Stirring was continued for 2 hr. at 5–10°. The supernatant oily layer was separated and the aqueous residue was extracted with three 50 ml. portions of ether. The combined extract and oil was dried over anhydrous sodium sulfate and distilled, giving 74 g. (83% based on olefin) of colorless cycloheptene oxide, b.p. 82–84°/50 mm., n_D^{25} 1.4621 (lit.[8] 83–85°/50 mm., n_D^{25} 1.4615–1.4620).

(±)-*trans*-2-*Aminocycloheptanol* from the reaction of cycloheptene oxide with ammonia has been mentioned without details of the procedure.[10] A mixture of 20 g. of cycloheptene oxide and 200 ml. of 28% aqueous ammonium hydroxide was heated on a rocking steel bomb at 125° for 1 hr. The brown solution was distilled at water-aspirator pressure at first at room temperature and finally at 30–35°. The residue was taken up in chloroform, treated with Norit and concentrated to a small volume. Addition of petroleum ether and cooling overnight gave 16.2 g. (70%) of colorless amino alcohol, m.p. 74–75°. An additional crystallization from chloroform–petroleum ether (30–60°) raised the m.p. to 75–75.5° (lit.[10] 72–73°). On standing exposed to the air, the melting point of the amino alcohol rises considerably, possible due to absorption of carbon dioxide. Treatment of the amino alcohol with phenyl isothiocyanate gave the *N-phenylthiocarbamyl derivative*, white plates from aqueous ethanol, m.p. 146.5°.

Anal. Calcd. for $C_{14}H_{20}N_2OS$: C, 63.60; H, 7.63; N, 10.60. Found: C, 63.76; H, 7.66; N, 10.93.

(±)-*trans*-2-*Aminocycloheptyl hydrogen sulfate.* Cold 95% sulfuric acid (8.1 g.) was cautiously added to a suspension of 10.0 g. of the amino alcohol in 10 ml. of water, and the light brown solution was heated in a metal bath so that the water was slowly distilled, first at atmospheric pressure, and finally for 45 min. at a bath temperature of 135–140°/20 mm. Recrystallization of the solid residue from water with concentration of the mother liquors to get a second crop gave a total of 12.6 g. (78%) of long needles which slowly decomposed without melting at 282–284° (uncorr.). Another recrystallization from water gave silky, white needles which had the same decomposition point.

(7) Melting points are corrected except where otherwise noted. Analyses are by Micro-Tech Laboratories, Skokie, Ill.

(8) A. C. Cope and W. N. Baxter, *J. Am. Chem. Soc.*, 76, 279 (1954).

(9) L. Goodman, A. Benitez, and B. R. Baker, *J. Am. Chem. Soc.*, 80, 1680 (1958).

(10) M. Godchot and M. Mousseron, *Compt. rend.*, 196, 1680 (1933).

Anal. Calcd. for $C_7H_{13}NO_4S$: C, 40.17; H, 7.22; N, 6.69. Found: C, 40.03; H, 7.24; N, 6.62.

Cycloheptenimine. A solution of 12.0 g. of the sulfate ester and 24 g. of sodium hydroxide in 30 ml. of water was heated in a distilling flask until the residue was nearly dry. The distillate was collected in a cooled receiver containing a little ether and sodium hydroxide pellets. The ethereal solution was separated and the aqueous solution was extracted with three 15 ml. portions of ether. The combined ether solution was dried over solid sodium hydroxide and distilled, giving 5.0 g. (78%) of colorless imine, b.p. 171–172° (uncorr.), $n_D^{20.5}$ 1.4863, $\lambda_{max}^{CCl_4}$ 3.07 μ (N—H band).

Anal. Calcd. for $C_7H_{13}N$: C, 75.61; H, 11.78; N, 12.59. Found: C, 75.33; H, 11.93; N, 12.64.

On treatment with phenyl isothiocyanate, the imine gave the *N-phenylthiocarbamyl derivative*, white needles from aqueous alcohol, m.p. 120.5°.

Anal. Calcd. for $C_{14}H_{18}N_2S$: C, 68.25; H, 7.36; N, 11.37. Found: C, 68.05; H, 7.70; N, 11.50.

Hydrolysis of cycloheptenimine. A solution of 0.8 g. of the imine and 1.0 ml. of 72% perchloric acid in 8 ml. of water was refluxed for 1 hr. The solution was made strongly alkaline by the addition of sodium hydroxide and extracted with three 10 ml. portions of chloroform. The chloroform solution was dried over anhydrous sodium sulfate and evaporated, leaving an oily residue which upon trituration with petroleum ether (30–60°) formed a crystalline solid, m.p. 70–71°. Recrystallization from chloroform-petroleum ether raised the m.p. to 74–75°, undepressed on mixing with authentic (±)-*trans*-2-aminocycloheptanol. The identity of the hydrolysis product was further confirmed by preparation of the *N*-phenylthiocarbamyl derivative, whose m.p. and mixture m.p. were identical with the authentic material.

Department of Chemistry
Illinois Institute of Technology
Chicago 16, Ill.

Malonic Ester Synthesis of δ-Aminolevulinic Acid. The Reaction of *N*-3-Bromoacetonylphthalimide with Malonic Ester

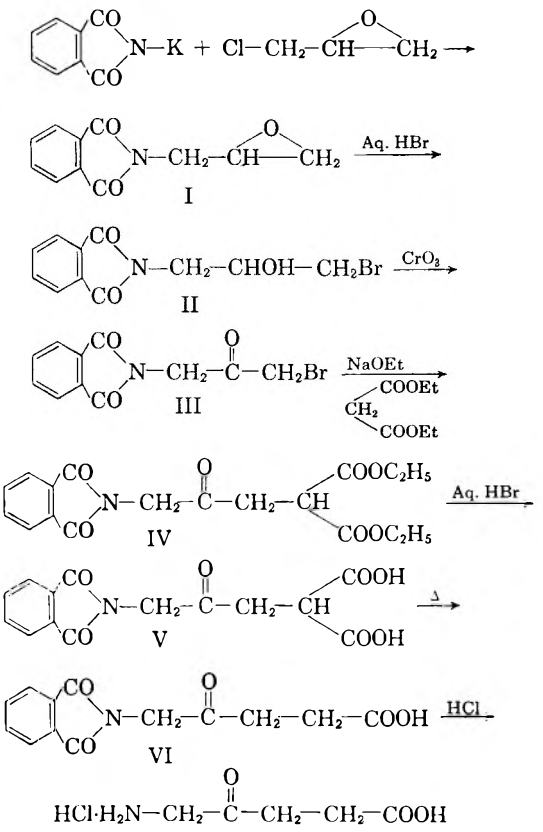
Donald P. Tschudy and Annie Collins

Received July 31, 1958

Shemin and Russell[1,2] and Neuberger and Scott[3,4] have shown δ-aminolevulinic acid (VII) to be the aliphatic precursor of the monopyrrole porphobilinogen, which is in turn the precursor of porphyrins. The biosynthesis of porphobilinogen involves an enzymatically-catalyzed Knorr condensation between two molecules of the amino ketone.[5] Of further interest is the recent demonstration by Shemin *et al.*[6] of VII as the precursor of the porphyrin-like moiety of vitamin B_{12}. Since there are relatively few organisms which do not synthesize porphyrins, it is probable that almost all living matter synthesizes VII.

A number of substituted levulinic acids have been previously prepared, but as Neuberger and Scott have indicated,[3] uniquely delta substituted derivatives were unknown until 1953 with two exceptions.[7,8] Shemin and Russell[1,2] synthesized VII by three separate routes: (1) the nitrosation of β-ketoadipic acid followed by reduction; (2) a Gabriel synthesis using δ-chlorolevulinic ester; (3) the exhaustive benzoylation of imidazolepropionic ester followed by hydrolysis.

During the course of synthesizing analogs of VII a new synthesis for this compound, outlined in the flow diagrams, was developed.



The syntheses of I, II, and III were based on those described by Weizmann and Malkova,[9] and Gabriel and Ohle.[10] The most difficult step is the coupling of III with malonic ester to form IV. Previously reported attempts at this reaction have failed to yield the desired product.[11] Thus, Haring-

(1) D. Shemin and C. S. Russell, *J. Am. Chem. Soc.*, **75**, 4873, (1953).

(2) D. Shemin, C. S. Russell, and T. Abramsky, *J. Biol. Chem.*, **215**, 613, (1955).

(3) A. Neuberger and J. J. Scott, *J. Chem. Soc.*, 1820 (1954).

(4) A. Neuberger and J. J. Scott, *Nature*, **172**, 1093 (1953).

(5) K. D. Gibson, A. Neuberger, and J. J. Scott, *Biochem. J.*, **61**, 618 (1955).

(6) D. Shemin, J. W. Corcoran, C. Rosenblum, and I. M. Miller, *Science*, **124**, 272 (1956).

(7) A. Windaus, W. Dörries, and H. Jensen, *Ber.*, **54**, 2745 (1921).

(8) R. W. Wynn and A. H. Corwin, *J. Org. Chem.*, **15**, 203 (1950).

(9) M. Weizmann and S. Malkova, *Bull. soc. chim. France*, **47**, 356 (1930).

(10) S. Gabriel and H. Ohle, *Ber.*, **50**, 822 (1917).

(11) C. R. Harington and J. Overhoff, *Biochem. J.*, **27**, 339 (1933).

ton and Overhoff state: "Very numerous attempts were made to condense phthalimidohalogenoacetones with ethyl sodiochloromalonate and indeed with ethyl sodiomalonate itself under various conditions, but all were in vain. The halogenoacetones reacted exothermically with the sodiomalonates with rapid elimination of the sodium halide, but normal condensation did not occur, the products consisting for the most part of highly pigmented resins."

The coupling of III with sodium diethylmalonate was studied in several solvents under various conditions and was found to yield several products. At refluxing temperature in alcohol sodium bromide was formed, but attempts to crystallize a product from alcohol, ether, and chloroform failed. A very small amount of material was crystallized from acetone, but was not studied further. When III was added as a solid to an alcoholic solution of sodium diethylmalonate at room temperature the reaction mixture crystallized spontaneously.

The material (obtained in high yield, but not the desired product) was recrystallized from 95% ethanol in which it is only slightly soluble, m.p. 278–279°. A sample was prepared for analysis by recrystallization from *N,N*-dimethylformamide by addition of water and also from alcohol-water.

The analysis suggested phthalimide (calculated for phthalimide: C: 65.30, H: 3.43, N: 9.52. Found: C: 65.24, H: 3.50, N: 9.10), but the compound differed from phthalimide in several important respects: (1) It melted 44° above phthalimide, (2) its infrared absorption spectrum was different from that of phthalimide, and (3) it was less soluble in alcohol water and *N,N*-dimethylformamide water than phthalimide. When III was allowed to react with sodium ethoxide in *N,N*-dimethylformamide, however, and the product isolated from cold dilute HCl, a considerable yield of phthalimide was obtained. Thus the desired product could not be obtained when the reaction was carried out in alcohol.

By condensing III with sodium diethylmalonate in *N,N*-dimethylformamide in dilute solution at room temperature, the desired product (IV) could be isolated by crystallization from acetone water or more readily from a large volume of petroleum ether. In the course of purification several crystalline products were obtained. The material melting at 83° was shown to be the desired product by analysis, infrared absorption spectrum and its stepwise conversion to VII. Furthermore it yielded the predicted amount of phthalic acid on acid hydrolysis (380 mg. phthalic acid recovered from hydrolysis of 840 mg. of IV, predicted: 386 mg.).

EXPERIMENTAL[12]

Ethyl-α-carbethoxy-γ-oxo-δ-phthalimidovalerate (IV). To a solution of 3.26 g. of sodium in 80 ml. dry ethanol was added 200 ml. of *N,N*-dimethylformamide and 23 ml. diethylmalonate. After allowing this to stand for 15 min. a solution of 40 g. of III in 500 ml. *N,N*-dimethylformamide was added. The temperature gradually rose to 48°. The mixture was allowed to stand overnight and then was evaporated to dryness *in vacuo*. The residue was extracted with chloroform and the NaBr filtered off. The chloroform was evaporated *in vacuo* and the residual oil was crystallized from either acetone water over a period of 4–5 days or more quickly from a large volume of petroleum ether. The 25.5 g. (49.8%) obtained was recrystallized from dilute alcohol and then water, m.p. 84°.

Anal. calcd. for $C_{18}H_{19}NO_7$: C, 59.83; H, 5.30. Found: C, 59.79; H, 5.33.

When the same reaction was carried out with III at twice the concentration reported above, 15 g. of the material melting at 278° was obtained. This was easily separated from the desired product by dissolving the latter in alcohol or petroleum ether, since the high melting side product is only slightly soluble in alcohol and insoluble in petroleum ether.

α-carboxy-γ-oxo-δ-pthalimidovaleric acid (V). Ten g. of IV were suspended in 100 ml. of 48% HBr and allowed to stand at room temperature overnight. It was then heated on the steam bath until all the compound dissolved. The solution was allowed to cool and then evaporated to dryness *in vacuo*. The residue was recrystallized from alcohol or water to yield 7 g. (83.0%) m.p. 171–172° (with evolution of gas).

Anal. calcd. for $C_{14}H_{11}NO_7$: C, 55.08; H, 3.63; N, 4.58. Found: C, 55.38; H, 3.73; N, 4.39.

δ-Phthalimidolevulinic acid (VI). Four g. of V were heated to 170° at a pressure of 3–4 mm. Hg until the evolution of gas ceased. The glass-like residue was recrystallized from boiling water yielding 3.1 g. (90.7%) m.p. 157–158° (Neuberger and Scott[3] reported 158.5°).

Anal. Calcd. for $C_{13}H_{11}NO_5$: C, 59.76; H, 4.24, N, 5.36. Found: C, 60.01; H, 4.42; N, 5.47.

δ-Aminolevulinic acid hydrochloride (VII). A mixture of 4 g. of VI, 4 cc. of 95% ethanol and 40 cc. of 7*N* HCl was refluxed for 6 hr. and allowed to cool overnight. The phthalic acid was filtered off and the filtrate evaporated to dryness *in vacuo*. The slightly yellow crystals of VII weighed 2 g. (78.2%). It was recrystallized from methanol ethyl acetate m.p. 148°. It had the same ultraviolet absorption spectrum as a sample prepared by another route and also the same RF value in butanol, acetic acid, and water (.11). It was further identified by mixed melting point.

Anal. Calcd. for $C_5H_{10}NO_3Cl$: C, 35.82; H, 6.01; N, 8.35; Cl, 21.15. Found: C, 36.01; H, 6.06; N, 8.07; Cl, 20.73.

METABOLISM SERVICE
NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD.

(12) All melting points are uncorrected.

The Crystal and Molecular Structures of Overcrowded Compounds. V.[1] The Double Cyclization of Diphenethylacetic Acids

(MRS.) E. R. CAHANA, G. M. J. SCHMIDT, AND K. H. SHAH[2]

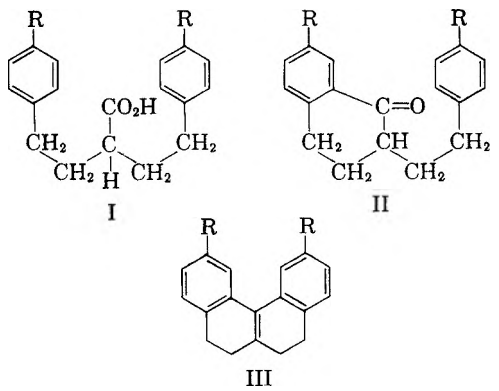
Received September 3, 1958

During our work on the crystal and molecular structures of overcrowded molecules we became

(1) Part IV. F. H. Herbstein and G. M. J. Schmidt, *J. Chem. Soc.*, 3314 (1954).

(2) Weizmann Memorial Fellow 1954–55.

interested in the problem of the 6,7-substituted benzo[*c*]phenanthrenes. Since the several known routes to this ring system do not lend themselves readily to the synthesis of such derivatives, we investigated a novel approach *via* the double cyclization of diphenethylacetic acids (I) to the tetrahydrobenzo[*c*]phenanthrenes (III).

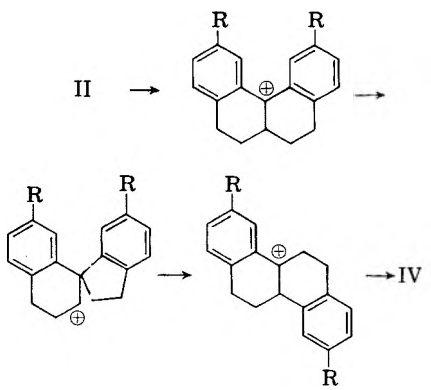


The acids I (R = H, OMe) were prepared in good over-all yields by procedures *A* and *B* and

A: $2ArCH_2CH_2Br + CH_2(CO_2Et)_2 \longrightarrow (ArCH_2CH_2)_2C(CO_2Et)_2 \longrightarrow (ArCH_2CH_2)_2CHCO_2H$

B: $(ArCH{:}CH)_2CO \longrightarrow (ArCH_2CH_2)_2CHOH \longrightarrow >CHOSO_2Me \longrightarrow >CHCN \longrightarrow (ArCH_2CH_2)_2CHCO_2H$

cyclized by HF and polyphosphoric acid; however, under all experimental conditions the reaction failed to produce benzo[*c*]phenanthrenes, but yielded instead the corresponding chrysenes of varying degrees of hydrogenation. Since the 2-phenethyltetralones (II) can be obtained as intermediates under mild conditions of cyclization, we may suppose that the rearrangement reaction takes place, by the mechanism of a double Wagner-Meerwein rearrangement, at the tertiary carbonium ion formed after final cyclization.



The identity of the reaction products obtained was checked by their preparation by known methods: tetrahydrochrysene (IV) was prepared from 1-phenethyltetralone-2; in the methoxy series the chrysene derivatives were prepared *via* the unambiguous double cyclization of the corresponding acyloin by the method developed by Johnson and co-workers.[3] In neither of the two series (R = H, OMe) investigated was any evidence obtained for the formation of the benzophenanthrene alongside the chrysene system. The cyclization of I (R = OMe) yielded, together with 3,9-dimethoxychrysene, small quantities, insufficient for further investigation, of a compound analyzing for a dimethoxyhexahydrochrysene; since it was also obtained from the acyloin on cyclization it is unlikely to be a benzo[*c*]phenanthrene derivative. It would appear that intramolecular compression forces, even within the 5,6,7,8-tetrahydrobenzophenanthrene system, are sufficient to displace equilibrium between the two ring systems completely to the side of chrysene.

We are attempting to provide further evidence for the reaction mechanism by the cyclization of 2,5-dibenzylcyclopentane-1-carboxylic acid and related compounds; however, the preparation of this acid by route *B* from any of the three stereoisomeric cyclopentanols has not yet been successful; attempts to prepare the acid by other methods are under way.

EXPERIMENTAL[4]

Diphenethylacetic acid. Route *A*, according to Leuchs.[5] Route *B*: Dibenzalacetone (23 g.) was reduced in 250 ml. of tetrahydrofuran with 0.5 g. 10% palladium-on-charcoal at an initial pressure of 50 lb./sq. in. After 2 hr. the solution was filtered, the solvent removed, the crude ketone dissolved in methanol and reduced with 6 molar equivalents of sodium borohydride. The product was worked up in the usual way; b.p. 165°/0.8 mm., m.p. 42–43°. (Zechmeister and Rom[6] give m.p. 42–44°.) Yield was 60% based on dibenzalacetone. To 20 g. of the carbinol dissolved in dry pyridine was added 10 g. of freshly distilled methyl sulfonyl chloride; the mixture was kept at 0° for 90 min., poured into ice water, and neutralized with sodium carbonate solution. The mesylate was extracted with ether; the ethereal solution was dried and worked up to give an oil which was dissolved in 150 ml. of dimethylformamide and treated with 3.0 g. of potassium cyanide dissolved in the minimum amount of water. The mixture was kept at 85° for 2 hr. and then poured into water. The product was fractionated, b.p. 157–159°/0.35 mm., yield 62%. The nitrile (5 g.) was added to 70 ml. of 40% sulfuric acid; hydrolysis was complete after 18 hours' refluxing. The acid was recrystallized from petroleum ether (30–60°), m.p. 49°, yield 75%. (Leuchs[5] gives m.p. 49–50°.)

Di(4-methoxyphenethyl)acetic acid. The method of preparation follows essentially the procedure just given. Because of the low solubility of the reduced ketone in methanol, the boron hydride reduction is best carried out in a methanol-tetrahydrofuran mixture, 70% yield of the carbinol, m.p. 80–81°, from methanol. (Straus and Grindel[7] give m.p. 80–81.5°.)

(3) W. S. Johnson, C. A. Erickson, and J. Ackerman, *J. Am. Chem. Soc.*, **74**, 2251 (1952).

(4) All melting points and boiling points are uncorrected. Microanalyses were carried out by Mr. E. Meier of the Microanalytical Laboratory, The Weizmann Institute of Science.

(5) A. Leuchs, *Ann.*, **461**, 44 (1928).

(6) I. Zechmeister and P. Rom, *Ann.*, **468**, 126 (1929).

(7) F. Straus and H. Grindel, *Ann.*, **439**, 306 (1924).

The mesylate of this carbinol is a solid, m.p. 56–58°, which gives, in an over-all yield from the carbinol of 52%, the nitrile, m.p. 92–94° from methanol.

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.66; H, 7.44; N, 4.53. Found: C, 77.24; H, 7.24; N, 4.48.

The acid, obtained in 72% yield from the nitrile, has m.p. 69–70° recrystallized from petroleum ether (60–80°).

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.17; H, 7.31. Found: C, 73.12; H, 7.49.

Monocyclization of I (R = H) with zinc chloride and acetic anhydride. Five grams of I, 30 ml. of glacial acetic acid, 20 ml. of acetic anhydride, and 0.4 g. of freshly fused zinc chloride were refluxed for 2 hr. and then poured onto ice; the mixture was made strongly alkaline with potassium hydroxide and extracted with ether; the ether extract was worked up in the usual way to give, in 95% yield, 2-phenethyltetralone identified as the semicarbazone, m.p. 166–167° (Leuchs[6] gives 166–167°) and 2,4-dinitrophenylhydrazone, m.p. 158–160°.

Double cyclization of I (R = H) with polyphosphoric acid. Two grams of I and 40 g. of polyphosphoric acid were heated with stirring for 3 hr. in an oil bath kept at 125°, allowed to cool, and poured into ice water. Tetrahydrochrysene (1.5 g.) (IV) was collected which, after recrystallization from methanol, melted at 105°. (Salzer[8] gives m.p. 105°.) No other compound could be isolated. The compound was found identical with an authentic sample of IV prepared according to Salzer[8] from 1-phenethyltetralone-2. It was smoothly dehydrogenated to chrysene on heating to 300° with 10% palladium-on-charcoal.

Anal. Calcd. for $C_{18}H_{16}$: C, 93.10; H, 6.90. Found: C, 93.24; H, 6.84.

Cyclization of I (R = H) with hydrofluoric acid. Three grams of I was treated with approximately 150 ml. of anhydrous hydrofluoric acid. After 48 hr. the semisolid residue was extracted with boiling methanol: the residue, 0.3 g., was chrysene, identified by mixed m.p.; the methanol solution deposited on cooling 0.5 g. of IV. From the methanol solution 2.0 g. of II were isolated, identified as the 2,4-dinitrophenylhydrazone.

Cyclization of I (R = OMe). Three grams of I was treated with approximately 50 ml. of anhydrous hydrofluoric acid. After 24 hr. the acid was evaporated and the remaining oil taken up in benzene and chromatographed through activated alumina. The column was washed with a mixture of benzene and petroleum ether (60–80°); except for a very small fraction of impure high-melting material, a colorless solid (2.4 g.) was obtained which, after recrystallization from methanol, melted at 85–86°, and which was identified as the 7-methoxy-2-(4-methoxyphenethyl)tetralone-1.

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.42; H, 7.10. Found: C, 77.86; H, 7.17.

Dinitrophenylhydrazone, m.p. 163°, from benzene and ethanol.

Anal. Calcd. for $C_{26}H_{26}N_4O_6$: N, 11.4. Found: N, 11.5.

Cyclization of I (R = OMe) with polyphosphoric acid. A mixture of 1 g. of I with 60 g. of polyphosphoric acid and 1 g. of phosphorus oxychloride was stirred and heated to 120° (bath temperature) for 90 min., left to cool, poured into cold water, and filtered. The residue was boiled with methanol and filtered hot. The remaining solid (0.79 g.) was recrystallized from a mixture of benzene and methanol, m.p. 235–238°. Its ultraviolet spectrum in dioxane solution showed it to be a chrysene derivative: maxima at 375, 357, 340, 325, 310, 278 mμ (log ε 3.52, 3.52, 3.34, 4.14, 4.16, 4.6).

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.33; H, 5.56; methoxyl, 10.4. Found: C, 83.23; H, 5.59; methoxyl, 10.2.

From the hot methanol solution a very small quantity of another material separated which, after recrystallization from petroleum ether (60–80°), melted at 166–167°.

Anal. Calcd. for 3,9-dimethoxy-5,6,11,12,13,14-hexahydrochrysene (?): $C_{20}H_{22}O_2$: C, 81.63; H, 7.48; methoxyl, 10.2. Found: C, 81.62; H, 7.47; methoxyl, 10.3.

3,9-Diacetoxychrysene. One gram of 3,9-dimethoxychrysene was boiled for 4 hr. with 57% hydriodic acid; the cold solution was poured into water and filtered, m.p. of crude dihydroxy compound 320°. The diphenol was boiled with 5 ml. of acetic anhydride in 50 ml. of pyridine for 2.5 hr. A solid separated which, after recrystallization from nitromethane, melted at 242–243°.

Anal. Calcd. for $C_{22}H_{18}O_4$: C, 76.74; H, 4.65. Found: C, 76.72; H, 4.79.

Preparation of 1,6-di(4-methoxyphenyl)hexanone-3-ol-4. The methyl ester of 4-methoxyphenylpropionic acid was prepared from methyl 4-methoxycinnamate by hydrogenation in ethyl acetate with 10% palladium-on-charcoal; b.p. 111–112°/0.6 mm. The acyloin was prepared according to Johnson and coworkers[3]: to a suspension of 9.5 g. of powdered sodium in 170 ml. of xylene kept at 105–110°, was added, over 0.5 hr., a solution of 20 g. of methyl 4-methoxyphenylpropionate in 170 ml. of xylene, the reaction being carried out in an atmosphere of pure nitrogen. Heating was continued for a further 0.75 hr., after which the mixture was allowed to cool and sufficient methanol added to destroy the remaining sodium; water was added and the xylene layer separated. After several washings with water the xylene solution was steam-distilled; the yellow oil was extracted with ether, dried over magnesium sulfate, and the ether removed *in vacuo*. The yield of acyloin was 12 g. (75%).

Cyclization of the acyloin with hydrofluoric acid. Five grams of acyloin were treated with approximately 150 ml. of hydrofluoric acid for 24 hr., when the acid was evaporated and the residue dissolved in ether. From the ethereal solution a yellow oil was obtained which was induced to crystallize by trituration with ethyl acetate. The solid (2.5 g.) after recrystallization from ethyl acetate, melted at 235–237°, and proved to be identical with the dimethoxychrysene of m.p. 235–238°, obtained by the polyphosphoric acid cyclization of I (R = OMe). The ethyl acetate solution was concentrated when it yielded a very small amount of a material, m.p. 168–169° after recrystallization from petroleum ether (60–80°) which showed no depression of m.p. with the second material, m.p. 166–167° obtained by the polyphosphoric acid cyclization of I (R = OMe).

Department of X-Ray Crystallography
The Weizmann Institute of Science
Rehovoth, Israel

(8) W. Salzer, *Z. physiol. Chem.*, **274**, 39 (1942).

Mesityl Mesitoate

G. W. Thiessen and W. N. Farr

Received September 9, 1958

Mesityl mesitoate does not appear in the chemical literature. The compound was made for comparison with an unidentified material from a Kolbe electrolysis, by way of the Schotten-Baumann reaction.

EXPERIMENTAL

Mesitoic acid,[1,2] 5 g. (0.030 mole), m.p. 153°, was converted to mesitoyl chloride by adding 4 ml. of thionyl chloride and refluxing over a water bath for 30 min. The sodium salt of mesitol was prepared by mixing 4 g. (0.037 mole) of

(1) D. M. Bowen, *Org. Syntheses*, **Coll. Vol. III**, 553 (1955).
(2) Prepared by B. T. Shawver, Monmouth College.

mesitol,[3] m.p. 72.5–73°, with 10 ml. of 6*N* sodium hydroxide. The mesitoyl chloride was slowly added to the sodium mesitolate through about 30 min., in a 125-ml. Erlenmeyer flask, with shaking. Release of heat resulted. After heat evolution ceased, the mixture was refluxed on a water bath for 30 min. It was then chilled in an ice bath. The crystals which formed were collected by vacuum filtration, washed with water, and recrystallized from approximately 100 ml. of ethyl alcohol; yield 3.75 g. (40%), m.p. 70.5–71.5°.

Anal. Calcd. for ($C_{19}H_{22}O_2$): C, 80.85 H, 7.80. Found: C, 80.55 and 80.29; H, 7.63 and 7.75.[4]

Hydrolysis. Alkaline hydrolysis: Mesityl mesitoate is a hindered ester and as such should be highly resistant to formation and saponification.[5] The ester, 0.25 g., was refluxed 6 hr. with 5 ml. of 6*N* sodium hydroxide. There remained undissolved 0.23 g. of the mesityl mesitoate which was collected by vacuum filtration. The clear filtrate did produce a slight precipitate when acidified.

Acid hydrolysis: One g. of ester in 5 ml. of cold conc. sulfuric acid was drowned with 40 ml. of cold water. The resulting mixture was extracted with ether. The mesitoic acid was next removed from the ether by three sodium bicarbonate washings, (0.2 g. recovered, m.p. 152°). Mesitol, 0.15 g., was extracted from the ether solution by three washings with 2*N* sodium hydroxide, and precipitated with hydrochloric acid while in an ice bath. The crystals were collected by filtration and vacuum desiccated for 48 hr.; m.p. 70–71°. Mixed with mesitol from Organic Research Chemical Ltd., the m.p. was 70.5–71.5°.

All melting points are corrected.

Acknowledgment. Aid from the National Science Foundation is gratefully acknowledged.

MONMOUTH COLLEGE
MONMOUTH, ILL.

(3) Supplied by Organic Research Chemical Ltd., Poyle Estate, Bucks, England.

(4) Clark Microanalytical Laboratory, P. O. Box 17, Urbana, Ill.

(5) H. P. Treffers and L. P. Hammett, *J. Am. Chem. Soc.*, 59, 1708 (1937).

Preparation of Crystalline Diphenyldiazomethane

J. B. MILLER

Received October 6, 1958

Diphenyldiazomethane has been used to analyze mixtures of carboxylic acids[1] and as a convenient "blocking agent" for acids since the resulting benzhydryl esters are easily hydrogenolyzed.[2] Benzhydryl esters should also prove useful as derivatives in view of their ease of preparation and the resulting increase in molecular weight.

Hydrazones have been converted to diazo compounds by treatment of the *N*-tosylates with base[3,4] and by oxidation of hydrazones with mercury acetamide,[5] potassium permanganate,[6] Tollens' reagent[5] mercuric oxide,[7] air,[8,9] silver oxide,[10] and manganese dioxide.[10]

The usual preparative method for diphenyldiazomethane by the mercuric oxide oxidation of benzophenone hydrazone requires six hours and yields an oil.[11] The procedure described here requires 75 minutes and gives a crystalline product in high yield. This procedure is an extrapolation of the method of Nenitzescu and Solomonica for the preparation of benzoylphenyldiazomethane[12] and diazofluorene.[12] Diethyl ether rather than petroleum ether[11] is used as the solvent in spite of the reported lower rate of oxidation in ether[13] because of the greater solubility of the hydrazone in ether. Most important is the use of a basic catalyst.

We suggest the role of the basic catalyst is that shown below.

$$(C_6H_5)_2C{=}N{-}NH_2 + HgO \longrightarrow$$

$$(C_6H_5)_2C{=}N{-}\overset{+}{N}H_2HgO^- \longrightarrow$$

$$(C_6H_5)_2C{=}N{-}NH{-}HgOH \xrightarrow[-H_2O]{OH^-}$$

I

$$(C_6H_5)_2C{=}N{-}\overset{-}{N}{-}HgOH \longrightarrow$$

$$(C_6H_5)_2CN_2 + HgOH^-$$

$$HgOH^- \longrightarrow Hg + OH^-$$

This reaction path is similar to that suggested for the mercuric acetate oxidation of tertiary amines[14] and an analogous mechanism serves to explain the mercuric oxide oxidation of 1,1-disubstituted hydrazines, R_2NNH_2, to tetrazines, $R_2NN{=}NNR_2$.[15] Mercuric acetate oxidation of hydrazones yields, in fact, organomercury compounds which are considered to be formed, however, by further reaction of the diazo compound initially formed.[16]

(1) J. D. Roberts and C. M. Regan, *Anal. Chem.*, 24, 360 (1952).

(2) E. Hardegger, Z. E. Heweihi, and F. G. Robinet, *Helv. Chim. Acta*, 31, 439 (1948).

(3) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952); M. P. Cava and R. L. Litle, *Chem. & Ind. (London)*, 367 (1957).

(4) M. P. Cava, R. L. Litle, and D. R. Napier, *J. Am. Chem. Soc.*, 80, 2257 (1957).

(5) M. O. Forster and A. Zimmerli, *J. Chem. Soc.*, 97, 2156 (1910).

(6) L. Wolff, *Ann.* 394, 23 (1912).

(7) Th. Curtius and K. Thun, *J. prakt. Chem.*, [2] 44, 161 (1891).

(8) H. Staudinger and Alice Gaule, *Ber.*, 49, 1951 (1916).

(9) H. Staudinger and K. Miescher, *Helv. Chim. Acta*, 2, 578 (1919).

(10) W. Schroeder and L. Katz, *J. Org. Chem.*, 19, 718 (1954).

(11) L. I. Smith and K. L. Howard, *Org. Syntheses*, III, 351 (1955).

(12) C. D. Nenitzescu and E. Solomonica, *Org. Syntheses*, II, 496 (1943).

(13) H. Staudinger, E. Anthes, and F. Pfenninger, *Ber.*, 49, 1928 (1916).

(14) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, 77, 439 (1955); N. J. Leonard and D. F. Morrow, *J. Am. Chem. Soc.*, 80, 371 (1958).

(15) W. E. Bull, J. A. Seaton, and L. F. Audrieth, *J. Am. Chem. Soc.*, 80, 2516 (1958).

(16) A. N. Nesmeyanov, O. A. Reutov, and A. S. Loseva, *Proc. Acad. Sci. U.S.S.R. Sect. Chem. (English Translation)*, 111, 713 (1956).

The intermediate, I, has been previously postulated as the initial product of the reaction of mercuric oxide with a hydrazone.[17,18]

Yellow mercuric oxide is more effective than red mercuric oxide in this reaction and this is generally thought to be due to the smaller particle size[19] of the yellow form. However, since red mercuric oxide is usually prepared by igniting the nitrate whereas the yellow form is usually prepared by adding a base to a soluble mercuric salt, we feel that contamination of the yellow mercuric oxide by base may be more important than the particle size in explaining the long standing preference for the yellow form. This may also explain the preference for freshly precipitated material[20] and the observed variations with different samples of mercuric oxide.[8] In agreement with this we find that by using slightly more catalyst red mercuric oxide performs as well as the yellow form (see Table I).

TABLE I

PREPARATION OF DIPHENYLDIAZOMETHANE[a]

Mercuric Oxide, g.	Time, min.	Yield, %	M.P., °C.
35 (yellow)	75	12[b,c]	...
28.7 (yellow)	60	54.5	26.5–28.5
35 (yellow)	75	88, 95	30.1–31.1, 29–33
36.5 (yellow)	75	89	30–31
44 (yellow)	70	83	29-30.5
44 (yellow)	90	79	30–32
35 (red)	75	4, 9[b,c]	...
35 (red)	75	20.5, 30, 46, 55, 81, 88	26–28.5 to 29–31
35 (red)	75	81[d]	28–31.5
35 (red)	75	95[d]	29–33
35 (red)	75	86[d]	27–29

[a] From 13 g. of benzophenone hydrazone, 15 g. of anhydrous sodium sulfate, 200 ml. of ether, and 5 ml. of ethanol saturated with potassium hydroxide (except where noted). [b] Based on recovered hydrazone. [c] No basic catalyst. [d] Ten ml. of basic catalyst.

This method of oxidation is, however, not always applicable. Thus, although the mercuric oxide oxidation of the 2-hydrazone of 4,7-dimethyl-1,2-indanedione showed definite basic catalysis, the yield was very low[4] and the base catalyzed mercuric oxide oxidation of *p*-chlorobenzophenone hydrazone gave erratic results.[10] Similarly, we find that contrary to some reports[17,18,21] and in agreement with Vollmann[22] the base catalyzed mercuric oxide oxidation of camphor hydrazone yields diazocamphane but in only trace amounts.

(17) H. Meerwein and K. Emster, *Ber.* **53**, 1815 (1920).
(18) German Patent **353,933** (1922).
(19) A. B. Garrett and A. E. Hirschler, *J. Am. Chem. Soc.*, **60**, 299 (1938).
(20) M. Busch and R. Knoll, *Ber.*, **60**, 2243 (1927); P. C. Guha and D. K. Sankaran, *Ber.* **70**, 1688 (1937).
(21) H. Staudinger and S. Schotz, *Ber.*, **53**, 1105 (1920).
(22) H. Meerwein and K. Emster, *Ber.*, **53**, 1816, footnote 2 (1920).

EXPERIMENTAL

Diphenyldiazomethane. A mixture of 13 g. (0.066 mole) of benzophenone hydrazone, 15 g. of anhydrous sodium sulfate, 200 ml. of ether, 5 ml. (10 ml. if red mercuric oxide is used) of ethanol saturated with potassium hydroxide, and 35 g. (0.16 mole) of yellow (or red) mercuric oxide was shaken for 75 min. in a pressure bottle wrapped in a wet towel. The reaction mixture was filtered and the solvent removed from the filtrate under reduced pressure at room temperature. The dark red oil thus obtained was dissolved in petroleum ether (b.p. 30–60°) and again filtered. Removal of the solvent from the filtrate under reduced pressure at room temperature gave an oil. Freezing this oil in a stoppered flask with Dry Ice and then allowing the flask to warm spontaneously to room temperature gave dark red crystals which, after drying on a porous plate, had m.p. 29–32° (reported[13] 29–30°), average yield 89% (see Table I). Reaction of this product with benzoic acid[2] gave benzhydryl benzoate, m.p. 88–91° (reported[2] 87°).

Diazocamphane. A potassium-sodium *tert*-butoxide solution was prepared by dissolving 2.05 g. of potassium-sodium eutectic alloy[23] in 100 ml. of *tert*-butyl alcohol. A mixture of 5 ml. of the above solution, 35 g. of mercuric oxide (yellow), 15 g. of sodium sulfate, 150 ml. of ether, and 10.6 g. of camphor hydrazone[24] (m.p. 52–57°, b.p. 130–133° [22 mm.]) was stirred for 3 hr. and then filtered. This filtrate was bright red in agreement with Vollmann[22] and Heubaum[25] and effervesced on acidification. The presence of the diazo group was shown by infrared absorption at 4.82 microns[26] which disappeared on acidification or treatment with anhydrous copper sulfate. Ethanolic potassium hydroxide solution worked less well than the *tert*-butoxide solution but in neither case was sufficient diazo compound formed to allow its isolation as bornyl or isobornyl chloride.

EXPLOSIVES DEPARTMENT
EXPERIMENTAL STATION
E. I. DU PONT DE NEMOURS & CO., INC.
WILMINGTON, DEL.

(23) A product of the MSA Research Corporation, Callery, Pa.
(24) L. Wolff, *Ann.*, **394**, 86 (1912).
(25) U. Heubaum and A. Noyes, *J. Am. Chem. Soc.*, **52**, 5070 (1930).
(26) P. Yates and B. L. Shapiro with N. Yoda and J. Fugger, *J. Am. Chem. Soc.*, **79**, 5756 (1957).

Acid Catalyzed Reactions between Carbonyl Compounds and Organic Azides. II. Aromatic Aldehydes[1]

J. H. BOYER AND L. R. MORGAN, JR.

Received October 10, 1958

An acid-catalyzed reaction between aromatic aldehydes and alkyl azides leading to the formation of amides (II) was recently reported.[2] It was suggested that elimination of a proton at an intermediate stage such as I followed by or accom-

(1) Financial assistance under a National Institutes of Health Grant No. H-2295 and Contract No. DA-01-009-ORD-428 with the Office of Ordnance Research, U. S. Army, is gratefully acknowledged.
(2) J. H. Boyer and J. Hamer, *J. Am. Chem. Soc.*, **77**, 951 (1955). Part I.

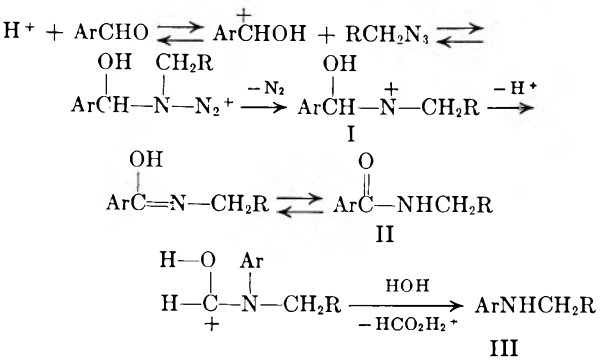
TABLE I

N-SUBSTITUTED ANILINES FROM BENZALDEHYDE AND AZIDES

Azide	Aniline Derivative	B.P. or M.P., °C	Refractive Index	Yield, %	Derivative	M.P. °C
n-Butyl	*N*-*n*-Butyl	120 (5 mm.)	n_D^{20} 1.5381	21.9	Hydrochloride	114–115
n-Hexyl	*N*-*n*-Hexyl	158 (28 mm.)[a]	n_D^{20} 1.4235[a]	25	*p*-toluenesulfonamide	67–68[a]
n-Octyl	*N*-*n*-Octyl	118 (25 mm.)[b]	n_D^{25} 1.6381	18	*p*-toluenesulfonamide	42–43[b]
Phenyl	*N*-Phenyl	53–54.5[c]		10	*p*-toluenesulfonamide	64[d]

[a] W. J. Hickinbottom, *J. Chem. Soc.*, 1119 (1937) reported b.p. 165° (35 mm.), n_D^{20} 1.4240, *p*-toluenesulfonamide, m.p. 69°. [b] W. J. Hickinbottom, *J. Chem. Soc.*, 1119 (1937), reported b.p. 119–120° (20 mm.), *p*-toluenesulfonamide, m.p. 41–42°. [c] P. P. Karpiklien, *J. Chem. Ind.* (*Moscow*), **23**, 1627 (1929). [d] I. Goldberg, *Ber.*, **40**, 4543 (1907) reported m.p. 65°.

panied with tautomerization accounted for amide formation. The expected migration of an aryl group from carbon to nitrogen with subsequent formation of formanilides or their hydrolysis products, secondary amines (III), was not detected.



In the present work this migration is detected insofar as the predicted amines (III) are isolated. From each of three different primary alkyl azides and benzaldehyde the corresponding *N*-alkylaniline is isolated in 18–25% yields; diphenylamine is obtained from phenyl azide and benzaldehyde in 10% yield. Each reaction is carried out in benzene which contains equimolar quantities of azide and aldehyde together with sulfuric acid is catalyst.

Curiously amides (II) are not found. In contrast amides (II) (requiring no rearrangement) but not amines (III) were products of those reactions which used an excess of aldehyde as solvent in place of benzene.[2] Apparently aldehyde solvation of intermediates represses migration.

The presence of strong electron releasing groups in positions *ortho* or *para* to the carbonyl carbon atom inhibits a reaction between aldehydes and azides probably as a result of a decrease in the acidity of the corresponding aldehyde conjugate acids.[2] In the present work *p*-anisaldehyde is nearly quantitatively recovered from attempted reactions with alkyl azides in benzene or nitrobenzene containing sulfuric acid at temperatures ranging from 75–190°. On the other hand *p*-tolualdehyde was successfully transformed into *N*-*n*-butyl-*p*-toluidine using *n*-butyl azide.

Electron attracting ring substituents in the aromatic aldehyde had no apparent effect upon the efficiency of its transformation, using ethylene azidohydrin, into an oxazoline.[2] Unexpectedly *m*- and *p*-nitrobenzaldehyde have now been nearly quantitatively recovered from attempted reactions with *n*-butyl azide in benzene or nitrobenzene containing sulfuric acid at temperatures from 75–190°.

EXPERIMENTAL

Preparation of n-butylaniline. A mixture of 3.18 g. (0.03 mole) of benzaldehyde in 50 ml. of benzene and 5 ml. of concentrated sulfuric acid was warmed to 75°. At a rate which maintained gentle reflux, 2.97 g. (0.03 mole) of *n*-butyl azide was added dropwise with efficient stirring. Gas evolution was complete about 5 min. after the last drop of azide was added. The reaction mixture was then treated with 50 ml. of ice and water, the layers were separated, and the water layer was neutralized with sodium carbonate and extracted with ether. Distillation of the combined dried ether extracts gave 0.9 g. (21.9%) of *N*-*n*-butylaniline, b.p. 120° (2 mm.), n_D^{20} 1.5381, hydrochloride m.p. 114–115°.[3] Trace amounts of benzaldehyde were recovered from the benzene layer which also contained a large amount of tar.

In a similar manner *N*-substituted anilines were obtained from other azides and benzaldehyde; results are summarized in Table I.

In a similar reaction with 6.00 g. (0.05 mole) of *p*-tolualdehyde and 4.95 g. (0.05 mole) of *n*-butyl azide in benzene containing concentrated sulfuric acid there was obtained 1.6 g. (21%) of *p*-methyl-*N*-*n*-butylaniline, b.p. 105–106° (3 mm.)[4] hydrochloride, m.p. 150–151°,[4] picrate m.p. 90°.[4]

DEPARTMENT OF CHEMISTRY
TULANE UNIVERSITY
NEW ORLEANS, LA.

(3) J. Reilly and W. J. Hickinbottom, *J. Chem. Soc.*, **113**, 99 (1918).

(4) J. Reilly and W. J. Hickinbottom, *J. Chem. Soc.*, **117**, 103 (1920); **113**, 974 (1918).

Theophylline in the Mannich Reaction[1]

J. H. BURCKHALTER AND DALE R. DILL

Received October 13, 1958

As a continuation of studies employing the Mannich reaction, we wished to determine if theo-

(1) This investigation was supported by Research Grant H-1756 from the National Heart Institute, U.S. Public Health Service.

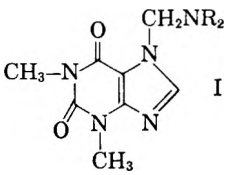
TABLE I

7-(SUBSTITUTED AMINOMETHYL)THEOPHYLLINES

No.	NR_2	M.P., °C (dec.)	Yield	Formula	Analyses, % C Calcd.	C Found	H Calcd.	H Found
1	Diethylamino	110	38	$C_{12}H_{19}N_5O_2$[a,b]	54.32	54.17	7.22	7.03
2	1-Pyrrolidinyl	108	61	$C_{12}H_{17}N_5O_2$[a,b]	54.74	54.47	6.51	6.50
3	1-Piperidinyl	111	87	$C_{13}H_{19}N_5O_2.1/2H_2O$	54.52	54.52	7.04	7.02
4	4-Morpholinyl	177	92	$C_{12}H_{17}N_5O_3$[c,d]	51.60	51.65	6.14	6.06
5	1-*N*-Methylpiperazinyl	131	83	$C_{14}H_{20}N_6.1/2H_2O$	51.82	51.60	7.03	7.14
6	7-Bis(1,4-piperazinedimethyl)	305	99	$C_{20}H_{26}N_{10}O_4.2H_2O$[e,f]	47.42	47.44	5.97	6.15

[a] Yield may be improved by obtaining second crop crystals. [b] Theophylline may be dissolved in the reaction mixture by mild heating on the steam bath, giving better yields. [c] Product precipitated from solution before unreacted starting material could be filtered from solution. [d] Could be recrystallized from absolute ethanol once before reverting to theophylline. [e] Piperazine hexahydrate was used. [f] Two moles each of theophylline and formalin were used to one mole of piperazine.

phylline, which has acidic properties, would undergo the reaction. Also, the products of the reaction, presumed to be 7-α-dialkylamino derivatives of caffeine (I),[2] would be of interest pharmacologically as stimulants, diuretics and hypotensives.



I

For the synthesis of type I compounds (Table I), a mixture of molecular equivalents of theophylline, secondary amine and aqueous formaldehyde was stirred at room temperature for a few minutes. In general, the water-soluble products separated from solution in excellent yield after refrigeration, but they could not be recrystallized without reverting to theophylline. Only in the case of the morpholinyl Mannich base was the product stable enough for one recrystallization.

7-Chloromethyltheophylline was made in 75% yield from chloromethylation of theophylline. It could not be recrystallized without decomposition. For example, when recrystallized from alcohol, it was converted quantitatively to the stable 7-hydroxymethyltheophylline. Treatment of the hydroxymethyl compound with thionyl chloride reconverted it to 7-chloromethyltheophylline.

An attempt was made to confirm the assignment of the position of the chloromethyl substituent in 7-chloromethyltheophylline by reducing it to caffeine. Since 1-chloromethylbenzotriazole has been reduced to 1-methylbenzotriazole,[5] chloromethyltheophylline was similarly treated with lithium aluminum hydride in tetrahydrofuran, but only a tar was obtained. Hydrogenation using palladium on charcoal gave only recovered starting material plus some 7-hydroxymethyltheophylline, the latter resulting from hydrolysis in the presence of the alcoholic solvent. Stannous chloride in hydrochloric acid also gave only starting material. However, further support for presumed substitution at position 7 may be suggested by the observation of the same infrared peaks for chloromethyl-, *N*-pyrrolidinyl-, and *N*-piperidylmethyltheophylline as were obtained with caffeine: 1370–1380 cm.$^{-1}$ (*N*-methyl) and 1015-1020 cm.$^{-1}$ (tertiary amine). The spectrum of theophylline does not exhibit these peaks.

Numerous attempts were made to prepare the Mannich bases of Table I by treating chloromethyltheophylline with two equivalents of the appropriate amine. In no case could the desired product be obtained, and theophylline was isolated as shown by analysis and melting point determination. Thus, it is strongly suggested that a Mannich base forms, as indicated by a vigorous reaction between the amine and chloromethyltheophylline, and attempts at purification result in decomposition, as do the products from the Mannich reaction. This conclusion is supported by the fact that the chloromethyl derivative does not decompose to theophylline upon recrystallization but to hydroxymethyltheophylline, which is a stable compound.[6]

Biological activity. Compounds 1 and 2 possessed no hypotensive action at 20 mg./kg. oral dosage in the perinephritic rat, while 1,2, and 4 exhibited

(2) Although two tautomeric structures may be written for theophylline, the fact that caffeine is obtained in good yield from the methylation of theophylline[3] suggests that alkylation at position 7 is highly favored over position 9. Other studies similarly suggest alkylation of theophylline at position 7.[4]

(3) J. M. Gulland and T. F. Macrae, *J. Chem. Soc.*, 662 (1933).

(4) J. M. Gulland, E. R. Holiday, and T. F. Macrae, *J. Chem. Soc.*, 1639 (1934); D. B. Ishay, *J. Chem. Soc.*, 3975 (1946).

(5) J. H. Burckhalter, V. C. Stephens, and L. A. R. Hall, *J. Am. Chem. Soc.* 74, 3868 (1952).

cerebral stimulation in rats of the order of caffeine when administered subcutaneously. These results were kindly furnished by Dr. G. M. Chen of Parke, Davis and Company Research Laboratories. Also, Dr. D. A. McGinty, of the same laboratories, indicated that compounds 1, 2, and 4 show insufficient diuretic effect in the rat for further interest.

EXPERIMENTAL

7-(Substituted aminomethyl)theophyllines (Table I). To a well-stirred mixture of 0.01 mole of theophylline and 4 ml. of alcohol, 0.01 mole of the appropriate amine was added. Then, 0.9 ml. (0.01 mole) of 38% formaldehyde solution was added with stirring while heat was evolved. At this stage, usually the starting materials had dissolved. Any undissolved material was removed by filtration. The filtrate was refrigerated to achieve complete precipitation of the product, which was then collected by filtration and air dried for 72 hr.

7-Chloromethyltheophylline (A). A mixture of 8 g. (0.04 mole) of theophylline, 4 ml. (0.048 mole) of 38% formaldehyde solution and 23 ml. of concentrated hydrochloric acid was allowed to stand for 20 min. at room temperature, after which time all the solid had dissolved. Then, a vigorous stream of hydrogen chloride gas was passed into the solution, with the evolution of heat, and maintained until the solution had cooled to room temperature, which required about 30 min. The solution was diluted with ten volumes of acetone and then refrigerated for at least 2 days or until a good yield of white solid had been obtained. It could not be recrystallized without decomposition. Air drying for several days gave 7.7 g. (75% yield) of product, m.p. 257–258° dec. The solid was water soluble and gave a positive halogen test with silver nitrate.

Anal. Calcd. for $C_8H_9ClN_4 \cdot 1\text{-}^1/_2H_2O$: C, 37.58; H, 4.73; Cl, 13.87. Found: C, 37.77; H, 4.73; Cl, 13.86.

(B). To 0.2 g. (0.0095 mole) of 7-hydroxymethyltheophylline, 1.5 ml. of thionyl chloride was added slowly at room temperature. The mixture was heated at reflux temperature for 5 min. and then allowed to stand at room temperature for 20 min. Excess thionyl chloride was removed by distillation on the steam bath. Acetone was added to the residue and the mixture was stirred and cooled. The product was removed by filtration and washed well with acetone. The solid was air dried to yield 0.2 g. (82%) of 7-chloromethyltheophylline, m.p. 258–259°.

7-Hydroxymethyltheophylline was prepared from 7-chloromethyltheophylline by recrystallizing the latter from alcohol. The desired product, resulting from a hydrolytic action, was obtained in quantitative yield, m.p. 261–262° dec. Two more recrystallizations from alcohol were carried out without significant change in melting point.

Anal. Calcd. for $C_8H_{10}N_4O_4$: C, 45.71; H, 4.79. Found: C, 45.67; H, 4.88.

LABORATORY OF PHARMACEUTICAL CHEMISTRY
UNIVERSITY OF KANSAS
LAWRENCE, KAN.

(6) The ready hydrolysis of 7-chloromethyltheophylline to 7-hydroxymethyltheophylline may be explained by a neighboring group effect exhibited by the 6-keto group which, bearing a partial negative charge, would be expected to aid the removal of the chloro group bearing a negative charge. The resulting hydroxymethyltheophylline would be stabilized *via* hydrogen bonding through the same 6-keto group. Also, the instability of the Mannich bases may again be explained by consideration of perturbations at the 6-keto position. A resonance structure bearing a negative charge at the 6-keto and a positive one at the 7-position might be expected to yield the 7-theophylline anion.

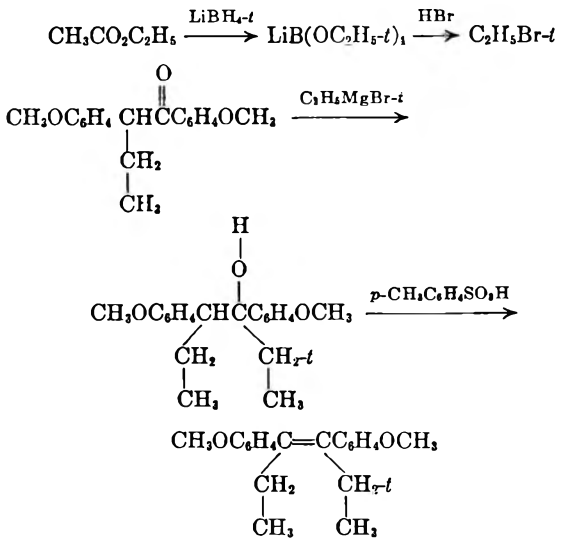
Synthesis of a Radioactive Estrogen, 3,4-Dianisyl-2-*t*-3-hexene

ERNEST M. HODNETT AND ROBERT GALLAGHER

Received October 13, 1958

Radioactive 3,4-dianisyl-3-hexene (the dimethyl ether of stilbestrol) was needed recently for feeding experiments with poultry.[1] It was necessary to use tritium as the tagging isotope in spite of the more laborious assays anticipated because of the quantity of estrogen desired. Because the hormone would be greatly dispersed in use, a high initial specific activity was required. Since this compound may be demethylated *in vivo* to stilbestrol, labeling of the compound on the methoxyl groups was undesirable. Hence tritium was incorporated into the molecule by chemical synthesis rather than by recoil[2] or exchange[3] reactions.

The method of synthesis was as follows:



Good weight and radioactivity yields were obtained in each step except the last one. The over-all radioactivity yield based on tritium gas was 3.2%.

EXPERIMENTAL

Preparation of 1-bromo-1-t-ethane. The procedure used was based on one devised by Smith, Wilzbach, and Brown[4] for methyl-*t* iodide. Lithium borohydride (0.1827 g.), obtained from Metal Hydrides, Inc., was contacted with a mixture of 250 mc. of tritium and 23 ml. of hydrogen for 36 hr. at

(1) Results of these experiments will be reported soon by Dr. Rollin Thayer and Mr. Don deSteiguer, Department of Poultry Science, Oklahoma State University. Financial support of this work came from this Department through the Agricultural Experiment Station and the Research Foundation of Oklahoma State University.

(2) (a) R. Wolfgang, F. S. Rowland, and C. N. Turton, *Science*, 121, 715 (1955); (b) F. S. Rowland and R. Wolfgang, *Nucleonics*, 14, No. 8, 58 (1956); (c) F. S. Rowland, C. N. Turton, and R. Wolfgang, *J. Am. Chem. Soc.*, 78, 2354 (1956).

(3) K. Wilzbach, *J. Am. Chem. Soc.*, 79, 1013 (1957).

200°. All except 8.5% of the tritium wax taken up by the lithium borohydride; the remaining gaseous tritium was converted to tritiated water.[5] Dry tetrahydrofuran (10 ml.) and 1.1890 g. of dry ethyl acetate were distilled into the flask containing tritium-enriched borohydride. The contents of the flask were warmed slowly and kept at reflux temperature for 8 hr. The solvent and a small amount of excess ester was removed by distillation. Twenty-five ml. of hydrobromic acid (Baker's Analyzed Reagent) was added slowly to the flask through a dropping funnel while the reflux condenser was cooled with water. The flask was heated to 90° for 2.5 hr. while a stream of nitrogen was passed through it and then through a trap immersed in liquid nitrogen. When the reaction was complete, the product in the trap was purified on the vacuum line, and only material boiling above −85° and lower than −58° at 1 micron pressure was retained. The vapor pressure of the product at 27° was 494 mm. compared to 475 mm. at 25.5° for a known sample of ethyl bromide. The radioactive ethyl bromide weighed 1.783 g.

Preparation of 3,4-dianisyl-2-t-3-hexene. A Grignard solution was prepared from the above ethyl bromide, 1.102 g. of non-radioactive ethyl bromide, 0.6398 g. of magnesium, and 20 ml. of diethyl ether. A solution of 7.51 g. of α-ethyldesoxyanisoin[6] in 10 ml. of ether was added and the mixture was refluxed. After 2 hr. the reaction flask had an oily layer at the bottom, indicating excess ketone. Another Grignard solution prepared from 5.77 g. of ethyl bromide and 1.50 g. of magnesium was added to the flask to insure complete reaction of the ketone. The mixture was hydrolyzed in acidified water and ice and worked up in the usual way.[7] A white solid weighing 6.07 g. and melting at 75–95° was obtained. Two forms of 3,4-dianisyl-3-hexanol have been reported,[8] one melting at 114–117° and one at 83–85.5°; the solid product was assumed to be a mixture of these two forms.

This mixture was dehydrated by the method of Wilds and Biggerstaff[8] with *p*-toluenesulfonic acid at 125–130° with a weight yield of only 35%. A total of 1.58 g. of active 3,4-dianisyl-3-hexene was obtained melting at 122.5–123.5° (literature,[6] 123–124°) with an activity of 5.02 mc./g.

DEPARTMENT OF CHEMISTRY
OKLAHOMA STATE UNIVERSITY
STILLWATER, OKLA.

(4) N. H. Smith, K. E. Wilzbach, and W. G. Brown, *J. Am. Chem. Soc.*, **77**, 1033 (1955).

(5) E. M. Hodnett, C. F. Feldman, and J. J. Flynn, Jr., *Experientia*, **13**, 96 (1957).

(6) E. C. Dodds, L. Goldberg, W. Lawson, and R. Robinson, *Nature*, **141**, 247 (1938).

(7) E. C. Dodds, L. Goldberg, W. Lawson, and R. Robinson, *Proc. Roy. Soc. (London)*, **127B**, 140 (1939).

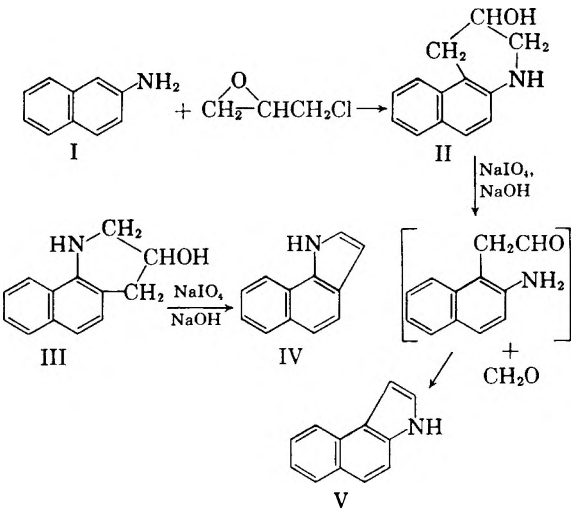
(8) A. L. Wilds and W. R. Biggerstaff, *J. Am. Chem. Soc.*, **67**, 789 (1945).

A New Indole Synthesis

F. C. PENNINGTON, M. JELLINEK, AND R. D. THURN

Received November 3, 1958

It is known that when hydroxyproline is oxidized with periodate, formaldehyde is split out and presumably an amino aldehyde is formed.[1] It would be expected that properly substituted β-hydroxypiperidines would likewise be oxidized, and the amino aldehydes thus formed might be cyclized to give indoles. Lange and others[2] have



reported the synthesis of suitable β-hydroxypiperidines, II and III, by the reaction of epichlorohydrin with β-naphthylamine and α-naphthylamine, respectively. The oxidation of II and III was investigated, therefore, and has led to the synthesis of 6,7-benzindole (IV) in 27% yield and the picrate of 4,5-benzindole (V) in 30% yield.

EXPERIMENTAL

Preparation of 4,5-benzindole (V) *by periodate oxidation of* II. II (2.00 g.) was dissolved in 50 ml. of ethanol and sodium metaperiodate (2.14 g.) was dissolved in 50 ml. of water. These solutions were added dropwise over a 3-hr. period to a 100-ml. solution of 8% sodium hydroxide through which steam was passing rapidly. The steam distillate was collected until the distillate no longer gave a red color with an acidic alcoholic solution of dimethylaminobenzaldehyde (Ehrlich's reagent). This required about 7 hr. The distillate was then extracted with benzene, the benzene extract dried over sodium sulfate, and the benzene removed *in vacuo*. The residual oil was dissolved in ethanol and treated with an ethanolic picric acid solution. Red needles of the picrate of V were recovered and dried; 1.20 g. (30%), dec. 205° with previous charring.

Anal. Calcd. for $C_{18}H_{12}N_4O_7$: C, 54.55; H, 3.05; N, 14.14. Found: C, 54.28; H, 3.20; N, 14.26.

An alkaline solution of the picrate was extracted with ether, and the ether extract was dried over potassium carbonate. The ether was removed, and the residual oil distilled, b.p. 145–150°/5 mm. The oil was purified further by dissolving it in benzene and chromatographing it on alumina. A sample boiling at 148°/5 mm. was analyzed.

Anal. Calcd. for $C_{12}H_9N$: C, 86.19; H, 5.43; N, 8.38. Found: C, 85.93; H, 5.45; N, 8.28.

An infrared spectrum of the oil (V) in chloroform showed a strong sharp band close to 2.9 μ but only weak absorption around 6.1 μ.

Preparation of 6,7-benzindole (IV) *by the oxidation of* III. Compound III (2.00 g.) was dissolved in 100 ml. of ethanol,

(1) H. E. Carter and H. E. Neville, *J. Biol. Chem.*, **170**, 301–304 (1947); H. E. Carter and Y. H. Loo, *J. Biol. Chem.*, **174**, 723–727 (1948).

(2) H. Lange, U. S. Patent 2,194,399, *Chem. Abstr.*, **30**, 1584 (1936); R. G. Gould, Jr., and W. A. Jacobs, *J. Am. Chem. Soc.*, **61**, 2890 (1939); N. N. Vorozhtsov, Jr., and S. I. Kutkevichus, *Zhur. Obschei. Khim.*, **27**, 2152–2160, 2521–2525 (1957).

and the oxidation procedure used for the preparation of 4,5-benzindole (V) was followed. The product (IV) was recovered from the steam distillate as white crystals; 0.45 g. (27%), m.p. 170–171°. By recrystallization from dilute ethanol an analytically pure sample (m.p. 172°) was prepared which gave a very strong positive test with Ehrlich's reagent. Its infrared spectrum in the 2.9 μ and 6.1 μ regions was similar to that of V.

Anal. Calcd. for $C_{12}H_9N$: C, 86.19; H, 5.43; N, 8.38. Found: C, 86.08; H, 5.40; N, 8.30.

Acknowledgment. This work was supported by a Frederick Gardner Cottrell Grant from the Research Corp.

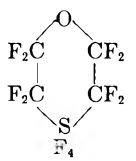
DEPARTMENT OF CHEMISTRY
COE COLLEGE
CEDAR RAPIDS, IOWA

Pyrolysis of Perfluorothioxane Tetrafluoride[1]

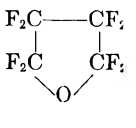
R. D. DRESDNER AND J. A. YOUNG

Received October 14, 1958

Fluorocarbon derivatives containing a SF_4 or SF_5 group have shown a marked tendency to pyrolyze[2,3] at much lower temperatures than fluorocarbon ethers or amines. The cyclic perfluorothioxane tetrafluoride (PTT), I, behaves similarly. Under a variety of pyrolysis conditions, the ether linkage is retained and SF_4 is eliminated. When PTT is pyrolyzed alone the recovered ether is perfluorotetramethylene oxide, II, when PTT is pyrolyzed in the presence of $CF_3N{=}CF_2$, perfluoro-2-azapropene, under some conditions II is a product while under other conditions perfluoroethyl ether $(C_2F_5)_2O$ results, plus other products.



I



II

EXPERIMENTAL

The PTT was prepared electrochemically in HF from thioxane.[4] It was purified by separation in large scale vapor phase chromatographic equipment.[5] Its properties were: b.p. 80.5°, m.p. 17.1–17.3°, n_D^{25} 1.3041. It had a purity of better than 99.5% by wt. as established by chromatographic analysis.

$CF_3N{=}CF_2$ was prepared from $(CF_3)_2NCOF$ by pyrolysis.[6]

Pyrolysis of PTT in a steel vessel. Forty g. (0.123 mole) of PTT was heated slowly in a 500 cc. stainless steel reaction vessel. At 325° and 8.8 atm. a sharp increase in pressure was noted. The pressure rose rapidly until it reached 18.7 atm. at 330° and then dropped over a 10-hr. period to 12 atm. When the vessel was evacuated, 28 g. of a clean liquid boiling below room temperature was recovered. The 12 g. of material not recovered were found in the vessel as elemental sulfur, 3.5 g., and FeF_3, 15.5 g. Apparently the SF_4 formed attacked the vessel and accounts for the solids and the associated drop in pressure under the conditions outlined. Twenty-five g. of the liquid boiled between 1.5 and 2.0°, had a mol. wt. of 216 and an infrared spectrum equivalent to that for $O(C_2F_4)_2$. The yield of the ether was not less than 90%.

Reaction of PTT with $CF_3N{=}CF_2$. Twenty-nine and a half grams. (0.22 mole) $CF_3N{=}CF_2$ and 20 g. (0.062 mole) PTT were heated in the 500 cc. (Hoke) reaction vessel to 336° at 22.6 atm. The isolated products amounted to 7.5 g. SF_4, 20.5 g. $CF_3N{=}CF_2$, mol. wt. 130–133, and 11.0 g. of material boiling at 1.5 to 4.5°. The last cut was washed with 20% NaOH, dried, and had a mol. wt. of 245–247. The infrared spectrum showed that it was preponderantly perfluoroethyl ether, $C_2F_5OC_2F_5$ (mol. wt. 254). The contaminant appeared to be the cyclic ether $O(CF_2)_4$. There was also 8 g. of material which boiled up to 150° without any temperature plateau. Part of it was reactive toward base, forming a white resinous solid.

A second similar trial was made with 25 g. $CF_3N{=}CF_2$ and 19 g. PTT at the lower temperature range of 260–277° and 17 atm. There was no serious pressure change over a 36-hr. heating period. Again, over the protracted heating period, much of the SF_4 produced attacked the vessel. The recovered products were 2.5 g. SF_4, 20.5 g. $CF_3N{=}CF_2$, 4.0 g. $C_2F_5OC_2F_5$ (mol. wt. 250) and 14 g. boiling up to 150°. The latter 14 g. was fractionated in a small column. A 2-g. fraction was isolated at 36–38° which had the correct properties for $(CF_3N{=}CF_2)_2$ [Reported b.p. 39°, mol. wt. 266, n_D^{25} 1.2596][7] mol. wt. 262–263 n_D^{25} 1.2606. The column did not reflux again until the head temperature reached 80°. There were 3 fractions (1) 80–123°, 2 g.; (2) 123–150°, 5 g.; (3) above 150°, 5 g. The latter two fractions were analyzed by gas chromatography and each showed 9 and 5 components respectively. These materials were not affected by base.

Flow pyrolysis of pure PTT. Some 40 g. of PPT (0.13 mole) was pyrolyzed in a vertical nickel reactor filled with NaF pellets without a carrier gas. It was flash-vaporized on a hot surface as it entered the reactor at the rate of 10 g./hr. Some 12 g. SF_4 and 22 g. of the cyclic ether were isolated from the reaction products. Only 4.5 g. of starting material were recovered. The yield of products was accordingly about 90%. The reaction temperature was 475°.

Flow reaction with PTT and $CF_3N{=}CF_2$. In this trial $CF_3N{=}CF_2$ was bubbled through PTT at 45°C. The $CF_3N{=}CF_2$ was present in the reaction mixture molewise in six fold excess. The mixture was fed into a nickel reactor packed with NaF pellets at the rate of 10 g./hr. at 430°. However, except for the decomposition of PTT to form SF_4 and II, no other reactions were in evidence.

Reaction of $CF_3N{=}CF_2$ and PTT at over 75 Atm. This final reaction was to determine the effect of high pressure. Sixty g. of each reactant were charged in a stainless steel pressure reactor (Aminco) and heated for 40 hr. at between 290 and 320° at from 75.6 to 79.2 atm. In the main the temperature did not exceed 300° until near the end of the trial. The products found were SF_4 and II in the usually good

(1) This work was supported by the Chemistry Branch, Office of Naval Research; all or any part of this paper may be reproduced for purposes of the United States Government.

(2) R. D. Dresdner, *J. Am. Chem. Soc.*, **77**, 6633 (1955).

(3) R. D. Dresdner, *J. Am. Chem. Soc.*, **79**, 69 (1957).

(4) R. D. Dresdner and J. A. Young, *J. Am. Chem. Soc.*, **81**, 574 (1959).

(5) T. M. Reed, J. F. Walter, R. R. Cecil, and R. D. Dresdner, *Ind. & Eng. Chem.*, **51**, 271 (1959).

(6) J. A. Young, T. C. Simmons, and F. W. Hoffman, *J. Am. Chem. Soc.*, **78**, 5637 (1956).

(7) J. A. Young, W. S. Durrell, and R. D. Dresdner, 134th Meeting A.C.S. Chicago, Ill., September 1958.

yields but in incomplete conversions. Fourteen g. of PTT were recovered despite the long heating period. The only other product was a 4-g. fraction of the $CF_3N{=}CF_2$ dimer. There was no material boiling above 80.5°.

Acknowledgment. Support of this work by the Chemistry Branch, Office of Naval Research is gratefully acknowledged.

DEPARTMENTS OF CHEMICAL ENGINEERING AND CHEMISTRY
UNIVERSITY OF FLORIDA
GAINESVILLE, FLA.

A New Procedure for the Dehydrogenation of Flavanones with *N*-Bromosuccinimide[1]

J. H. LOOKER AND MYRON J. HOLM[2,3]

Received October 17, 1958

The application of *N*-bromosuccinimide (NBS) to dehydrogenation of flavanone derivatives has been reported by Lorette, Gage, and Wender,[4] who converted flavanone glycosides to flavone glycosides, and subsequently by a number of workers[5] to dehydrogenation of other flavanone derivatives. In each case, the essential steps were bromination with *N*-bromosuccinimide and dehydrohalogenation of the bromination product with an organic or inorganic base. It is noteworthy that two groups[5b,6] described the bromination mixture as assuming a reddish-brown color, which later disappeared. In the present note, we report that the usual NBS dehydrogenation procedure can be modified by removing by-product bromine, with marked improvement in the yield of flavone.

In applying the NBS reaction to hesperetin triacetate (4′-methoxy-3′,5,7-triacetoxyflavanone) we observed rapid development of a reddish-brown product. Since this substance was volatile with the carbon tetrachloride vapors and blackened moist starch-iodide paper, it was considered to be bromine. Concomitant formation of hydrogen bromide could not be detected. Later, the bromine-red color increased in intensity, but after the solid NBS had disappeared, diminished rapidly and finally faded completely. Hydrogen bromide was evolved during this late reaction stage. In another experiment, the solvent, carrying with it bromine, was distilled from the reaction vessel and collected. Titration of the distillate with standard sodium bisulfite solution showed that it contained most of the bromine originally present in the NBS. The residue afforded a good yield of diosmetin triacetate (sequel).

These observations are interpreted as indicating that the NBS first brominated the flavanone, possibly in the 2-position.[7] Then the bromoflavanone yielded the flavone by elimination of hydrogen bromide, which attacked unreacted NBS to produce bromine and succinimide.[8] A possible final step would be bromination of the flavone by free bromine. This sequence, which is somewhat similar to that proposed by Stuckwisch and co-workers[9] in their study of the oxidation of alcohols by NBS, is shown in Chart 1.

(1) Flavanone + NBS ⟶ 2- or 3-Bromoflavanone + Succinimide

(2) Bromoflavanone ⟶ Flavone + HBr

(3) HBr + NBS ⟶ Br_2 + Succinimide

(4) Flavone + Br_2 ⟶ Brominated flavone + HBr

CHART I

A practical result of these observations has been development of a new procedure for the dehydrogenation of flavanones. From Chart 1, it is apparent that step (4) would be undesirable, and the key step in our procedure is removal of bromine by distillation. This method affords an alternative to the recently described neutralization of hydrogen bromide in NBS reaction mixtures[9] which also prevents deleterious side reactions due to bromine. The flavanone in carbon tetrachloride solution was

(1) This investigation was supported by a research grant (E-1703) from the National Institute of Allergic and Infectious Diseases, Public Health Service.

(2) DuPont Postgraduate Teaching Assistant, 1956–1957; Standard Oil of Indiana Foundation Fellow, 1957–1958.

(3) Abstracted from a portion of the Ph.D. thesis of Myron J. Holm, University of Nebraska, 1958.

(4) N. B. Lorette, T. B. Gage, and S. H. Wender, *J. Org. Chem.*, **16**, 930 (1951).

(5) (a) R. C. Chen and C. H. Yang, *J. Taiwan Pharm. Assoc.*, **3**, 39 (1951); *Chem. Abstr.*, **49**, 10277 (1955); (b) N. R. Bannerjee and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **36A**, 134 (1952); (c) S. Hishida, S. Sasaki, M. Suzuki, and M. Takatori, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **74**, 697 (1953); *Chem. Abstr.*, **48**, 12094 (1954); (d) K. Nakagawa and H. Tsukashima, *J. Chem. Soc. Japan*, **75**, 485 (1954); Chem. Abstr. **51**, 11339 (1957); (e) R. Bognar and M. Rakosi, *Chem. & Ind. (London)*, **1955**, 773; (f) H. R. Arthur, W. H. Hui, and C. N. Ma, *J. Chem. Soc.*, **1956**, 632.

(6) G. W. K. Cavill, F. M. Dean, A. McGookin, B. M. Marshall, and A. Robertson, *J. Chem. Soc.*, **1954**, 4573.

(7) This possibility is based partly on the observation of Stuckwisch and co-workers [ref. (9)] that bromination of the position *alpha* to a carbonyl group in certain ketones is effected by by-product bromine rather than by the primary reactant, NBS. In addition, we have noted (unpublished observations) that the 3-bromohesperetin triacetate of G. Zemplen and R. Bognar [*Ber.*, **76B**, 454 (1943)] does not undergo elimination of hydrogen bromide under the conditions of the NBS reaction.

(8) An observation that a very unstable bromo compound can undergo dehydrohalogenation before bromination is complete, liberate free bromine by reaction of evolved hydrogen bromide with NBS, and cause side reactions due to bromine has been recorded by P. Wieland and K. Miescher, *Helv. Chim. Acta*, **30**, 1876 (1947). Also see R. A. Barnes *J. Am. Chem. Soc.*, **70**, 145 (1948), who attributed an orange-red color in NBS reaction mixtures to the equilibrium, HBr + NBS → succinimide + Br_2, and stated that it is diagnostic for HBr in the mixture.

(9) C. G. Stuckwisch, G. G. Hammer, and N. F. Blau, *J. Org. Chem.*, **22**, 1678 (1957).

reacted with a 2-molar quantity of NBS in presence of benzoyl peroxide as catalyst. When the bromine-red color appeared, the solvent and bromine were distilled from the reaction vessel, with simultaneous addition to the reaction mixture of requisite pure solvent. Upon exhaustion of solid NBS, the product was collected and purified in the usual manner. Application of this procedure to hesperetin triacetate gave diosmetin triacetate (4′-methoxy-3′, 5,7-triacetoxyflavone) in 86% yield.[10] Naringenin triacetate gave apigenin triacetate (4′,5,7-triacetoxyflavone) in 95% yield. A bromine containing flavone[11] of undetermined structure was obtained from 5-methoxyflavanone.

EXPERIMENTAL

Dehydrogenation of hesperetin triacetate. In a two-necked flask equipped with dropping funnel, and side arm connected to a cooled receiving vessel, were placed 1 g. of hesperetin triacetate, m.p. 143–144°,[12] 0.83 g. of NBS, a few grains (*ca.* 1 mg.) of benzoyl peroxide, and 50 ml. of carbon tetrachloride. After 15 min. of heating, bromine evolution began. The heat was increased so that solvent and bromine distilled from the side arm and collected in the receiver. Fresh solvent was added through the dropping funnel, and benzoyl peroxide was added as needed to maintain bromine evolution. The reaction was complete in 2 hr. A 2.15 mmol. (92% of theory) quantity of sodium bisulfite was required to decolorize the distillate.

The volume of liquid in the reaction vessel was reduced to 25 ml. and the mixture cooled to 0°. The precipitated solid was removed by filtration and washed with 100 ml. of hot water. After drying, the residue weighed 0.86 g. (86%), m.p. 195–197°. Repeated crystallization from ethanol gave diosmetin triacetate, m.p. 198.5–199° (lit.[13] m.p. 195–196°). The infrared spectrum was identical with that of diosmetin triacetate prepared by an independent procedure (elimination of hydrogen bromide from 3-bromohesperetin triacetate).[12]

Dehydrogenation of naringenin triacetate. A 1.0 g. quantity of naringenin triacetate, m.p. 116–117°,[14] was reacted with 0.89 g. of NBS in the same manner as described immediately above. The reaction was complete in 30 min. A 0.94 g. quantity (95%) of apigenin triacetate, m.p. 186–187° (lit.[15] m.p. 186°) resulted. Deacetylation of this product gave apigenin, m.p. 350–352° (lit.[16] m.p. 352°).

Reaction of 5-methoxyflavanone with NBS. A 0.45 g. quantity of 5-methoxyflavanone, m.p. 144–146°,[16] was reacted with 0.66 g. of NBS according to the procedure previously outlined. Chilling of the carbon tetrachloride solution gave a precipitate (0.26 g. after removal of succinimide). Two recrystallizations from ethanol gave a compound, m.p. 186–189°. A magnesium-hydrochloric acid test was positive (orange color). Analysis indicated the presence of bromine.

Anal. Calcd. for $C_{16}H_{11}O_3Br$: Br, 24.1. Found: Br, 21.4.

The infrared spectrum (KBr disk) of the NBS bromination product of 5-methoxyflavanone showed strong or medium bands at 1643, 1590, 1480, 1454, 1444, 1373, 1285, 1107, 1094, 1037, 1023, 837, 798, 775, 767, 745, 688, 666, and 643 cm.$^{-1}$. The carbonyl band at 1643 cm.$^{-1}$ is considered to be indicative of a flavone rather than a flavanone derivative.[17] The strong bands at 837 and 745 cm.$^{-1}$ have no corresponding bands in the spectrum of 5-methoxyflavone, and are interpreted as indicating a difference in arrangement of substituents (including the substituent bromine) on a benzene ring.[18] 5-Methoxyflavone,[19] m.p. 131°, in KBr disk gave an infrared spectrum showing absorption maxima at 1645, 1600, 1476, 1456, 1442, 1380, 1305, 1288, 1268, 1097, 1035, 1021, 851, 799, 775, 760, 764, 715, 677, and 648 cm.$^{-1}$. The virtually identical location of 12 bands (5 cm.$^{-1}$ difference or less) indicates a marked similarity in the structure of the two compounds.

AVERY LABORATORY
THE UNIVERSITY OF NEBRASKA
LINCOLN, NEB.

(10) An alternate procedure involving the use of pyridine to remove HBr and prevent bromine formation [see ref. (9)] gave *ca.* a 45% yield of diosmetin triacetate, m.p. 180–188° after one crystallization from ethanol.

(11) Other workers also have observed nuclear bromination during reaction of methoxyflavanones with NBS. See ref. (5) (b) and (6).

(12) Arthur *et. al.* (ref. (5) (f)) report m.p. 139–141° for (±)-Hesperetin triacetate.

(13) A. Lovecy, R. Robinson, and S. Sugasawa, *J. Chem. Soc.*, **1930**, 817.

(14) M. K. Seikel and T. A. Geissman [*J. Am. Chem. Soc.*, **72**, 5725 (1950)] report a m.p. of 125.5–126.5° for pure naringenin triacetate.

(15) M. Nakano, *J. Pharm. Soc. Japan*, **52**, 341 (1932); Chem. Abstr., **26**, 4534 (1932).

(16) Prepared in this laboratory by W. W. Hanneman by the procedure of T. R. Seshadri and V. Venkateswarlu [*Proc. Indian Acad. Sci.*, **26A**, 189 (1948)], who report a m.p. of 148–150°.

(17) H. L. Hergert and E. F. Kurth [*J. Am. Chem. Soc.*, **75**, 1622 (1953)] report that, in solid state spectra, flavanone itself shows a carbonyl band at 1680 cm.$^{-1}$ and three acetoxyflavanones show bands in the range 1680 to 1703 cm.$^{-1}$. However, a pentamethoxyflavanone showed a band at 1649 cm.$^{-1}$ In solid state spectra, flavones showed carbonyl bands in the region 1638 to 1655 cm.$^{-1}$ In solution, flavones without a 3-hydroxyl or methoxyl group displayed carbonyl bands between 1638 and 1655 cm.$^{-1}$ (B. L. Shaw and T. H. Simpson, *J. Chem. Soc.*, 1955, 655). In view of the manner of synthesis and marked similarity of the spectrum of the NBS bromination product with that of authentic 5-methoxyflavone, a flavone structure seems indicated.

(18) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 64–8.

(19) Prepared in this laboratory by W. W. Hanneman and J. I. Dappen by the procedure of S. Rajagopalan, K. V. Rao, and T. R. Seshadri, *Proc. Indian Acad. of Sci.*, **25A**, 432 (1946). The Indian workers report m.p. 130–131°.

Infrared Spectra of Some *p*-Benzoquinone Monoximes

G. E. PHILBROOK AND T. C. GETTEN[1]

Received November 3, 1958

The infrared spectra of *p*-benzoquinone-4-oximes in the solid state are similar to those of the *p*-benzoquinones. The spectrum of the addition complex formed by the nitrosation of 3-chlorophenol confirms the structure proposed by Kraaijeveld and Havinga. In no case does a nitrosophenol structure appear to be present.

Hodgson[2] assigned quinone monoxime or nitroso

(1) Taken in part from the Masters thesis of T. C. Getten.

(2) H. H. Hodgson and F. H. Moore, *J. Chem. Soc.*, **127**, 2260 (1925).

TABLE I

MAJOR ABSORPTION BANDS[a] OF *p*-BENZOQUINONE-4-OXIMES
(in cm.$^{-1}$)

Unsubstituted	2-Methyl	2-*i*-Propyl 5-methyl	2,6-Dimethyl	2-Chloro	2-Bromo	3-Chloro	Addition Compound[b]
3289sh	3125sh	3125	3175	3390	3165	3145	3115b
3155	2994sh	3021	3077	3175	1629bs	3030	2188s
1656sh	1637s	1637s	1647sh	1653	1553	1626s	2165
1645s	1600s	1603s	1634s	1637s	1312s	1553s	1634s
1563s	1550s	1567	1608s	1563	1206	1445s	1600
1366sh	1350	1441	1558	1439sh	1117	1348	1511s
1155	1316	1370sh	1427	1316s	1063sh	1305	1481s
1057	1266	1239	1342	1307s	1050s	1127s	1399
1035s	1235	1056s	1305s	1073s	985s	1053s	1294
870	1109s	1015s	1049s	1064s	906s	1006	1247
809s	1032	1002s	1004	1006	866	895	1131s
797	989	907s	919s	906	856s	862	1073s
	899s	853s	717	885s	823s	798s	1050
	820b	777		826s	807	781	1008
	784			773w			925
	730						881s
							808
							769

[a] b-broad; s-strong; sh-shoulder; w-weak. [b] 3-chloro-p-benzoquinone-4-oxime: 3-chlorobenzene-6-diazo oxide.

phenol structures to a number of compounds in 1925. Anderson[3] and his co-workers confirmed Hodgson's assignment for 3-chloro-*p*-benzoquinone-4-oxime but rejected his structure for 3-chloro-4-nitrosophenol without suggesting an alternative. Hodgson[4] defended his conclusions and reviewed the field in 1937. Kraaijeveld and Havinga[5] demonstrated in 1954 that Hodgson's 3-halo-4-nitrosophenols are 1:1 addition compounds of 3-halo-*p*-benzoquinone-4-oxime and 3-halobenzene-6-diazooxide.

We have examined the infrared spectra of a number of substituted *p*-benzoquinone-4-oximes and the addition complex formed by the nitrosation of 3-chlorophenol. The major absorption bands of the compounds are given in Table I.

EXPERIMENTAL

The quinone oximes were prepared from the corresponding phenols by standard nitrosation methods. In addition samples of *p*-benzoquinone-4-oxime and the 2-chloro- and 2-bromo- derivatives were prepared by the oximation of the corresponding quinone. Except in the case of the 2-chloro- derivative the spectra were not distinguishable from those made on samples prepared by nitrosation.

Spectra of the oximes were determined on mineral oil mulls using the cell-in cell-out technique on a Perkin-Elmer Model 112 spectrometer with sodium chloride optics. A rock salt plate was used as the reference. The instrument was calibrated with carbon dioxide, water vapor, and ammonia. Mineral oil mulls of the addition compound were stable for only five to ten minutes. The point by point spectrum of this compound was determined on a potassium bromide pellet. Comparison of automatically recorded energy traces of the mull and pellet form showed no significant differences.

The insolubility of these compounds in suitable solvents prevented a study of the solution spectra.

DISCUSSION

Region 3350–2860 cm.$^{-1}$. With the exceptions of 2-bromo-*p*-benzoquinone-4-oxime, which shows only a weak side hill at 3049 cm.$^{-1}$, and the addition compound of 3-chloro-*p*-benzoquinone-4-oxime, all of the compounds examined show two distinct bands in this region. One band, present in all compounds, is almost constant in position and falls in the region 3175–3115 cm.$^{-1}$ A band occurs in this region in cyclopentanone oxime[6] (3175 cm.$^{-1}$), cyclohexanone oxime[6] (3175 cm.$^{-1}$), and 1,4-naphthoquinone-4-oxime[6] (3125 cm.$^{-1}$). The frequency of this band is high for C-H stretching in trans olefins and we therefore assign it to the OH stretching vibration. The band is sharp.

Region 2860–1667 cm.$^{-1}$. In the addition compound of 3-chloro-*p*-benzoquinone-4-oxime with 3-chlorobenzene-6-diazo oxide a strong band is present at 2188 cm.$^{-1}$ and a second medium strength band is present at 2165 cm.$^{-1}$. These bands are near the upper limit of 2165 cm.$^{-1}$ given by Shenker and Syrkin[7] for the azido group. There appears to be no other reasonable source for these bands. This confirms the assignment of structure made for this compound by Kraaijeveld and Havinga.[5]

A very weak band was found at 2165 cm.$^{-1}$ in the spectrum of the 2-chloro- derivative prepared by nitrosation. This band was absent in the sample

(3) L. C. Anderson and M. B. Geiger, *J. Am. Chem. Soc.*, **54**, 3064 (1932); L. C. Anderson and R. L. Yanke, *J. Am. Chem. Soc.*, **56**, 732 (1934).

(4) H. H. Hodgson, *J. Chem. Soc.*, **140**, 520 (1937).

(5) A. Kraaijeveld and E. Havinga, *Rec. Trav. Chim.* **73**, 537 (1954).

(6) Unpublished data from this laboratory.

(7) Yu. N. Shenker and Ya. N. Syrkin, *Izvest. Akad. Nauk. S. S. S. R., Ser. Fiz.*, **14**, 478 (1950); *Chem. Abstr.*, **45**, 3246 (1951).

prepared by oximation of the quinone and probably arises from contamination by a small quantity of diazo oxide. It could not be removed by recrystallization. No band appears in this region for any other compound examined.

Region 1667–1538 cm.$^{-1}$. Yates, Ardao, and Fieser[8] have discussed the spectra of *p*-benzoquinones between five and fifteen microns (2000–667 cm.$^{-1}$). They assign absorptions in the 5.97–6.14μ (1675–1629 cm.$^{-1}$) region to the carbonyl stretching vibration and observe that this band is split into two bands in some instances. All of our compounds show a strong band in the range 1645–1626 cm.$^{-1}$ which is probably the carbonyl absorption. In three cases a second weaker band at 1656–1647 cm.$^{-1}$ appears. This band is probably the C=N stretching vibration. The C=N band varies in intensity and position[9] and failure to identify this band in all compounds is not surprising.

Yates *et al.*[8] assign bands in the 6.17–6.49μ (1621–1543 cm.$^{-1}$) region to C=C stretching. All of our compounds show a medium to strong band between 1567 cm.$^{-1}$ and 1550 cm.$^{-1}$ which we assign to the C=C stretching. In the alkyl substituted compounds and in the addition complex an additional band is present at 1608–1600 cm.$^{-1}$.

Region 1538–667 cm.$^{-1}$. Numerous bands occur in this region. The majority cannot be assigned to any definite structural feature. Yates *et al.*[8] observe that quinones with an isolated hydrogen atom on the ring show a medium to strong band in the 10.8–11.4μ (926–877 cm.$^{-1}$) region in the solid state. The same feature is present in our spectra. *p*-Benzoquinone-4-oxime has no band in this region. The same authors report that carbon disulfide solutions of compounds having adjacent hydrogen atoms on the ring show a band at 11.9–12.4μ (840–807 cm.$^{-1}$). They do not report a band in this region in most of their solid state spectra. In the quinone oximes studied all compounds with adjacent hydrogen atoms on the ring show a medium to strong band in the 826–794 cm.$^{-1}$ region. This band is absent in compounds without adjacent hydrogens.

In the region from 769 cm.$^{-1}$ to 667 cm.$^{-1}$ only very shallow, very broad absorptions are present. The spectra are immediately recognizable as nonaromatic in character.

Conclusion. The bands which are characteristic of aromatic structures at 2000 cm.$^{-1}$ to 1660 cm.$^{-1}$, at 1600 cm.$^{-1}$ to 1500 cm.$^{-1}$, and from 1200 cm.$^{-1}$ to 667 cm.$^{-1}$ could not be identified in these compounds. This fact coupled with the presence of the carbonyl absorption and the olefinic absorption together with the close over-all similarity to the spectra of *p*-benzoquinones makes it almost certain that the structure of these compounds in the solid state is quinoid. There appears to be no justification for the assignment of a nitroso phenol structure.

Acknowledgment. The author wishes to express his appreciation to Dr. H. H. Jaffe for a very helpful discussion of this probelm.

CHEMISTRY DEPARTMENT
UNIVERSITY OF GEORGIA
ATHENS, GA.

(8) P. Yates, M. A. Ardao, and L. Fieser, *J. Am. Chem. Soc.*, **78**, 650 (1956).

(9) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, 1st. Ed. John Wiley and Sons, Inc., New York, 1954, p. 226.

Structures of 4-Nitro- and 5-Nitro-2-propionylpyrroles

THOMAS S. GARDNER, E. WENIS, AND JOHN LEE

Received November 5, 1958

In a previous paper,[1] the structure 5-nitro-2-propionylpyrrole was suggested for the product, m.p. 100–101°, prepared by nitrating 2-propionylpyrrole. The assignment of structure was based on a negative Ehrlich test which usually indicates complete substitution in the α-positions in pyrrole compounds.

It has been pointed out to us by Professor H. J. Anderson[2] that the work of Rinkes[3] and Anderson[4] would indicate that nitration would more likely occur preferentially in the 4- than in the 5-position. Further examination of our product confirms this prediction. Extraction of a sodium carbonate solution of the nitration product with ether[3] yields a larger proportion of a less acidic 4-nitro-2-propionylpyrrole, m.p. 136–137° and on acidification a lesser amount of more acidic 5-nitro-2-propionylpyrrole, m.p. 134–135°. Mixed m.p. of roughly equal proportions, 102–104°.

Both the mono nitro-2-propionylpyrroles fail to give the Ehrlich test given by the parent substance, 2-propionylpyrrole. Similarly, 4-nitro and 5-nitro-2-acetylpyrrole failed to give the Ehrlich test, while the parent substance, 2-acetylpyrrole, gave a positive test.

The assignment of structure above follows Rinkes[3] and is further supported by an absolute proof of structure. Rinkes[3] states that acidity of the nitration products of 2-acetyl- or 2-carboxyethylpyrrole is determined by the proximity of the nitro group to the acidic NH, the closer the group the more acidic the product. However, there does not appear to be any absolute proof to support this reasonable assertion.

(1) T. S. Gardner, E. Wenis, and J. Lee, *J. Org. Chem.*, **23**, 823 (1958).

(2) H. J. Anderson, private communication, July 12, 1958.

(3) I. J. Rinkes, *Rec. trav. chim.*, **53**, 1167 (1934).

(4) H. J. Anderson, *Can. J. Chem.*, **35**, 21 (1957).

The relationship of the pair, 4-nitro-2-propionylpyrrole [maxima at 247 mμ (log ε = 4.16); 300 mμ (log ε = 3.89); minimum at 278 mμ (log ε = 3.77)] and 4-nitro-2-acetylpyrrole [maxima at 245 mμ (log ε = 4.15) and 299 mμ (log ε = 3.81); minimum at 278 mμ (log ε = 3.80)], is established by the practical superposition of their ultraviolet spectra as is also that of 5-nitro-2-propionylpyrrole [maxima at 240 mμ (log ε = 4.03), 3.28 mμ (log ε = 4.15); minimum at 265 mμ (log ε = 3.38)] and 5-nitro-2-acetylpyrrole [maxima at 239 mμ (log ε = 4.00); 328 mμ (log ε = 4.11) and minimum at 264 mμ (log ε = 3.34)].

The structure of 1-methyl-4-nitro-2-pyrrolecarboxylic acid, m.p. 199–200° has been related to that of 4-nitro-2-acetylpyrrole by Anderson.[4] The synthesis of the ester of this acid by an unequivocal method has been reported.[5] This, on saponification, gave 1-methyl-4-nitro-2-pyrrolecarboxylic acid,[4] m.p. 199–200°. Decarboxylation of this acid gave 1-methyl-3-nitropyrrole,[4] m.p. 63–64°. This represents an absolute proof of the structures of all the nitro-2-acylpyrroles described.

EXPERIMENTAL[6]

4-Nitro-2-propionylpyrrole. The mixed 4-nitro and 5-nitro-2-propionylpyrroles (5.15 g.) previously reported as 5-nitro-2-propionylpyrrole[1] were dissolved in 300 ml. of 10% sodium carbonate solution and extracted ten times with 100 ml. portions of ether. The combined ether extracts were concentrated to a solid and crystallized from boiling water to yield very pale yellow crystals; yield, 2.02 g., m.p. 136–137°.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.0; H, 4.8. Found: C, 50.3; H, 4.9.

5-Nitro-2-propionylpyrrole. The sodium carbonate solution after the extraction of the 4-nitro-2-propionylpyrrole was acidified using 10% sulfuric acid solution. The acidified solution was then extracted ten times with ether as previously described and the combined ether extracts concentrated to a solid. The solid residue was crystallized from boiling water to give yellow fibrous needles; yield, 0.975 g., m.p. 134–135°.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.0; H, 4.8. Found: C, 50.5; H, 5.1.

A mixed melting point of the separated 4-nitro- and 5-nitro-2-propionylpyrroles was 102–104°. The melting point of the previously reported[1] unseparated isomers was 100–101°.

4-Nitro-2-propionylpyrrole semicarbazone. 4-Nitro-2-propionylpyrrole (3.0 g.), 4.0 g. of sodium acetate, and 4 g. of semicarbazide hydrochloride were dissolved in 100 ml. of warm water. After standing for 20 days, fine yellow needles had separated which were recrystallized from hot water; yield, 2.4 g., m.p. 229–230°.

Anal. Calcd. for $C_8H_{11}N_5O_3$: C, 42.7; H, 4.9. Found: C, 42.8; H, 4.6.

5-Nitro-2-propionylpyrrole semicarbazone. 5-Nitro-2-propionylpyrrole (0.98 g.) was treated with 1.0 g. of sodium acetate and 1.5 g. of semicarbazide hydrochloride in 100 ml. of 25% ethanol water solution. After standing for 20 days the yellow-orange product separated and was recrystallized from hot water; yield, 0.9 g., m.p. 211–212°.

Anal. Calcd. for $C_8H_{11}N_5O_3$: C, 42.7; H, 4.9. Found: C, 42.4; H, 4.7.

A mixed melting point of the 4-nitro- and 5-nitro-2-propionylpyrrole semicarbazones was 203–205°. The previously reported[1] semicarbazone of the unseparated isomers was 203–204°.

Acknowledgment. We are indebted to Dr. Al Steyermark and his associates for the microanalyses and Messrs. A. Motchane and S. Traiman for the ultraviolet spectra.

HOFFMANN-LAROCHE, INC.
ROCHE PARK
NUTLEY, N. J.

(5) M. J. Weiss, J. S. Webb, and J. M. Smith, *J. Am. Chem. Soc.*, 79, 1266 (1957).

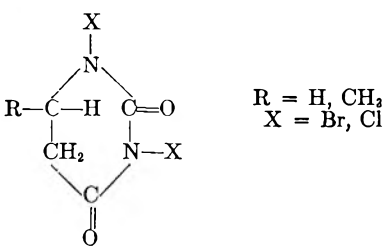
(6) All melting points are corrected.

Chemistry of Hydrouracils. 1,3-Dihalohydrouracils

FRANK B. SLEZAK, ALFRED HIRSCH, LEWIS I. KRIMEN,[1] AND HENRY A. MCELRAVY, JR.

Received November 6, 1958

During the course of investigating the chemical and biological activity of various *N*-halogen compounds, the preparation of a number of heretofore unknown 1,3-dihalohydrouracils became of interest to us.



It was found that the efficiency of the halogenation in an aqueous medium was dependent on the *p*H at which the halogenation was carried out. Chlorination gave fair results (30–40% yield) when the reactions were carried out at a *p*H greater than 7 and gave good results (70–80% yield) when the reaction bath was maintained in the range *p*H 1–3. Bromination, on the other hand, was carried out successfully only at a *p*H greater than 4.

1,3-Dichlorohydrouracil, in concentrations as low as 1 p.p.m., completely inhibited the growth of the test organisms *Erwinia amylovora*, *Xanthomonas phaseoli*, *Micrococcus pyogenes* var. *aureus*, and *Escherichia coli*.[2] 4-Methyl-1,3-dichlorohy-

(1) Present address: International Minerals and Chemical Corporation, Skokie, Ill.

(2) Biological data by Boyce Thompson Institute for Plant Research, Inc., Yonkers, N. Y.

drouracil gave 95–100% growth inhibition of these same organisms at a concentration of 1000 p.p.m. or greater.

The chlorine derivatives appear to be quite stable while the bromine compounds are somewhat less so. One sample of 4-methyl-1,3-dibromohydrouracil decomposed spontaneously after a few days while a companion sample remained undecomposed after some months. It would seem advisable that compounds of this type should be handled with some care.

EXPERIMENTAL[3]

1,3-Dichlorohydrouracil. Hydrouracil[4] (57 g., 0.5 mole) was suspended in one liter of water in a two-liter beaker furnished with a gas dispersion tube, a mechanical stirrer, and an addition funnel. The electrodes of a Beckman model H-2 *p*H meter were so arranged that the *p*H of the contents of the beaker could be followed continuously. Chlorine (75 g., 1.05 mole) was passed in over a 2-hr. period while 6*N* sodium hydroxide was added at such a rate as to maintain the *p*H of the reaction mixture in the range *p*H 1–3. The resulting solid was filtered off, washed with water, and dried. Yield 73 g. (80%). The solid crystallized from a mixture of chloroform and carbon tetrachloride to give white plates, m.p. 128–129°.

Anal. Calcd. for $C_4H_4Cl_2N_2O_2$: C, 26.2; H, 2.2; Cl, 38.8; N, 15.3; avail. Cl, 77.5. Found: C, 26.7; H, 2.4; Cl, 38.6; N, 15.2; avail. Cl, 76.5.

4-Methyl-1,3-dichlorohydrouracil. 4-Methylhydrouracil[5] (64 g., 0.5 mole) was chlorinated in the manner described above. A lower *p*H (1–2) seemed advantageous. The solid, after washing and drying, weighed 77 g. (78%). Crystallization from carbon tetrachloride gave white plates, m.p. 87–87.5°.

Anal. Calcd. for $C_5H_6Cl_2N_2O_2$: C, 30.4; H, 3.1; Cl, 36.0; N, 14.2; avail. Cl, 72. Found: C, 30.7; H, 3.0; Cl, 37.4; N, 14.2; avail. Cl, 71.7.

4-Methyl-1,3-dibromohydrouracil. 4-Methylhydrouracil (12.8 g., 0.1 mole) was suspended in 500 ml. of water in a one-liter beaker furnished as described above except that the gas dispersion tube was replaced with a second addition funnel. Bromine (37 g., 0.23 mole) was added dropwise over a one-hour period while the *p*H of the mixture was maintained in the range *p*H 6.5–8.6 by the addition of 6*N* sodium hydroxide. The pale yellow solid which remained after filtration, washing and drying, weighed 17.5 g. (61%) and melted at 130–131°.

Anal. Calcd. for $C_5H_6Br_2N_2O_2$: C, 21.2; H, 2.1; N, 9.8; avail. Br, 112. Found: C, 21.3; H, 2.0; N, 9.9; avail. Br, 111.

1,3-Dibromohydrouracil. Hydrouracil (11.4 g., 0.1 mole) was treated as above over a 1.8-hr. period. The pale yellow solid obtained after workup weighed 8 g. (30%) and melted 268–270° with decomposition.

Anal. Calcd. for $C_4H_4Br_2N_2O_2$: avail. Br, 118. Found: avail. Br, 117.9.

RESEARCH DEPARTMENT
DIAMOND ALKALI COMPANY
PAINESVILLE, OHIO

(3) All melting points are uncorrected. Elemental analyses by Diamond Alkali Company Research Analytical Laboratory. Available halogen determinations by sodium thiosulfate titration. The percent available halogen is taken as twice the weight percent of halogen attached to nitrogen.

(4) J. S. Mackay and S. Frank, U. S. Patent 2,688,020 (1954).

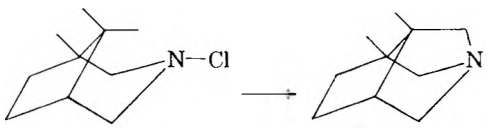
(5) E. Fischer and G. Roeder, *Ber.* **34B**, 3751 (1901).

Synthesis of 3,8-Endomethylene-3-azabicyclo[3.2.1]octane (Cyclocamphidine)[1]

W. R. HERTLER AND E. J. COREY

Received November 21, 1958

The free-radical chain decomposition of *N*-chloro secondary amines ("Hofmann-Loeffler-Freytag reaction")[2,3] has been used recently to effect the selective introduction of functional groups at the C_{18} (C/D fusion) angular methyl group in steroids.[4,5] We have also applied this useful technique in the camphor series to functionalize one of the "unactivated" π-methyl groups. Irradiation of *N*-chlorocamphidine (I) in sulfuric acid solution gave, after basification, a tertiary amine which was isolated as the crystalline hydrobromide in 67% yield. Chemical and physical evidence clearly show that the cyclocamphidine should be formulated as II. The infrared spectrum of the hydrobromide lacks the absorption peak shown by camphidine hydrobromide at 1400 cm.$^{-1}$ which is characteristic of the *gem*-dimethyl grouping. The nuclear magnetic resonance spectrum of the cyclocamphidine hydrobromide (see Experimental) demonstrates the presence of only two methyl groups and is in complete accord with II.



I II

The above synthesis of II, which doubtless can be effected conveniently on large scale from camphor, makes this one of the most readily available bridgehead amines.

EXPERIMENTAL

Camphidine hydrobromide. Camphidine, which has been prepared by the electrolytic reduction of camphoric imide,[6] was made by lithium aluminum hydride-reduction. Camphoric imide (6.2 g., 0.0343 mole) was dissolved in 150 ml. of tetrahydrofuran and added dropwise to a stirred slurry of 2.6 g. of lithium aluminum hydride in 75 ml. of tetrahydrofuran. The resulting mixture was refluxed with stirring for 11 hr., and then treated with water. The precipitate was

(1) This investigation was supported by fellowship AF-7544 to W. R. Hertler from the National Institute of Arthritis and Metabolic Diseases, Public Health Service.

(2) (a) A. W. Hofmann, *Ber.*, **18**, 5, 109 (1885); (b) K. Loeffler and C. Freytag, *Ber.*, **42**, 3427 (1909); (c) K. Loeffler, *Ber.*, **43**, 2035 (1910).

(3) For a brief review see R. Lukes and M. Ferles, *Coll. Czech.*, **20**, 1227 (1955).

(4) E. J. Corey and W. R. Hertler, *J. Am. Chem. Soc.*, **80**, 2903 (1958).

(5) P. Buchschacher, J. Kalvoda, D. Arigoni and O. Jeger, *J. Am. Chem. Soc.*, **80**, 2905 (1958).

(6) J. Tafel and K. Eckstein, *Ber.*, **34**, 3274 (1901).

removed by filtration, and the filtrate was dried over potassium carbonate. Dry hydrogen chloride was bubbled through the dry solution, and the oil which separated was dissolved in 3*N* sodium hydroxide. The basic solution was extracted with ether-pentane. After drying over sodium sulfate, hydrogen bromide was passed into the solution, and the precipitated camphidine hydrobromide weighed 2.231 g. (28%). Crystallization from ethanol-ether gave granules, m.p. 304–307°, $[\alpha]_D^{29}$ +11.1° (50% ethanol, *c*, 3.2). No efforts were made to study the reduction with a view to determining optimal conditions.

Cyclocamphidine hydrobromide. Camphidine hydrobromide (968.3 mg., 4.14 mmol.) was chlorinated in pentane solution by the procedure of Coleman.[7] Removal of the solvent left an oil to which was added 30 ml. of 90% sulfuric acid cooled to 0°. The solution was placed in a quartz flask and irradiated with a mercury arc lamp at 0°. After 16 hr. the solution was poured onto ice and made alkaline with sodium hydroxide. The resulting suspension was heated to boiling, allowed to cool, and extracted twice with ether. Dry hydrogen bromide was passed into the ether solution, and the oily precipitate was stirred with 3*N* sodium hydroxide solution and 3 ml. of benzenesulfonyl chloride overnight. The solution was acidified with hydrochloric acid, and the benzenesulfonamide of secondary amine was removed by washing with ether. The aqueous solution was made alkaline with sodium hydroxide and extracted with ether. The ether was dried over magnesium sulfate, and dry hydrogen bromide was passed in. The amine hydrobromide was filtered and dried over phosphorus pentoxide at 0.1 mm. The product weighed 0.6444 g. (67%) and crystallized from ethanol-ether as microcrystals, m.p. 353–357° (dec.), $[\alpha]_D^{29}$ +2.4° (50% ethanol, *c*, 2.5).

Anal. Calcd. for $C_{10}H_{18}NBr$: C, 51.73; H, 7.81; N, 6.03. Found: C, 52.02; H, 7.78; N, 6.00.

Picrate, crystals from ethanol, m.p. 259.5–262° (dec.).

Anal. Calcd. for $C_{16}H_{20}N_4O_7$: C, 50.52; H, 5.30; N, 14.73. Found: C, 50.80; H, 5.34; N, 14.63.

The nuclear magnetic resonance spectrum of cyclocamphidine hydrobromide (in D_2O solution with methylene chloride as the external standard) had a split band at 62 cps. (at 40 megacycles), ($+N—CH_2—$), a split band at 116 cps. (CH_2), and a sharp doublet at 172 cps. (CH_3). The nuclear magnetic resonance spectrum of camphidine hydrobromide had split bands at 55–71 cps. ($+N—CH_2—$), a band at 111 cps. (CH_2) and a sharp triplet at 143, 149, and 151 cps. (CH_3). The ratio of the area under the peaks corresponding to $+N—CH_2—$ to the area under the peaks corresponding to CH_3 in the product divided by the same ratio found in the starting material is equal to 2.66. The theoretical value based on the change camphidine → cyclocamphidine II is 2.25.

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILL.

(7) G. H. Coleman, G. Nichols, and F. F. Martens, *Org. Syntheses*, Coll. Vol. III, 159 (1955).

New Dihydrotriazines of Chemotherapeutic Interest

SAMUEL SCHALIT AND ROYAL A. CUTLER

Received November 27, 1957

From the urine of animals and human volunteers who had received chlorguanide, [1-(*p*-chlorophenyl) - 5 - isopropylbiguanide], Rose[1] and coworkers isolated a metabolite which they characterized as 4,6-diamino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine (I, free base, R_1 = Cl, R_2, R_3 = CH_3). In addition their studies indicated that this metabolite was ten times as active as the parent drug against infections of *P. gallinaceum* in chicks. Subsequent work by Carrington,[2] Loo,[3] Basu,[4] Modest,[5] and Lux[6] elaborated on the structure, synthesis, and chemotherapeutic activity of the above compound and of a number of its analogs.

Since work done in our laboratories had demonstrated the superior antibacterial properties of racemic *threo*-2-dichloroacetamido-1-(*p*-methylthiophenyl)-1,3-propanediols[7] as compared to the corresponding *p*-chloro analog,[8] it was considered of interest to examine the effect on chemotherapeutic activity of replacing the *p*-chloro atom in the chlorguanide metabolite by groups such as alkylthio as well as other suitable substituents. Accordingly we synthesized a number of compounds which may be represented by the general formula I and which are listed in Table I.

Preliminary testing[9] of the dihydrotriazine hydrochlorides against *P. lophurae* infections in ducks indicated a similar level of activity for the *p*-methylthio-2,2-dimethyl (Ia) and the *p*-chloro analogs.[1] However the latter proved to be considerably more toxic with evidence of toxicity even at the lower effective dose levels. The *p*-sulfamyl analog (Ie) showed slight[10] and the *p*-acetyl analog (Id) moderate antimalarial activity.[11]

It was also found that the *p*-methylthio-2,2-dimethyl compound (Ia) when combined with bithionol [2,2′-thiobis(2,4-dichlorophenol)] gave a synergistic or potentiated mixture having a greater anticoccidial effect in fowl than the sum of the anticoccidial effects of the individual ingredients.

Two of the hydrochlorides, the *p*-methylthio-2,2-dimethyl compound (Ia) and the *p*-methylthio-2-(*n*-propyl) compound (Ic), showed moderate anthelmintic activity against the oxyurid worms

(1) H. C. Carrington, A. F. Crowther, D. G. Davey, A. A. Levi and F. L. Rose, *Nature*, **168**, 1080 (1951).

(2) H. C. Carrington, A. F. Crowther, and G. J. Stacey, *J. Chem. Soc.*, 1017 (1954).

(3) T. L. Loo, *J. Am. Chem. Soc.*, **76**, 5096 (1954).

(4) U. P. Basu, A. K. Sen, and A. K. Ganguly, *Sci. and Culture (Calcutta)*, **18**, 45 (1952).

(5) E. J. Modest, *J. Org. Chem.*, **21**, 1 (1956); E. J. Modest and P. Levine, *J. Org. Chem.*, **21**, 14 (1956).

(6) R. E. Lux, *Antibiotics & Chemotherapy*, **4**, 971 (1954).

(7) R. A. Cutler, R. J. Stenger, and C. M. Suter, *J. Am. Chem. Soc.*, **74**, 5475 (1952).

(8) Ng. Ph. Buu-Hoï, Ng. Hoan, P. Jacquignon, and Ng. H. Khoï, *J. Chem. Soc.*, 2766 (1950).

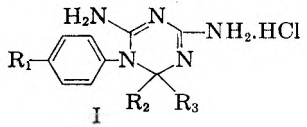
(9) Preliminary testing of these compounds was done by the biology division of these laboratories.

(10) No report of antimalarial activity was given by Basu, *et al.* (ref. 4).

(11) This compound was found by Lux (ref. 6) to be inactive against *E. tenella* infections in chicks, but no report was made of its antimalarial activity.

TABLE I

SUBSTITUTED PHENYLDIHYDROTRIAZINE MONOHYDROCHLORIDES



I

	R_1	R_2	R_3	Time of Reflux, Hr.	Yield, %	Solvent[a]	Cryst. Form	M.P., °C.	Formula	Analyses: Chlorine Calcd.	Chlorine Found	Nitrogen[i] Calcd.	Nitrogen[i] Found
Ia	CH_3S	CH_3	CH_3	4	65.6	H_2O[b]	White needles	204.4–207.8	$C_{12}H_{17}N_5S.HCl$	11.83	11.69	23.36	23.44
Ib	C_2H_5S	CH_3	CH_3	5	56.5	H_2O[b]	White prisms	214.2–220.8	$C_{13}H_{19}N_5S.HCl$	11.30	11.10	22.33	22.20
Ic	CH_3S	H	$CH_2CH_2CH_3$	4 (at 50°)	67.3	abs. EtOH	White powder	230.2–231.1	$C_{13}H_{19}N_5S.HCl$	11.30	11.23	22.33	22.51
Id	CH_3CO[c]	CH_3	CH_3	6	81.3	H_2O[b]	White needles	210.0–211.6[d]	$C_{13}H_{17}N_5O.HCl$	11.99	11.70	23.68	23.90
Ie	H_2NSO_2[c]	CH_3	CH_3	6	90.6	H_2O[b] then EtOH-H_2O 5:1	White powder	207.4–214.8[e]	$C_{11}H_{16}N_6O_2S.HCl$	10.65	10.66	[f]	[f]
Free Bases of Above Substituted Phenyldihydrotriazine Monohydrochlorides													
	CH_3S	CH_3	CH_3		54		White prisms	149.2–152.2	$C_{12}H_{17}N_5S$	[g]	[g]		
	C_2H_5S	CH_3	CH_3		59		Pale yellow powder	132.0–138.7	$C_{13}H_{19}N_5S$	[h]	[h]	25.25	25.15
	CH_3S	H	$CH_2CH_2CH_3$		65.3		White	143.0–144.6	$C_{13}H_{19}N_5S$			25.25	24.92

[a] Charcoal was added in most of the recrystallizations. [b] Where water alone was used as the solvent, a few drops of conc. hydrochloric acid were added. [c] Subsequent to the preparation of Id and Ie, these compounds were disclosed in the literature. See refs. 6 and 4, respectively. [d] No melting point was reported by Lux (ref. 6) for this compound. [e] Basu, *et al.* (ref. 4) reported a m.p. of 206–208° with resolidification and decomposition for the hydrate. No m.p. of the anhydrous triazine was given. [f] Sulfur: calcd., 9.64; found, 9.52 [g] Sulfur: calcd., 12.17; found, 12.35. [h] Sulfur: calcd., 11.56; found, 11.23. [i] Compounds Ia, b, d were Dumas determinations. Compound Ic and the two bases were Kjeldahl determinations.

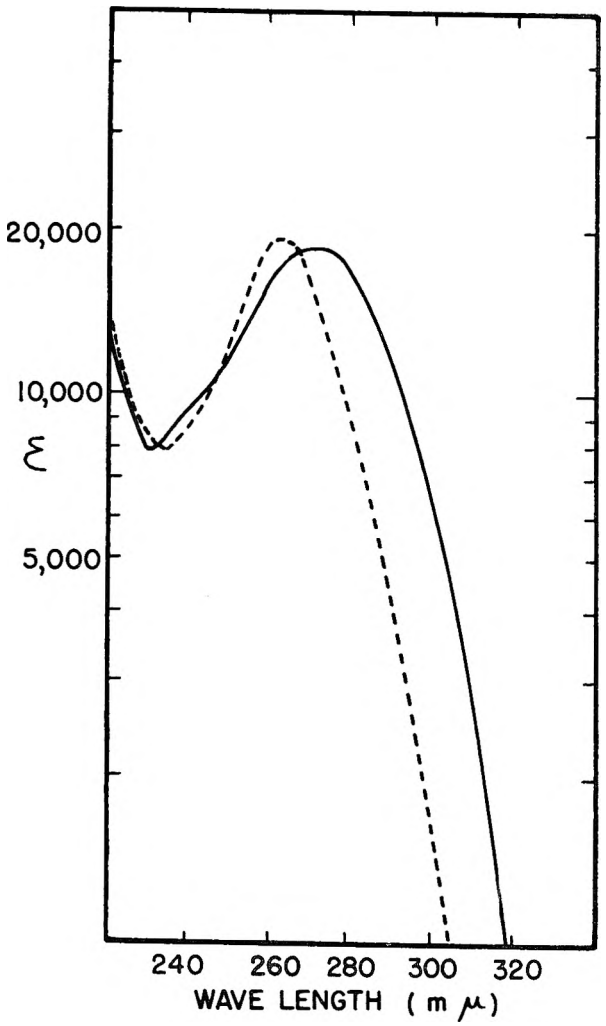
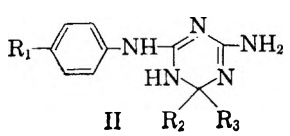


Fig. 1. Ultraviolet absorption spectra in water. ------, 4,6-diamino-1,2-dihydro-1-(*p*-methylthiophenyl)-2-(*n*-propyl)-*s*-triazine hydrochloride (Ic), [$\lambda_{max.}^{H_2O}$ 262 mμ, ε19,200; $\lambda_{min.}^{H_2O}$ 235 mμ, ε8200]; ————, 4-amino-1,2-dihydro-1-(*p*-methylthioanilino)-2-(*n*-propyl)-*s*-triazine hydrochloride (IIc), [$\lambda_{max.}^{H_2O}$ 269 mμ, ε18,600; $\lambda_{min.}^{H_2O}$ 232 mμ, ε8,000].

Syphacea obvelata and *Aspicularis tetraptera* in mice. Further details of the biological activity of the newly prepared dihydrotriazines will appear in subsequent papers.

In the preparation of the *p*-methylthio-2-(*n*-propyl) compound (Ic), the triazine was first isolated as the free base after treatment of the reaction liquid at 5° with excess strong alkali. Since triazines of this type have been shown to isomerize when heated with excess alkali to the corresponding anilino compound II[5] (for IIc, R_1 = CH_3S, R_2 = H, R_3 = n-C_3H_7), it was thought of interest to prepare the isomerized anilino base and hydrochloride for comparison of the properties of Ic and IIc. The isomerization of Ic was done by



heating the hydrochloride with a large excess of alkali in water. Ultraviolet absorption data for the hydrochlorides Ic and IIc (Fig. I) show the same type of shift that has been shown in the literature[2,5] for similar compounds. Also, in line with previous work,[5] the pK_a of the anilino dihydrotriazine base is 10.6 while that of the aryl dihydrotriazine base (Ic) is 11.0.

EXPERIMENTAL[12]

4,6-Diamino-1,2-dihydro-2,2-dimethyl-1-(p-methylthiophenyl)-s-triazine hydrochloride (Ia). The preparation of Ia illustrates the general method used for the synthesis of Ia, b, d, and e (hydrochlorides). The method of preparation of the free base was the same for all compounds.

To a warm solution of 29.4 g. (0.211 mole) *p*-methylthioaniline in 300 ml. acetone was added first 17.4 g. (0.207 mole) dicyandiamide, then 18 ml. (0.216 mole) conc. hydrochloric acid. All of the solid dissolved on addition of the acid but 5–10 min. after the beginning of reflux solid began to separate. After about 1 hr. of reflux all solid had again dissolved and after 1.5 hr. of reflux solid began to separate. The reaction mixture was refluxed for a total of 4 hr. after which it was chilled and the product collected. Further details on the yield, purification, and properties of the solid are found in Table I.

To prepare the free base, 1 g. (0.00334 mole) of the pure triazine hydrochloride was dissolved in 10 ml. boiling water. To this solution was added 0.27 ml. (0.00336 mole) of 35% aqueous sodium hydroxide solution and the resulting reaction mixture was immediately chilled. The white solid which separated was collected. None of the free bases required further purification. In each case, reconversion of the base to the hydrochloride with one equivalent of hydrochloric acid gave a solid which, by mixed melting point determination, appeared to be identical with the original hydrochloride. Ultraviolet spectral data (Table II) on the hydrochlorides obtained from the reaction and after reconversion from the base also show the compounds to be the same, thus indicating that rearrangement to the corresponding anilino compound (II) had not occurred.

TABLE II

ULTRAVIOLET SPECTRAL DATA ON ORIGINAL AND RECONVERTED HYDROCHLORIDES

	Original Hydrochloride		Reconverted Hydrochloride	
	$\lambda_{max(m\mu)}^{H_2O}$	ε	$\lambda_{max(m\mu)}^{H_2O}$	ε
Ia	260	20,000	260	19,300
Ib	260	18,500	261	17,833
Ic	260	19,200	261	18,900

4,6-Diamino-1 2-dihydro-1-(p-methylthiophenyl)-2-(n-propyl)-s-triazine hydrochloride (Ic). A mixture of 55 g. (0.212 mole) 1-(*p*-methylthiophenyl)biguanide hydrochloride, 300 g. (4.15 moles) *n*-butyraldehyde, 17.9 ml. (0.215 mole) conc. hydrochloric acid, and 595 ml. water was heated at 50 ± 2° for 4 hr. The two-phase reaction liquid was treated with charcoal and filtered through Filter Cel. After evaporation *in vacuo* to about one half the original volume the residual liquid was treated with charcoal and filtered

(12) The analyses and melting point determinations were performed by the staffs of M. E. Auerbach and K. D. Fleischer of these laboratories. All melting points, unless otherwise specified, are corrected. The ultraviolet absorption spectra were obtained by the staff of F. C. Nachod of these laboratories.

through Filter Cel. To the yellow filtrate was added 550 ml. ether and the mixture was cooled to 5°. On addition of 49.5 ml. (0.62 mole) of 35% aqueous sodium hydroxide solution, yellow solid separated. This was collected, washed with ether, and dried; yield, 41 g. (69.6%), m.p. 136–140° (uncorr.). Thirty-four g. of the crude base was taken up in 170 ml. dilute hydrochloric acid and the resulting liquid was treated with charcoal and filtered through Filter Cel. After cooling the filtrate to 0–5°, conc. ammonium hydroxide was added until the mixture was neutral. The yellow solid was collected and dried. Details on yield, purification, and properties of the solid are found in Table I.

4-Amino-1,2-dihydro-6-(p-methylthioanilino)-2-(n-propyl)-s-triazine. To a warm solution of 8.6 g. (0.0274 mole) 4,6-diamino-1,2-dihydro-1-(*p*-methylthiophenyl)-2-(*n*-propyl)-*s*-triazine hydrochloride in 86 ml. water was added 11.2 ml. (0.14 mole) 35% aqueous sodium hydroxide. White solid separated immediately which then changed to an oil on further heating. After 1.5 hr. of heating on a steam bath the mixture was cooled to room temperature, whereupon the oil changed to a gum. The supernatant liquid was decanted and the gum was washed once with water. After decantation, as much water as possible was removed *in vacuo*. Absolute ether was added and the mixture was allowed to stand. The powdery white solid which separated was collected and washed with absolute ether; yield 3 g. (39.4%), m.p. 125.8–129.2°.

Anal. Calcd. for $C_{13}H_{19}N_5S$: N, 25.25; S, 11.56. Found: N, 24.93; S, 11.50.

The hydrochloride was formed from the above base by warming 3 g. (0.0108 mole) of the base with 6 ml. (0.121 mole) of 2.02*N* hydrochloric acid in 15 ml. water. After chilling, the hydrochloride separated as a white powder; yield 2.3 g. (67.9%), m.p. 137–141° (uncorr.). Recrystallization from ethanol gave a white powder, m.p. 158.8–161.4°.

Anal. Calcd. for $C_{13}H_{19}N_5S.HCl$: Cl, 11.30; S, 10.22. Found: Cl, 11.50; S, 10.40.

p-Alkylthioanilines. These compounds, used in the preparation of Ia, b, and c, were prepared through a known method[13] using an iron–acetic acid reduction of the appropriate alkyl *p*-nitrophenylsulfide.[14]

1-(p-Methylthiophenyl) biguanide. The biguanide hydrochloride was obtained in 73% yield by the method of Curd[15] who made 1-(*p*-chlorophenyl) biguanide. The crude hydrochloride, a pink solid with m.p. 215–217° (uncorr.), was used to prepare Ic. Treating a hot aqueous solution of the biguanide hydrochloride with an excess of 35% aqueous sodium hydroxide gave crude pink base; yield, 84%, m.p. 147–150° (uncorr.). After two recrystallizations with water-ethanol (20:1) mixtures, the free base was obtained as yellow platelets, m.p. 152.9–154°.

Anal. Calcd. for $C_9H_{13}N_5S$: N, 31.37. Found: N, 31.36.

STERLING-WINTHROP RESEARCH INSTITUTE
RENSSELAER, N. Y.

(13) W. R. Waldron and E. E. Reid, *J. Am. Chem. Soc.*, **45**, 2399 (1923).

(14) P. Oxley, M. W. Partridge, T. D. Robson, and W. F. Short, *J. Chem. Soc.*, 763 (1946).

(15) F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 362 (1946).

Decyanoethylation of *N,N*-Bis(2-cyanoethyl)amides

L. A. PURSGLOVE*

Received August 25, 1958

The preparation of 3,3′-iminodipropionitrile from ammonia and acrylonitrile,[1–3] and its reaction with acyl halides to form *N,N*-bis(2-cyanoethyl)-amides[4–7] are well known. Some work has been reported on the pyrolytic decyanoethylation of these amides to form β-alanine derivatives, and this route has even been suggested as a possible practical preparative method for β-alanine itself.[8,9] This note deals with a more satisfactory method of decyanoethylation.

Treatment of *N,N*-bis(2-cyanoethyl)amides with bases such as sodium ethoxide and KOH in alcoholic solution leads smoothly to the formation of the corresponding *N*-(2-cyanoethyl)amides at temperatures below 100°, considerably below those necessary for pyrolytic decyanoethylation. A similar reaction was noted in passing by Petersen and Müller with substituted ureas, but the product was not isolated and the yield is unknown.[10]

Both infrared analysis and vapor phase chromatography indicated that 3-ethoxypropionitrile was produced in the decyanoethylation of *N,N*-bis (2-cyanoethyl)benzamide in NaOEt-EtOH, indicating that the alcohol used as solvent forces the reaction to completion by combining with the acrylonitrile formed. The reaction apparently does not proceed in pure benzene.

Further decyanoethylation would lead to a primary amide, which might compete with the ethanol for acrylonitrile, thus explaining why only one mole of acrylonitrile is removed.

Under anhydrous conditions, the reaction proceeds smoothly with *N,N*-bis(2-cyanoethyl)benzamides, acetamides, and benzenesulfonamides. If the reaction is carried out in the presence of water, it leads to an *N*-acyl-β-alanine or to an *N*-(2-carbamoylethyl)amide.

For example, it has recently been shown by Misra and Asthana[11] that alkaline hydrolysis of *p*-chloro-*N,N*-bis(2-cyanoethyl)benzenesulfonamide leads to decyanoethylation and formation of *N*-(*p*-chlorobenzenesulfonyl)-β-alanine. We have found that use of smaller amounts of water leads to formation of *N*-(2-carbamoylethyl)benzamide

(*) Bay City Junior College, Bay City, Mich.

(1) F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. Weisel and W. Yanko, *J. Am. Chem. Soc.*, **66**, 725 (1944).

(2) O. F. Wiedeman and W. H. Montgomery, *J. Am. Chem. Soc.*, **67**, 1994 (1945).

(3) S. R. Buc, *Org. Syntheses*, **27**, 3 (1947).

(4) A. N. Kost, *Vestnik Moskov. Univ.*, No. 2, 141 (1947); *Chem. Abstr.*, **42**, 3722i.

(5) A. P. Terent'ev, K. I. Chursina, and A. N. Kost, *Zhur. Obshchei Khim.*, **20**, 1073 (1950).

(6) H. Feuer and S. M. Pier, *J. Am. Chem. Soc.*, **74**, 4706 (1952); **76**, 105 (1954).

(7) A. A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1369 (1947).

(8) F. E. Kung, U. S. Patent 2,401,429 (1946).

(9) Saul Chodroff, Roland Kapp, and Charles O. Beckmann, U. S. Patent 2,492,554 (1949); *J. Am. Chem. Soc.*, **69**, 256 (1947).

(10) S. Petersen and E. Müller, *Chem. Ber.*, **81**, 31 (1948).

(11) G. S. Misra and R. S. Asthana, *J. prakt. Chem.*, [4], **4**, 270 (1957).

TABLE I

Ac	Starting Material (AcN(CH₂CH₂CN)₂) M.P. (°C.)	% N[a] Calcd.	% N[a] Found	Recryst. Yield (%)	Product (AcNHCH₂CH₂CN) M.P. (°C.)	% N[a] Calcd.	% N[a] Found
C_6H_5CO—	109.5–112° (lit. 112°)[4]			60	94–95° (lit. 96–98°)[7]		
o-Cl—C_6H_4CO—	85–87.5°	16.07	15.99	70	82–82.5°	[b]	[b]
p-Cl—C_6H_4CO—	116–117.5°	16.07	15.93	62	154–156°	13.41	13.40
p-NO_2—C_6H_4CO—	150.5–152.5°	20.6	20.64	87	154–155° (lit. 151–153°)[10]		
CH_3CO—	45–48° (lit. 50°, 146°)[4,6]			61	64–65° (lit. 63°)[6]		
p-Cl—$C_6H_4SO_2$—	132.5–133.5° (lit. 132°)[11]			65	91–92.5°	11.43	11.19

[a] Nitrogen analyses are given only for compounds not previously reported in the literature. Infrared spectra of all compounds are in agreement with the structure given. Chlorine and/or carbon-hydrogen analyses also agree. [b] Nitrogen analysis was not run for this compound; chlorine content was found to be 17.06% (calcd. 17.0%).

from *N*,*N*-bis(2-cyanoethyl)benzamide, indicating that decyanoethylation occurs fairly early in the reaction.

The decyanoethylation may even occur in the course of a reduction reaction using alkaline ferrous ion; the product isolated from reduction of *N*,*N*-bis(2-cyanoethyl)-*p*-nitrobenzamide was *p*-amino-*N*-(2-cyanoethyl)benzamide instead of the expected *p*-amino-*N*,*N*-bis(2-cyanoethyl)benzamide.

EXPERIMENTAL

1. *Decyanoethylation. General method.* A number of *N*,*N*-bis(2-cyanoethyl)amides were prepared by known methods from 3,3′-iminodipropionitrile. A solution of 0.5 mole of the amide in a liter of absolute ethanol (or benzene containing a little alcohol) was treated at reflux with 0.2–0.5 g. of sodium (or 1–1.5 g. KOH) dissolved in absolute ethanol.

The solution was refluxed for 2–5 hr., after which time evaporation of the solvent gave an essentially quantitative yield of the *N*-(2-cyanoethyl)amide (often 90% or better in purity by infrared).

This general method was used for the preparation of *N*-(2-cyanoethyl)benzamide and its *o*-chloro, *p*-chloro, and *p*-nitro derivatives as well as *N*-(2-cyanoethyl)acetamide. For decyanoethylation of *p*-chloro-*N*,*N*-bis(2-cyanoethyl)-benzenesulfonamide, more than molar quantities of sodium ethoxide were needed, because of the acidic nature of the product.

One recrystallization of the crude products gave 60–90% recovery of the pure *N*-(2-cyanoethyl)amide. *N*-(2-Cyanoethyl)benzamide and its chloro derivatives were recrystallized from 5 ml. chloroform per gram of crude product; the *N*-(2-cyanoethyl)-*p*-nitrobenzamide from 10 ml. ethanol per gram; the *N*-(2-cyanoethyl)acetamide from 2 g. chloroform plus 4 g. carbon tetrachloride per gram; and the sulfonamide from 10 ml. methylchloroform per gram. Table I summarizes these results.

2. *Hydrolytic decyanoethylation.* A solution of 0.2 g. sodium in 20 ml. butyl alcohol was added to a solution of 0.2 mole *N*,*N*-bis(2-cyanoethyl)benzamide in 400 ml. butyl alcohol at 80°. The mixture was heated at 80–90° for 3 hr., 200 g. of the solvent was distilled off at 260–290 mm. Hg and 21.5 g. precipitate (m.p. 140–150°) was recovered on cooling. This was too high-melting to be the expected *N*-(2-cyanoethyl)benzamide. Recrystallization from 100 ml., then 50 ml. of water, gave 10 g. of *N*-(2-carbamoylethyl)-benzamide, best fraction of which had a m.p. 167–169°; lit. 174–176°.[12] It appears that the butyl alcohol used contained enough moisture to cause partial hydrolysis. The final product contained 14.71% *N* (calcd. for $C_{10}H_{12}N_2O_2$: 14.57%). When 0.2 mole *N*,*N*-bis(2-cyanoethyl)benzamide in 400 ml. 95% ethanol was treated in a similar fashion with 0.5 g. KOH in 30 ml. 95% ethanol, the resulting 40 g. of crude mixture recovered contained both *N*(2-cyanoethyl)-benzamide and *N*-(2-carbamoylethyl)benzamide.

3. *Reductive decyanoethylation.* A boiling suspension of 0.1 mole *N*,*N*-bis(2-cyanoethyl)-*p*-nitrobenzamide in 100 ml. water was added in small quantities to a solution of 0.007 mole $FeSO_4$ in 250 ml. water. Aqueous ammonia was added in small portions with stirring, to make the solution alkaline. The mixture was heated 5 min., then filtered hot. Cooling resulted in recovery of 11.5 g. crude product. Two recrystallizations from 95% ethanol gave 7.5 g. of *p*-amino-*N*-(2-cyanoethyl)benzamide (m.p. 111–115°).

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.4; H, 5.85; N, 22.21. Found: C, 63.58; H, 5.41; N, 22.60.

EDGAR C. BRITTON RESEARCH LABORATORY
THE DOW CHEMICAL CO.
MIDLAND, MICH.

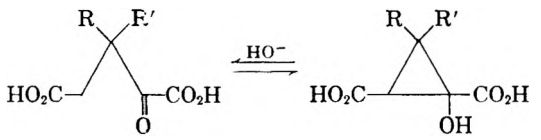
(12) A. A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1372 (1947).

Communications TO THE EDITOR

On the Ring-Chain Tautomerism of α-Ketoglutaric Acids[1]

Sir:

One of the classic examples of the effect of *gem*-dialkyl groups on the stability of small ring compounds is the ring-chain tautomerism of the α-ketoglutaric acids which was investigated by Thorpe and his co-workers[2]:



The size of the alkyl group was reported to have a marked effect on the position of equilibrium, the larger groups giving predominately the cyclic isomer.

In view of the interest in these compounds,[3] and the known instability of cyclopropanol,[4] the structure of the compounds in which R and R′ were ethyl have been reinvestigated. Both acids (the "keto" form, herein designated as *A*, and the "cyclic" form, herein designated as *B*) gave dimethyl esters on treatment with diazomethane. (Ester *A*: liquid, b.p. 112–114 at 0.5 mm., *Anal.* Calcd. for $C_{11}H_{18}O_5$: C, 57.4; H, 7.9. Found: C, 57.4; H, 8.1. ester *B:* m.p. 58–60°, *Anal.* Calcd.: C, 57.4; H, 7.9. Found: C, 57.6; H, 7.6.). Each ester could be converted back to the corresponding acid by basic hydrolysis. The absence of a hydroxy band in the infrared for either ester indicates that the cyclic structure is incorrect.

The further observations that neither acid will react with lead tetraacetate[5] or with 2,4-dinitrophenylhydrazine, even with prolonged reaction times show that neither is an α-keto acid. The semicarbazone reported[1] for *A* has now been shown to be a semicarbazonium salt (Calcd. for $C_{10}H_{19}O_6N_3$: C, 43.3; H, 6.9; N, 15.2. Found: C, 43.6; H, 6.9; N, 15.3.)

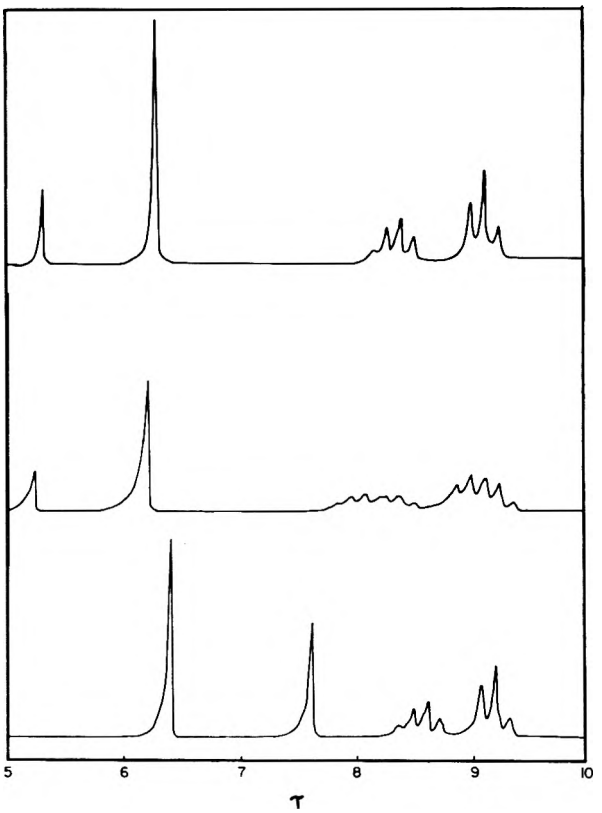


FIG. 1. NMR spectra: upper curve, ester *B*; middle curve, ester *A*; bottom curve, dimethyl β,β-diethylglutarate. The values are in p.p.m. referred to tetramethylsilane as the internal reference (τ values).

The correct structures are indicated by the NMR spectra (Fig. 1). The bands at 9.1–9.2[6] arise from the methyl of the ethyl group, and the methylene contributes the bands at 8.1–8.7. The band at 6.2–6.4 is due to the methyl of the ester, and the band at 7.64 of dimethyl β,β-diethylglutarate is attributed to the methylene groups attached to the carboxylate groups.

Both of the unknown esters have a band at 5.3, which must arise from a proton attached to a carbon bearing two electron withdrawing groups. (Formals have a band at 5.4 whereas a methylene attached to a single oxygen leads to a band at 5.8.) Furthermore, the two protons which are responsible for this band show no spin-spin splitting and therefore the adjacent carbons probably do not bear

(1) This work was supported by the Office of Ordnance Research, U. S. Army.

(2) S. S. Deshapanda and J. F. Thorpe, *J. Chem. Soc.*, 121, 1430 (1922); E. W. Lanfear and J. F. Thorpe, *J. Chem. Soc.*, 123, 1683 (1923). See however, K. C. Bhattacharyya, *Current Sci. (India)*, 21, 312 (1952).

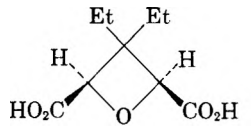
(3) *Cf.* G. S. Hammond in *Steric Effects in Organic Chemistry*, M. Newman, Ed., John Wiley & Sons, New York, 1956, pp. 463–464; E. A. Royals, *Advanced Organic Chemistry*, Prentice-Hall, New York, 1954, p. 178.

(4) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, 73, 3176 (1951).

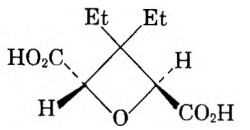
(5) It is improbable that steric effects prevented reaction with lead tetraacetate since α-methyl-β,β-diethyl-α′-ketoglutaric acid reacts with lead dioxide under conditions similar to those used here: J. Cologne and D. Joly, *Ann. chim.*, 18, 286 (1943).

(6) Observed shift in ppm referred to tetramethylsilane (10.0) as the internal standard in dilute carbon tetrachloride solution in accord with the suggestion of G. V. Tiers, *J. Phys. Chem.*, 62, 1151 (1958).

other protons. Only structures Ia and Ib will accommodate this spectrum.



Ia



Ib

The spectrum also permits assignment of configuration, for in the ester of *B*, the methyl bands at 9.1 have the normal three components, whereas the corresponding band of *A* has five components of which part must originate from a chemical shift. Thus, the ethyl groups of *B* have the same environment and those of *A* have different environments, and correspondingly, *A* must be the *cis* isomer and *B* the *trans* isomer. This assignment is also in agreement with the ratio of ionization constants (K_1/K_2 = 40 for *A*, and 9 for *B*).

A consideration of the factors which favor the formation of a keto acid or a trimethylene oxide in the reaction by which the acids Ia and Ib are formed (the reaction of the α,α'-dibromoglutaric esters with strong base) will be postponed until the structures of all of the compounds in Thorpe's series have been reinvestigated.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF WASHINGTON
SEATTLE 15, WASH.

KENNETH B. WIBERG
HOWARD W. HOLMQUIST

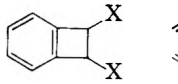
Received February 23, 1959

1,2-Bisdimethylaminobenzocyclobutene and its Rearrangement to α-Dimethylamino-o-Tolualdehyde

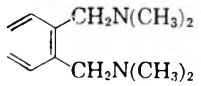
Sir:

Recently derivatives of benzocyclobutene have been studied by several groups of workers.[1-4] 1,2-Diiodobenzocyclobutene (I) has been prepared by Cava and co-workers[1,2] and has been shown to exist as *cis* and *trans* isomers.[3] It has been stated that I is inert to nucleophilic attack.[2]

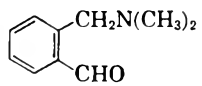
Treatment of pure *trans* I with excess dimethylamine yielded two equivalents of dimethylammonium iodide and a highly reactive liquid, b.p. 100–102°/2.5 mm., n_D^{25} 1.5094, for which we suggest the 1,2-bisdimethylaminobenzocyclobutene structure (II). The liquid II began to decompose within 15 minutes after distillation, making it impossible to obtain direct analytical data. Reduction of II with Raney nickel in dry petroleum ether



I, X = I
II, X = $N(CH_3)_2$



III



IV

yielded α,α'-dimethylamino-*o*-xylene (III), b.p. 80–82/4.2 mm., n_D^{25} 1.5024, which when treated with picric acid yielded a dipicrate, m.p. 192.6–194.1°. *Anal.* Calcd. for $C_{24}H_{26}N_8O_{14}$ ($C_{12}H_{20}N_2$ + $2C_6H_3N_3O_7$): C, 44.31; H, 4.03; N, 17.23. Found: C, 44.61; H, 4.09; N, 16.93. The infrared spectrum of III was identical to that of an authentic sample of α,α'-dimethylamino-*o*-xylene prepared by the method of von Braun and Cahn,[5] and a mixture melting point of the two dipicrates showed no depression.

Treatment of II with dilute acid followed by isolation of the basic material yielded α-dimethylamino-*o*-tolualdehyde (IV), b.p. 84–86°/2.5 mm., n_D^{23} 1.5356. *Anal.* Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03. Found C, 73.65; H, 8.13. The infrared spectrum of IV contained a conjugated carbonyl band at 1690 cm.$^{-1}$ and a band characteristic of *ortho* disubstitution at 760 cm.$^{-1}$ The ultraviolet spectrum is similar to that of other aromatic aldehydes $\lambda_{max}^{isooctane}$ 284 mμ (log ε = 3.11), 243 mμ (log ε = 4.05). The compound IV reduced Tollen's reagent and formed a *2,4-dinitrophenylhydrazone*, m.p. 175–176°. *Anal.* Calcd. for $C_{16}H_{17}N_5O_4$: C, 55.97; H, 4.99; N, 20.40. Found: C, 55.94; H, 4.96; N, 20.34. A *picrate* was also formed, m.p. 148–149°. *Anal.* Calcd. for $C_{16}H_{16}N_4O_8$. C, 48.98; H, 4.11; N, 14.28. Found: C, 49.22; H, 4.19; N, 14.31.

That dimethylamine was lost in the reaction of II to form IV was shown by treatment of II with picric acid in 95% alcohol. After five recrystallizations, analytically pure dimethylamine picrate was isolated. A mixture melting point of this picrate with that of an authentic sample of dimethylamine picrate showed no depression.

Cava has suggested that in the conversion of 1,2-dibromobenzocyclobutene to I there is elimination of bromine to form benzocyclobutadiene, followed by addition of iodine to the highly reactive double bond.[2] The possibility of a nucleophilic displacement of bromine by iodide ion was ruled out. The present results can be rationalized by a similar mechanism by postulating a *cis* elimination of hydrogen iodide followed by addition of dimethylamine to the benzocyclobutadiene intermediate. This would have to be followed by a second elimination and addition to give II. An alternative mechanism involving direct nucleophilic displacement of the iodine atoms is also possible.

(1) M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.*, **78**, 500 (1956).

(2) M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.*, **79**, 1701 (1957).

(3) W. E. Coleman and F. R. Jensen, *J. Org. Chem.*, **23**, 869 (1958).

(4) W. E. Coleman and F. R. Jensen, *J. Am. Chem. Soc.*, **80**, 6149 (1958).

(5) J. von Braun and R. S. Cahn, *Ann.*, **436**, 262 (1924).

Attack of water or hydroxide ion on singly protonated II, followed by ring opening, a proton shift and hydrolysis of the resulting amino alcohol, could give the aldehyde IV.

Further work is being carried out on the mechanism of formation of II, on its reactions and on the possibility of reactions of I with other nucleophilic reagents.

SCHOOL OF CHEMISTRY
UNIVERSITY OF MINNESOTA
MINNEAPOLIS 14, MINN.

STUART W. FENTON
MELVIN W. HANNA

Received January 28, 1959

α-Oximino Ketones. I. The "Normal" and "Abnormal" Beckmann Rearrangements

Sir:

The Beckmann rearrangement of α-oximino ketones possessing the *anti* or α-configuration is commonly described[1,2,3] as proceeding "normally," to a secondary amide and/or the hydrolysis products thereof, when brought about by an acid or an acid chloride, but "abnormally," to a nitrile and a carboxylic acid, when brought about by an acylating agent and base[1,4] (rearrangement of the "second order"[5]). It was reported originally that rearrangement of α-oximino ketones in polyphosphoric acid was "normal",[6] but more recent work[7,8] has shown that actually the "abnormal" route is followed.

In this laboratory both types of rearrangement have been studied by submitting several unsymmetrical α-oximino ketones to the action of 85% sulfuric acid ("normal") and benzenesulfonyl chloride and aqueous base ("abnormal"). All products obtained are reported in Table I, except that no attempt was made to isolate two-carbon materials. Of particular interest are the first two pairs of α-oximino ketones, since if a secondary amide intermediate were formed in the "normal" reaction, both 2-oximino-1-phenyl-1-propanone and 1-oximino-1-phenyl-2-propanone should give *N*-acetylbenzamide or the same hydrolysis products therefrom, and 1,3-diphenyl-2-oximino-1-propanone and 1,3-diphenyl-1-oximino-2-propanone should give *N*-benzoylphenylacetamide or the same hydrolysis products.

TABLE I

BECKMANN REARRANGEMENTS OF α-OXIMINO KETONES

α-Oximino Ketone R	R′	Products and Yields from 85% H_2SO_4	Products and Yields from $PhSO_2Cl$ + NaOH
Ph	Me[a]	$PhCO_2H$ (84%)	$PhCO_2H$ (91%)
Me	Ph[b]	$PhCONH_2$ (92%)	PhCN (87%)
Ph	CH_2Ph[c]	$PhCH_2CONH_2$ (47%)	$PhCH_2CN$ (68%)
		$PhCO_2H$ (86%)	$PhCO_2H$ (74%)
$PhCH_2$	Ph[d]	$PhCONH_2$ (61%)[e]	PhCN (77%)
		$PhCH_2CO_2H$ (68%)	$PhCH_2CO_2H$ (74%)
Me	Bu[f]	$BuCONH_2$ (59%)	BuCN (70%)
Me	CH_2Ph[g]	$PhCH_2CONH_2$ (83%)[h]	$PhCH_2CN$ (87%)
Pr	Et[i]	$EtCONH_2$ (19%)	EtCN (45%)
		$PrCO_2H$ (78%)	$PrCO_2H$ (84%)

[a] Purchased from Distillation Products Industries, Rochester, N. Y. [b] M.p. 162–163°. H. Rheinboldt and O. Schmitz-Dumont, *Ann.* **444**, 113 (1925) report 164–165°. [c] M.p. 126–127.5°. W. Schneidewind, *Ber.*, **21**, 1323 (1888) reports 125–126°. [d] M.p. 114–114.5°. *Anal.* Calcd. for $C_{15}H_{13}O_2N$: C, 75.29; H, 5.48; N, 5.85. Found: C, 75.46; H, 5.43; N, 5.81. [e] An 8% yield of $PhCO_2H$ was obtained also. [f] M.p. 59–60°. *Anal.* Calcd. for $C_7H_{13}O_2N$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.85; H, 9.25; N, 9.77. [g] M.p. 80–81°. G. Ponzio, *Gazz. chim. ital.*, **35**, 394 (1905) reports 80–81°. [h] A 12% yield of $PhCH_2CO_2H$ was obtained also. [i] B.p. 62–63° (0.45 mm.), n_D^{35} 1.4548. *Anal.* Calcd. for $C_7H_{13}O_2N$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.97; H, 9.30; N, 9.51.

The results obtained show that in both so-called types of rearrangement the nitrogen in the products was attached to the radical which originally bore the oxime carbon, and the conclusion seems inescapable that both reactions proceeded by the same path, except that hydrolysis of the nitrile took place in sulfuric acid. Additional confirmation for this view was obtained when other typical catalysts for the "normal" reaction were examined: Phosphorus pentachloride gave valeronitrile (70%) from 3-oximino-2-heptanone, and phenylacetonitrile (86%) from 2-oximino-1-phenyl-3-butanone; thionyl chloride gave benzonitrile (88%) from 1-oximino-1-phenyl-2-propanone. Trifluoroacetic acid, which has been shown[9–11] to give normal amide products from simple ketoximes, gave

(1) A. H. Blatt, *Chem. Revs.*, **12**, 215 (1933).
(2) N. V. Sidgwick, *The Organic Chemistry of Nitrogen* (revised and rewritten by T. W. J. Taylor and W. Baker), Oxford University Press, 1942, p. 182.
(3) V. Migrdichian, *Org. Syntheses*, **1**, Reinhold Publishing Corp., New York, 1957, p. 376.
(4) A. H. Blatt and R. P. Barnes, *J. Am. Chem. Soc.*, **56**, 1148 (1934).
(5) A. Werner and A. Piguet, *Ber.*, **37**, 4295 (1904).
(6) E. C. Horning, V. L. Stromberg, and H. A. Lloyd, *J. Am. Chem. Soc.*, **74**, 5153 (1952).
(7) C. T. Elston, doctoral dissertation, University of Illinois (1954), quoted by F. D. Popp and W. E. McEwen, *Chem. Revs.*, **58**, 372 (1958).
(8) R. T. Conley and F. A. Mikulski, *J. Org. Chem.*, **24**, 97 (1959).
(9) M. L. Huber, U. S. Patent 2,721,199, Oct. 18, 1955.
(10) M. Hudlicky, *Chem. listy*, **51**, 490 (1957); *Collection Czechoslov. Chem. Communs.*, **23**, 462 (1958).
(11) W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 6522 (1957).

valeronitrile (58%) from 3-oximino-2-heptanone, and benzonitrile (94%) and benzoic acid (88%) from α-benzil monoxime.

It seems reasonable to conclude that all Beckmann rearrangements of α-oximino ketones possessing the *anti* configuration proceed by the same route, and therefore that the terms "normal" and "abnormal" as applied to this reaction are superfluous. The term "second order" might well be retained to refer to the rearrangement of all α-oximino ketones, which, since it appears to involve shift of a pair of electrons only,[12] is mechanistically quite distinct from the rearrangement of simple ketoximes, which involves shift of an electron pair and the accompanying organic group.

Full details of this study will be reported later.

CENTRAL RESEARCH LABORATORY ARTHUR F. FERRIS
FOOD MACHINERY AND CHEMICAL CORPORATION
PRINCETON, N. J.

Received March 11, 1959

(12) A. L. Green and B. Saville, *J. Chem. Soc.*, 3887, (1956).

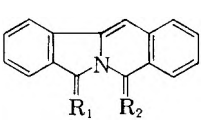
Novel Synthesis of a 1,2,5,6-Dibenzocycl[3,2,2]-azine[1]

Sir:

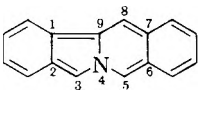
The recent synthesis of cycl[3,2,2]azine by Boekelheide and Windgassen[2] suggested that the readily available 1,2,6,7-dibenzo-3,5-dihydro-3,5-diketopyrrocoline,[3] I, might lend itself to synthesis of additional examples of this interesting class of heterocycles. Inspection of accurate molecular models[4] of pyrrocoline and of possible Diels-Alder adducts of pyrrocoline clearly indicated that the steric requirements alone of 3,9- or 5,8-adducts should effectively preclude their formation, while a 3,5-adduct (the product of 1,8- rather than 1,4-Diels-Alder addition) should be quite free of strain. Formation of a 3,5-adduct should be favored by the resonance energy of such a product, which would be expected to be greater than that of 3,9- or 5,8-adducts. Finally molecular orbital calculations indicate that the localization energy for simultaneous attack at the 3- and 5-positions is comparable to that of normal Diels-Alder additions.[5] In the case of III, formation of a 3,5-adduct carries the additional advantage of the recovery of the full resonance energy of two benzenoid rings.

The starting material I was prepared in 91% yield by heating the dry diammonium salt of 2,2′-dicarboxydesoxybenzoin[3] to 240° in the presence of a heat-transfer agent such as diphenylamine. Reduction of I with tin and hydrochloric acid in refluxing acetic acid produced II, which was recrystallized from benzene-hexane, m.p. 193–194°, (Found: C, 82.15; H, 4.77; N, 6.04: λ_{max} 6.05 μ) in 62% yield. Reduction of II to III proceeded in 71% yield when carried out with excess lithium aluminum hydride in refluxing ether for 3 days. The product, 1,2,6,7-dibenzopyrrocoline, III, was purified by solution in dilute acid, treatment with charcoal, and reprecipitation with sodium bicarbonate. Although all operations were carried out under nitrogen, the yellow-green product which melted at 200–202° under vacuum was so sensitive to oxygen that satisfactory analyses could not be obtained.

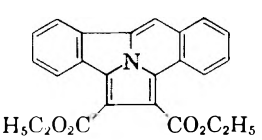
1,2,5,6 - Dibenzo - 3,4 - dicarbethoxycycl[3,2,2]-azine, IV (Found: C, 74.77; H, 5.17; N, 3.87), yellow crystals, m.p. 125–126°, was obtained in 54% yield when toluene solutions of diethyl acetylenedicarboxylate and III containing a catalytic amount of 10% palladium-on-charcoal and a trace of hydroquinone were mixed and refluxed for 14 hr. under nitrogen. The product possesses no basic properties and has a strong yellow-green fluorescence in ether or benzene solution. Its infrared spectrum (CCl_4) has characteristic absorptions at 5.82 μ (shoulder), 5.98 μ, and 8.20 μ, while its ultraviolet spectrum in ethanol has λ_{max} 232 (log ε 5.59), 255 (5.28), 293 (5.42), 317 (5.36), 343 (shoulder), and 420 (4.11). The picrate, m.p. 134–135° (Found: C, 58.53; H, 3.77; N, 9.19), and *sym*-trinitrobenzene adduct, m.p. 161–163° (Found, C, 60.38; H, 3.87; N, 9.56) were prepared in absolute ethanol.



I, $R_1 = R_2 = O$
II, $R_1 = H_2$, $R_2 = O$



III



IV

(1) Work done at the School of Chemistry, Rutgers, The State University, New Brunswick, N. J.

(2) V. Boekelheide and R. J. Windgassen, Jr., *J. Am. Chem. Soc.*, **80**, 2020 (1958); R. J. Windgassen, Jr., W. H. Saunders, and V. Boekelheide, *J. Am. Chem. Soc.*, **81**, 1459 (1959).

(3) J. Ephraim, *Ber.*, **24**, 2820 (1891).

(4) J. C. Godfrey, *J. Chem. Educ.*, **36**, 140 (1959).

(5) R. A. Barnes, private communication.

BRISTOL LABORATORIES INC. JOHN C. GODFREY
SYRACUSE 1, N. Y.

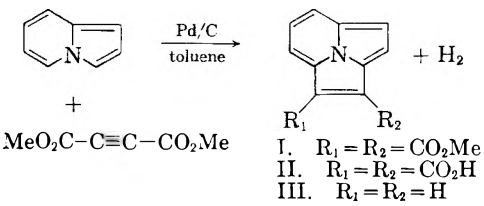
Received March 24, 1959

Reaction of Dimethyl Acetylenedicarboxylate with Pyrrocoline

Sir:

The Diels-Alder condensation is an important synthetic procedure for the formation of six-membered rings. A consideration of possible mechanisms[1a,b,c] for the Diels-Alder reaction would suggest that the formation of five- and seven-membered rings should be possible. We have now found that the reaction of pyrrocoline with dimethyl acetylenedicarboxylate under dehydrogenation conditions provides an interesting example of the formation of a five-membered ring and offers an exceptionally direct method for the synthesis of cycl[3,2,2]azine derivatives.[2]

In their studies on the reaction of various heterocyclic amines with dimethyl acetylenedicarboxylate, Diels and his co-workers discovered a series of interesting products which were formulated in a rather unusual fashion.[3] However, apparently because of its unavailability, pyrrocoline was not investigated. Recently, Godfrey observed that the reaction of 1,2,6,7-dibenzopyrrocoline with dimethyl acetylenedicarboxylate in the presence of a dehydrogenation catalyst gave a product corresponding to a 1:1 adduct with loss of hydrogen.[4] That addition had occurred across the 3 and 5 positions of the pyrrocoline ring to give a cycl[3,2,2]azine derivative was suggested by a comparison of the ultraviolet absorption spectrum of the adduct with known cycl[3,2,2]azine derivatives.[2] This hypothesis has now been verified for the case of pyrrocoline itself where the adduct (I) has been degraded to the parent heterocycle (III).



I. $R_1 = R_2 = CO_2Me$
II. $R_1 = R_2 = CO_2H$
III. $R_1 = R_2 = H$

Treatment of pyrrocoline[5] with dimethyl acetylenedicarboxylate in boiling toluene using a 5% palladium-on-charcoal catalyst afforded a dark crystalline solid which, after chromatography over alumina with benzene as solvent, gave I as yellow prisms, m.p. 91–92° (Found: C, 65.45; H, 4.31; N, 5.57), in 50–66% yield. Hydrolysis of this diester in methanolic potassium hydroxide followed by acidification yielded the corresponding acid II as yellow crystals, m.p. > 320° (Found: C, 62.77; H, 3.21; N, 6.17) in essentially quantitative yield. Decarboxylation of II proceeded in 70–80% yield using copper chromite in quinoline to cycl[3,2,2]-azine (III), whose identity was proved by mixture melting point and infrared spectral comparison with an authentic sample.[2]

In addition to I, a second substance was obtained from the chromatogram as colorless crystals, m.p. 180–180.5° (Found: C, 64.48; H, 5.07; N, 5.50), in 10–15% yield. Although the structure of this product has not yet been established, its composition would suggest that it is the result of a simple substitution reaction of the type well known for pyrrole.[6]

The possible extension of this method using dienophiles other than dimethyl acetylenedicarboxylate as well as nuclei other than pyrrocoline is under investigation.

Department of Chemistry
University of Rochester
Rochester, N. Y.

Andrew Galbraith[7]
Theodore Small[8]
V. Boekelheide

Received March 24, 1959

(1)(a) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 711; (b) C. Walling and J. Peisach, *J. Am. Chem. Soc.*, **80**, 5819 (1958); (c) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

(2)(a) R. J. Windgassen, Jr., W. H. Saunders, Jr., and V. Boekelheide, *J. Am. Chem. Soc.*, **81**, 1459 (1959); (b) V. Boekelheide and R. J. Windgassen, Jr., *J. Am. Chem. Soc.*, **80**, 2020 (1958).

(3) See O. Diels and H. Schrum, *Ann.*, **530**, 68 (1937) for leading references.

(4) J. C. Godfrey, *J. Org. Chem.*, **24**, 581 (1959). We are indebted to Dr. Godfrey for disclosing his observations to us at an early stage and for subsequent suggestions and stimulating informal discussions.

(5) V. Boekelheide and R. J. Windgassen, Jr., *J. Am. Chem. Soc.*, **81**, 1456 (1959).

(6) O. Diels, K. Alder, H. Winckler, and E. Petersen, *Ann.*, **498**, 1 (1932) and earlier papers.

(7) Alfred P. Sloan Foundation Fellow.

(8) Monsanto Predoctoral Fellow, 1958–59.